Four decades of European medicines regulation: What have they brought us?

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Abstract. This article gives an overview of the development of the European regulatory system. In 1965 the First Directive on medicinal products was adopted. In 2005 a total revision of the system will come into force. How effective the European Union legislation and regulatory system has been and why has the focus of regulation changed over the years? A famous philosopher said that to know the future, the past has to be explored. From the history of EU pharmaceutical legislation it becomes clear why the law has become as it is.

1. 1000 BC–1965: Focus on quality defects and adulteration

Mankind has since the old times been using medicinal products. A famous quotation is of Sir William Osler, who said: ‘Man has an inborn craving for medicine. The desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures’ [2]. In many societies the profession of pharmacist has a much longer reputation than that of the physician. Pharmacopoeias and formularies are known for a longer time than clinical pharmacotherapy textbooks. Many of the drugs that were used until the beginning of the last century were harvested in nature. The main focus of drug control was on identity of the substance and the freedom of contaminations of the drug. The history of pharmacovigilance started on 29 January 1848 when 15 year old Hannah Greener died during a routine anaesthesia with chloroform [8]. In 1906 the US Federal Food and Drug Act was signed into law. This law required that pharmaceuticals should be “pure” and “free of any contamination”. Efficacy was not an issue at that time. Experience of doctors and pharmacists was more important in evaluating efficacy. Only after 1950 a totally new concept came into vision: randomised placebo-controlled clinical trial. Because of this development, efficacy could be measured much more precisely.

Two disasters were important for further drug regulation. Around 1936, 107 lethal cases of poisoning by diethyleneglycol happened, because this solvent was used to solubilize sulphanilamides. The US law was amended two years later, establishing the FDA. In the year 1961 many cases of phocomelia occurred. It took another two years to recognise the causality between this condition and the use of thalidomide (Softenon®) during pregnancy by the mother. Because this apparent risk of the use of medicinal products, preclinical and clinical testing of medicinal products was introduced in many countries. In several European countries regulatory bodies were established and pre-marketing approval of

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1Particular malformation of the extremities of the newborn.

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medicines was required. The European Commission at that time recognised the importance of a harmonised approach to the marketing authorisation of medicinal products and proposed an EEC Directive on proprietary medicinal products.

2. 1965–1975: Focus on evaluation of design for Proprietary Medicinal Products

Directive 65/65/EEC [3] was one of the first European legislations that were adopted in a policy area that was connected to, but not part of the ideologies of the Treaty of Rome. It concerned the possible Public Health risks caused by the free movement of goods in the European Economic Community. It was considered important to have a harmonised approach to the pre-marketing authorisation of medicinal products, on the basis of a dossier containing results of tests that had to be performed on the medicinal products to confirm their safety and efficacy.

Directive 65/65/EEC had a limited scope: it was only applicable to proprietary medicinal products – what we now call generic medicines were not under considered – and exemptions existed for homeopathic medicines, radiopharmaceuticals, blood products and immunological medicinal products, like sera and vaccines.

The key article of Directive 65/65/EEC was article 4:

Article 4

In order to obtain an authorisation to place a proprietary medicinal product on the market as provided for in Article 3, the person responsible for placing that product on the market shall make application to the competent authority of the Member State concerned. The application shall be accompanied by the following particulars and documents:

1. Name or corporate name and permanent address of the person responsible for placing the product on the market (…)
2. Name of the proprietary product (…)
3. Qualitative and quantitative particulars of all the constituents of the proprietary product (…)
5. Therapeutic indications, contra-indications and side-effects.
6. Posology (…)
7. Control methods employed by the manufacturer (analysis and assay of the constituents (…).
8. Results of:
   - physico-chemical, biological or microbiological tests;
   - pharmacological and toxicological tests;
   - clinical trials.

However:

(a) a List of published references relating to the pharmacological tests, toxicological tests and clinical trials may be substituted for the relevant test results in the case of:

(i) a proprietary product with an established use, which has been adequately tested on human beings so that its effects, including side-effects, are already known and are included in the published references;
(ii) a new proprietary product, in which the combination of active constituents is identical with that of a known proprietary product with an established use;
(iii) a new proprietary product consisting solely of known constituents that have been used in combination in comparable proportions in adequately tested medicinal products with an established use.
In the original text of 65/65 it was mentioned that results of preclinical and clinical tests should be submitted, but there were no detailed requirements for the extend to which these tests should give information about the safety and efficacy of the medicinal product. In the first medicinal products Directive there was also the possibility for waivers of obligations in the case there has already been enough experience with a product. In the first 10 years of European regulation for the six founding Member States the situation remained quite open: plenty of room for national regulation and national approaches existed.

3. 1975–1985: Harmonisation between Member States is put on track; dossier requirements form part of legislation

In 1975 the Second Directive on medicinal product was adopted: Directive 75/319/EEC [10]. This Directive extended the scope of European legislation to the other aspect of regulation of medicinal product: authorisation of manufacturers. On the point of the Marketing Authorisation, the CPMP\(^2\) was set up as a scientific body in the European Community. At this point in time the CPMP was not yet a decision making body, it only had an advisory role [1]. Also the Pharmaceutical Committee was established as an advisory body to the European Commission, on any issue of policy or legislation.

Probably much more important might be the other Directive that was adopted on the same day: Directive 75/318/EEC [4]. This directive did not contain any important article, but it had a very important Annex: Annex I to Directive 75/318/EEC. This Annex contained the required content of the dossier that has to be submitted for the application of a Marketing Authorisation. The Annex was, and still is\(^3\), a description of the data that have to be gathered before an application can be made.

At this time the CPMP was not acting as a regulator. The focus of decision making and scientific discussion was still in the Member States. In Brussels, where the CPMP met, regulatory discussions were more important than scientific decisions. However, the CPMP created several working groups for the development of guidelines on the requirements for the documentation to be included in the dossier. These European guidelines started to gradually overrule existing national ones.

At the national level it was realised that drug regulation required closer cooperation between countries. In 1973 the Benelux\(^4\) agency for the regulation of medicines was established. However, industry was not very much interested in the offer of a combined procedure for new medicines. Moreover, mutual trust between regulators was far away, only improving at the end. In 1981 this experiment ended in the light of closer cooperation between EU member states. A cooperation like the Benelux agency also existed in the Nordic countries.

4. 1985–1995: New categories of products and new aspects of medicinal products are taken up in the system; European cooperation is becoming more important

In the third decade of European Medicinal Products regulation the scientific role of the CPMP became more prominent, especially with regard to medicines derived from biotechnology. Moreover an extension of the scope of European medicines legislation took place.

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\(^2\) Committee on Proprietary Medicinal Products. The name of this committee has only recently been changed to CHMP, Committee on Medicinal Products for Human Use.

\(^3\) Now the Annex I is Annex I to Directive 2001/83/EC, and it has been amended in 2003 (Commission Directive 2003/63/EC) to contain the dossier format that has been agreed between Japan, EU and US, the Common Technical Document.

\(^4\) Belgium, the Netherlands and Luxembourg.
In 1987 the so-called 'Concertation Procedure' was introduced with Council Directive 87/22/EEC [5]. This procedure was the first European procedure for the authorisation of medicinal products. Applications for authorisation of 'biotech' medicines had to go through the so-called 'concertation procedure' in the CPMP. The outcome was an opinion which was not binding for the Member States. The advice was quite important anyway, because it is was not easy for National Competent Authorities to take decisions that went against the CPMP opinion. Even though the authorisation of the product was normally agreed upon, it was often difficult to reach a common view on the authorised product information, the SmPC.5 Often an opinion was reached with a SmPC, giving flexibility to member states to modify. Gradually more products were approver with a (harmonised) SmPC.

As far as the extension of the scope of European legislation concerns, the first important new step was the regulation of new categories of medicinal products that were unregulated before:

- generic medicines; followed by the
- immunological medicinal products (Sera, Vaccines and Allergens) (Directive 89/342/EEC);
- Radiopharmaceuticals (Directive 89/343/EEC);
- Blood products (Directive 89/381/EEC); and the

Through those new directives the European system encompassed the complete spectrum of medicinal products on the market as far as marketing authorisations were concerned.

In the year 1992 the so-called 'Rational Use' package was adopted. In this legislative package four Directives were given on:

- Wholesale distribution of medicinal products (Directive 92/25/EEC);
- Classification for the supply (Directive 92/26/EEC);
- Labelling and Patient Information leaflet (Directive 92/27/EEC);

In these years the European system was completed, in the sense that all rules that are relevant for medicinal products had become harmonised. For this reason, it started to make more and more sense that national competent authorities collaborated and shared their opinions on scientific issues concerning the authorisation of medicinal products. The year 1992 was the year that the Single Market was established, so it was important to have a functioning market for medicinal products in place. Furthermore, experience in collaboration between the then 12 Member States’ competent authorities was gathered through discussions in the CPMP (on the scientific and regulatory level) and the Pharmaceutical Committee (on policy level). New Member States (from 6 to 12) were joining the EU in this period, without any difficulties in the regulatory system.

5. 1995–2005: European authorisation procedures and pharmacovigilance

The first of January 1995 the 'new system' [6] came into force. Two European procedures for the authorisation of medicinal products came into existence. For 'biotech' medicines and for other real innovative medicinal procedures the Centralised Procedure (CP) and for other medicinal products the Mutual Recognition Procedure (MRP) were introduced. A European agency was established in London: the EMEA, holding two scientific committees, the CVMP for veterinary medicinal products and the CPMP
for medicines for human use. The CP became a truly European procedure. An application was made to the EMEA. The CPMP delivered an opinion, based on scientific evaluation by the national competent authorities, with a special responsibility for those NCA's that were appointed rapporteur and co-rapporteur and the European Commission would draft a European Marketing Authorisation, valid throughout the whole EU. The second procedure, the MRP, was initiated by a national application leading to a national marketing authorisation that had to be recognised by other Member States, the holder of the MA was interested in. The CP worked out to be a good procedure. The MRP led to some difficulties. In a few instances mutual recognition of new chemical entities was only partly applied. Other Member States raised so-called serious health concerns, which led to the withdrawal of the application in these Member States. But a more important issue concerned the mutual recognition of generics. Differences in the SmPC of nationally authorised innovators (before the MRP became mandatory) led to differences between the (harmonised) SmPCs of generics and the SmPC of the national reference product. Some Member States consider this national disharmony as a serious risk to public health. Of course such differences are difficult to explain to the public. Forced harmonisation of the SmPCs through an arbitration procedure, was hampered by the unwillingness of innovators to co-operate.

Another aspect that came into focus was the safety of medicines after they got onto the market. The European legislator realised the importance of recording and evaluating the 'real-life' safety of medicinal products and the concept of Pharmacovigilance was introduced. In the new legislation periodic safety reporting became mandatory and the development and promotion of systems of spontaneous reporting of adverse drug reaction was introduced in the legislation. It appeared that safety issues often came up after the authorisation of the product. Some products, authorised through the CP or the MRP, had to be revoked either early after authorisation, either after some years of marketing, when unexpected safety issues showed up.

The problems with the MRP and the flaws in the 'new system' led to an extensive review of the EU pharmaceutical legislation: Review 2001. Before the evaluation took place, a codification took place, to get all relevant legislation on medicinal products together in one code. The codification ended up in Directive 2001/83/EC [9], taking all existing legislation with the exception of the regulations, together in one legislative text.


European collaboration has grown up. At many levels decisions concerning the authorisation of medicinal products are discussed between all Member States. Since 1 May 2004 the EU family has grown to 27 Members (15 'Old' Member States, 10 'New Member States and Norway and Iceland) making it into one of the largest populations in the world. Review 2001 [7] fixes a number of issues that remained in the regulatory system. Also some new concepts are taken into the legislation like:

- Stronger centralised approach: more medicinal products have to be authorised through the centralised procedure;
- Transparency in decision making on the authorisation becomes rule: regulatory authorities become more accountable;
- Monitoring of authorised products in the market should become more prominent, and
- Better opportunities for the mutual recognition procedure.

6The MRP was introduced in 1995, but became mandatory from 1 January 1998.
The reasons behind all these changes are founded in the perception of the general public, and of politicians to the reality of the use of medicines. Trust in the protective power of drug regulation has diminished through affairs like QT-prolongation as an adverse drug reaction e.g. for cisapride, rhabdomyolysis caused by statins, deep venous thrombosis during the use of 3rd generation oral contraceptives and the problems with COX-2-inhibitors (provoking more cardiovascular events than expected). On the other hand, there seems to be a false believe in the absolute safety of medicines. One death, for example because of adverse drug effects of anti-conception, in millions of chronic users is perceived as an unacceptable risk to public health, where the probability of smokers dying from adverse effects of nicotine is manifold. There seems to be a misbalance between risk occurrence and the perception of risk.

The answer has to be that regulators ameliorate their procedures in the protection of public health therefore to improve public trust. For this reason Risk Management Plans are now being developed which will be mandatory in future applications.

An issue coming up on the other side of the spectrum is the growing regulatory burden. Industry complains on the steep rise of costs of a new medicinal products, incurred by rising standards of the competent authorities. Scientists complain that truly effective medicines become available late, because of all the regulatory predicaments that have to be fulfilled. In the Review 2001 new procedures as conditional approval or approval under exceptional circumstances, could speed up the process. This trend seems to be opposite to the pursuit of 100% safety. It is interesting how the outcome of these interacting trends will be.

Last but not least the evaluation of ‘value for money’ comes to the foreground. Due to economic reasons and the European belief in solidarity leading to social security systems, the effectiveness on a population basis of new and therefore expensive drugs becomes important.

7. Evaluation of 40 years of integration in Drug Regulatory affairs

Europe has changed over the last 40 years dramatically. Where the community started out with six Member States, now 25 countries are full members and more are on the threshold. The regulation of medicinal products has changed dramatically as well. From almost hardly any government control, medicinal products are now the most extensively regulated category of products. Through this regulation the protection of public health is managed in a better way. The outcome of all the effort however is both impossible to measure and always worse than high public expectations.

References

[1] Article 8, paragraph 2: “The responsibility of the Committee shall be to examine, in accordance with Articles 9 to 14, the questions referred to it by a Member State concerning the application of Articles 5, 11 or 20 of Directive 65/65/EEC.”


