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The Impact of European Integration on the German System of Pharmaceutical Product Authorization

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Abstract

The European Union has evolved since 1965 into an influential political player in the regulation of pharmaceutical safety standards. The objective of establishing a single European market for pharmaceuticals makes it necessary for member-states to adopt uniform safety standards and marketing authorization procedures. This article investigates the impact of the European integration process on the German marketing authorization system for pharmaceuticals. The analysis shows that the main focal points and objectives of European regulation of pharmaceutical safety have shifted since 1965. The initial phase saw the introduction of uniform European safety standards as a result of which Germany was obliged to undertake “catch-up” modernization. From the mid-1970s, these standards were extended and specified in greater detail. Since the mid-1990s, a process of reorientation has been under way. The formation of the European Agency for the Evaluation of Medicinal Products (EMEA) and the growing importance of the European authorization procedure, combined with intensified global competition on pharmaceutical markets, are exerting indirect pressure for EU member-states to adjust their medicines policies. Consequently, over the past few years Germany has been engaged in a competition-oriented reorganization of its pharmaceutical product authorization system the outcome of which will be to give higher priority to economic interests.

Zusammenfassung

Die Europäische Gemeinschaft ist in der Regulierung der Arzneimittelsicherheit seit 1965 zu einem einflussreichen politischen Akteur geworden. Das Ziel eines einheitlichen europäischen Marktes für Arzneimittel erfordert eine Vereinheitlichung der Sicherheitsstandards und Zulassungsverfahren in den Mitgliedstaaten. Im folgenden Beitrag wird der Frage nachgegangen, welche Auswirkungen der Prozess der Europäischen Integration auf das System der Arzneimittelzulassung in Deutschland hat. Es wird deutlich, dass sich die Schwerpunkte und Zielsetzungen der europäischen Regulierung der Arzneimittelsicherheit seit 1965 verschoben haben. Nach einer ersten Phase der Etablierung einheitlicher europäischer Sicherheitsstandards, die in Deutschland eine nachholende Modernisierung erforderlich machten, wurden diese Standards seit Mitte der 1970er Jahre ausgebaut und präzisiert. Seit Mitte der 1990er Jahre kommt es zu einer Neuausrichtung. Die Errichtung der europäischen Arzneimittelagentur EMEA und der Bedeutungsgewinn der europäischen Zulassungsverfahren erzeugen in Verbindung mit dem verschärften globalen Wettbewerb auf den Arzneimittelmärkten einen mittelbaren Anpassungsdruck auf die nationalen Arzneimittelpolitiken. In der Konsequenz wird in Deutschland seit einigen Jahren eine wettbewerbsorientierte Umgestaltung der Arzneimittelzulassung betrieben, die zu einer Aufwertung ökonomischer Interessen im Zulassungssystem führt.

Inhalt

1. Introduction

For a long time, government control of pharmaceutical safety was weak in the former West Germany compared with some other countries. While the United States established a national regulatory authority, the Food and Drug Administration (FDA), as early as 1906 and the Scandinavian countries brought pharmaceutical product authorization under state control in the 1920s, West Germany enacted its first national Medicines Act (Arzneimittelgesetz, AMG) only in 1961 (Stapel 1988). The 1961 Act still did not introduce a marketing authorization procedure based on material examination of pharmaceutical safety by a government agency. Instead, manufacturers were merely required to have their products registered by the Federal Health Office. The government's low-key role in regulating pharmaceutical safety was mainly attributable to Germany's corporatist political culture, in which industry ranked highly and was long able to prevent direct state intervention (Daemmrich 2003; Murswieck 1983).

From the early 1960s, this situation began to change. One can identify three developments that brought about a change in Germany's medicines policy. The first was the occurrence of medicine-related disasters, especially the thalidomide catastrophe in the late 1950s and early 1960s, which sensitized the general public to the risks associated with the supply of medicines and increased political pressure for stricter state regulation (Kirk 1999). Second, as markets for pharmaceuticals became increasingly international, the lack of state control over pharmaceutical safety became a hindrance to the export of German products (Maio 2001). The third development was the process of European integration, a core objective of which was to create a single European market and thus a common market for pharmaceuticals (Mossialos et.al. 2004).

Since the mid-1960s, in pursuit of its objective of creating a single European market "in which the free movement of goods, persons, services and capital is ensured in accordance with the Treaty" (Article 14 Paragraph 2 TEC), Europe has become an important player in medicines policy. The European Commission's Directorate-General for Enterprise and Industry is concerned with advancing harmonization of member-states' different legal bases in respect of the manufacture, authorization, trade in and use of pharmaceuticals. However, for a long time conflicts of interests between the Commission, member-states, the pharmaceutical industry and consumers made hard going of progress on creating a single European market for pharmaceuticals (Feick 2002). The range of pharmaceuticals on sale still differs widely from country to country (Folino-Gallo et.al.: 2001).

European pharmaceuticals policy is characterized as industry-oriented because a) the interests of manufacturers and the Directorate-General for Enterprise largely coincide, b) the Commission has more powers over industrial policy than over health policy and c) political decisions depend on industry's "information monopoly". At the same time, other stakeholders such as consumer protection associations or health policy actors are considerably less closely integrated into the European policy process than are pharmaceutical industry associations (Permanand 2008). How these developments at the European level will impact on authorization procedures for, and the safety of, pharmaceuticals, is debatable. Optimistic appraisals assume that the Europeanization of authorization procedures will lead to high-level harmonization based more on scientific expertise than on member-states' particular interests (Krapohl 2004). Sceptics, in contrast, see a risk that closeness to industry will produce a "commercial bias in drug regulation", toward competition policy goals, while safety standards and patient protection will tend to carry less weight (Abraham/Lewis 2003; Garattini/Bertele 2004).

This paper examines how the Europeanization of pharmaceuticals policy has impacted on the system of pharmaceuticals authorization in Germany. To this end it analyses the development of safety standards and the change in the legal and institutional foundations of pharmaceutical product authorization in the European Community and in Germany. This study investigated the impact of the European integration process on the regulation of pharmaceutical safety in Germany by analysing the content of European and German legal instruments. The research material comprised the European Directives and Regulations relevant to the regulation of pharmaceutical safety, along with the German acts and statutory orders that serve to implement European law (Table 1). The research covers the period from 1961 to 2007. Changes in the German legal position induced by European law were appraised with a view to ascertaining whether, directly or indirectly, they raised or lowered safety standards. Changes in the objectives of government regulation of pharmaceuticals were analysed on the basis of the recitals in EU secondary legislation and the statements of grounds for draft laws of the German federal government.

2. Three Phases of Europeanization

The development of Europeanization in the area of pharmaceutical safety can be divided into three chronological phases that differ in terms of subject matter, goals and intensity of regulation. This paper suggests that during the period from 1965 to 2007 European pharmaceuticals policy should be divided into three separate phases. It considers each phase

in the light of the substantial changes in the legal bases at EC/EU level and appraises its impact on the German regulatory system.

2.1. First Phase of Europeanization 1965–1976: Catch-up Modernization of German System of Pharmaceutical Product Authorization

The Europeanization of pharmaceuticals policy began in 1965 with the adoption of Directive 65/65/EEC. The statement of grounds for this Directive mentions Europeanization motives and states that the "primary purpose" is to safeguard public health. However, it goes on to say that this objective must be attained by means "which will not hinder the development of the pharmaceutical industry or trade in pharmaceuticals within the Community". This dual objective runs like a red thread through the history of European pharmaceutical regulation.

The main features of the first phase of Europeanization were the harmonization of basic concepts, the formulation of a general authorization requirement, and specification of the criteria for authorization and the documentation to be submitted. Directive 65/65/EEC stipulated that no pharmaceutical was to be placed on the market of an EC member-state unless a marketing authorization had been issued by the competent authorities of that member-state. The Directive mentions the authorization criteria quality, safety and efficacy, which are still valid today. It rests with the competent state authority to check whether the pharmaceutical in question meets these criteria. The Directive also lists a number of documents the applicant is required to submit for scrutiny. Along with the results of product tests, they included particulars of side-effects and contra-indications and of the control methods employed by the manufacturer.

The requirements laid down in Directive 65/65/EEC were stated more precisely and expanded in 1975, in Directives 75/318/EEC and 75/319/EEC. The manufacturing process now had to fulfil stricter criteria and government authorities were empowered to monitor companies' compliance with statutory regulations by way of regular inspections. The Directive on tests and trials (75/318/EWG) specified in detail the requirements that documentation submitted with the authorization application had to fulfil. It stipulated that the testing of pharmaceutical safety in EC member-states must be based on analytical and pharmaco-toxicological tests and clinical trials.

The European directives in the first phase of Europeanization marked the start of a process whereby powers that had previously rested solely with national states were trans-

ferred to the European level. At first, this was effected in tentative steps. At EC level, common definitions for the object of regulation were agreed and general requirements in respect of development, manufacture and authorization were formulated. Member-states' governments rejected any further-reaching transfers of power. At that time, the Commission was still far from attaining the objective of a common market in pharmaceuticals. Nonetheless, the first European regulations generated a not inconsiderable need for Germany to adjust its pharmaceuticals policy. The 1961 Medicines Act provided for only weak government regulation of the pharmaceuticals sector. In particular, it did not stipulate that new pharmaceuticals required state authorization. Nonetheless, the revised form of pharmaceutical product authorization was controversial both among politicians and in the industry. There was a significant delay before the requirements laid down in European directives were eventually incorporated into the 1976 Medicines Act (AMG 1976). This Act introduced a requirement for state authorization of pharmaceuticals such as had long existed in other countries (Table 2). The powers of the competent government authority, the Federal Health Office, were increased. In the context of the authorization procedure, it now had the task of subjecting manufacturers' applications to a material test. The European guidelines regarding the testing of medicines and the documentation to be submitted were incorporated into German law. For the first time, the quality, efficacy and safety of pharmaceuticals had to be proven before they were placed on the German market. The tests that manufacturers were required to carry out on pharmaceuticals were expanded on the basis of Directive 75/318/EEC (Table 3). Likewise induced by European law was the requirement that the documentation to be submitted must be evaluated by an expert whose report must also be submitted to the authority.

One could continue the list of more stringent requirements laid down in the 1976 Medicines Act. The introduction of compulsory authorization and the associated guidelines marked a qualitative transition in the regulation of pharmaceuticals in Germany that could be described as catch-up modernization. During this phase, the process of Europeanization resulted in a noticeable expansion of safety regulations.

2.2. Second Phase of Europeanization, 1976–1993: Extension and Detailed Specification of Authorization Requirements

The creation of a single European market remained a central objective of European pharmaceuticals policy after 1975. However, the second phase of Europeanization is marked more by incremental advances in the Europeanization process. The Commis-

sion's efforts to simplify market authorization in various countries, and EC-wide, failed on account of opposition from member-states. The multi-state procedure introduced in 1975 and amended in 1983 (Directives 75/319/EEC, 83/570/EEC) was designed to enable applicants to place pharmaceuticals that have marketing authorization in one member-state on the market in other member-states without going through the entire national authorization procedure there. For this, the authorities of the other member-states would have to recognize the initial marketing authorization. In practice, in nearly every case the member-states involved withheld their approval, so the procedure was hardly used. A similar thing happened to the concertation procedure introduced in 1987 (Directive 87/22/EEC) with the aim of ensuring uniform authorization of "high-technology medicinal products" throughout the Community. The European component of this procedure consisted in the newly established Committee for Proprietary Medicinal Products (CPMP) having to draw up an expert report on the pharmaceutical in question, including a recommendation on whether it should be authorized. However, the ultimate decision to authorize a pharmaceutical still rested with individual national authorities, which were not bound by the CPMP's recommendation. Since it was not binding, the concertation process did not represent a breakthrough in establishing a single European market for pharmaceuticals either.

In view of member-states' dogged resistance to a European authorization procedure and differences of opinion in the pharmaceutical industry (where many companies were keen to retain tried and trusted national procedures and agencies), in the period from 1975 to 1992 the main focus of European pharmaceuticals policy was on further development of the standards to be applied in testing pharmaceuticals and in authorization procedures. In the late 1980s and early 1990s a series of directives on individual aspects of pharmaceutical product authorization were adopted (Table 1). The scope of European regulation was extended to include immunological, radioactive and homoeopathic medicines and pharmaceuticals made from human blood or plasma (Directives 89/341/EEC, 89/342/EEC, 89/343/EEC, 89/381/EEC, 92/73/EEC). European guidelines for good manufacturing practice (GMP) were developed (Directives 89/341/EEC, 91/356/EEC), uniform regulations on prescription requirements were issued (Directive 92/26/EEC) and instructions for labelling and package leaflets were expanded (Directive 89/341/EEC, 92/27/EEC). In 1991, the legal and administrative provisions for pharmaceutical testing were revised to take account of recent scientific and technological developments (Directive 91/507/EEC). The European Community further imposed a Europe-wide ban on advertising to the general public medicines available only on prescription and those containing psychotropic or narcotic substances (Directives 89/552/EEC, 92/28/EEC).

Once more, the more detailed specification und consolidation of European regulations generated a need for Germany to adjust its pharmaceuticals policy accordingly. This was done mainly through the 1994 Medicines (Amendment) Act (AMG-Änderungsgesetz). Unlike in the first phase, there was now no need for a fundamental reform of authorization-relevant standards. On the contrary, the Medicines Act of 1976 had gone beyond the scope of the European standard in some respects, so there was less need for amendment (e.g. the compulsory package leaflet).

The authorization objectives formulated in the previous phase were not fundamentally changed. No new quality in the Europeanization of pharmaceuticals policy is discernible in the second phase, and there was no change in the apportionment of powers between national governments and European institutions. While there was further standardization of definitions, norms and standards at the European level, decisions on allowing pharmaceuticals access to member-states' markets remained within the remit of national agencies alone. As regards regulation of pharmaceutical safety in Germany, the process of Europeanization between 1975 and 1993 led in some areas to an expansion of the previously established authorization system.

2.3. Third Phase of Europeanization, 1993–2007: Pharmaceutical Product Authorization in Twofold Competition

Though no breakthrough toward a single European market for pharmaceuticals was achieved during the second phase, some important decisions concerning the further course of the European integration process had been taken. In the field of pharmaceuticals, they began to show effects in 1993. The starting point for the accelerated Europeanization of pharmaceutical regulation during the third phase was the 1985 White Paper on Completing the Internal Market, which lent a new dynamic to the European integration project after a phase of stagnation (Commission 1985). A central concern of the Commission was to remove the obstacles to trade presented by differing technical norms and standards. Along with efforts to harmonize standards throughout Europe, it now consolidated the strategy of mutual recognition of existing national product regulations.

Regulation 93/2309/EEC established the European Agency for the Evaluation of Medicinal Products (EMEA) and introduced a centralized authorization procedure, and Directive 93/39/EEC established the mutual recognition procedure. These fundamentally changed the institutional and procedural bases of pharmaceutical product authorization in the EU.

The centralized authorization procedure replaced the concertation mechanism and created an EC-wide marketing authorization for “high-technology medicinal products”. This centralized procedure is obligatory in the EC for pharmaceuticals derived from biotechnology. In other words, national authorization procedures are no longer permitted for a defined group of innovative medicines. Member-states may opt to use the centralized procedure for a further group of “innovative compounds”. The EMEA, or rather the affiliated Committee for Proprietary Medical Products (CPMP), draws up an expert report that forms the basis for the Commission’s decision on authorization. The Committee, whose members are representatives of national regulatory agencies, refers an application for a marketing authorization to a rapporteur who is a representative of a national regulatory agency. The rapporteur examines the documentation and draws up an evaluation report that is passed to the Commission. Member-states’ governments are given a say in the authorization decision through the intergovernmental Standing Committee on Medicinal Products for Human Use, which is located in the Commission. If the Standing Committee opposes the Commission’s vote, the decision is referred to the European Council. However, the Standing Committee has no veto and can be outvoted by a qualified majority of the Council.

The multi-state procedure initiated in 1975 had very little impact. National authorizing agencies continued to make autonomous decisions and seldom recognized marketing authorizations granted by other member-states. The new mutual recognition procedure (Directive 93/39 EEC) was therefore extended to include a binding European arbitration process. Now, if there are irreconcilable differences of opinion between a member-state in which a particular pharmaceutical has been authorized (the reference member-state or RMS) and a member-state where an application for recognition of the authorization has been lodged (the concerned member-state or CMS), the matter is referred to the CPMP. The CPMP draws up its own expert report evaluating the risk to public health and votes for or against authorization. The Commission takes a decision on this basis, with the participation of the Standing Committee (and, if need be, the Council). All the member-states involved, whether RMS or CMS, are bound by the Commission’s (or the Council’s) decision.

The formation of the EMEA and extension of the European authorization procedure, the scope of which was further expanded in 2004 (Regulation 726/2004, Directive 2004/27/EC), did not substantially change the criteria and standards to be followed for marketing authorization. However, since 1993 they have led to a far-reaching shift of powers to European institutions. In particular, the CPMP, which in 2005 was renamed the

Committee for Medicinal Products for Human Use (CHMP) has been elevated into the main player in the authorization of pharmaceuticals in Europe. Although the Committee is made up of representatives of member-states, they are obliged to act within the framework of procedural and normative regulations set at the European level and are subject to mutual scrutiny. Expert reports by the Committee form the basis for decisions by the Commission or the Council on authorizing a pharmaceutical for the entire EU market. National authorization procedures have lost much of their relevance since 1995. A different division of labour is evolving within the EU, with national authorities assuming a new role. Now, they increasingly act as part of the European regulatory network, either as a member of the CHMP or as an RMS or CMS in the mutual recognition procedure.

The new European division of labour has prompted an institutional transformation in the German pharmaceuticals authorization system. Internal restructuring was initiated in 2004 with the aim of improving the speed and efficiency with which the Federal Institute for Drugs and Medical Devices (BfArM) processes applications for marketing authorization (BMGS 2005). In 2007 the German federal government published a draft bill to usher in the transformation of the BfArM into the German Drugs Agency (DAMA). It is taking this action in pursuit of an adjustment to the Europeanization of pharmaceutical product authorization that does not directly serve to implement European legal instruments but is a consequence of developments since 1995. In the preamble to the bill, the German government argues that a situation of twofold competition exists. On the one hand, pharmaceutical enterprises face tougher international competition. On the other, the German medicines licensing agency is in competition with other national authorities in Europe. Like the European Commission, the German government sees the outlook for European pharmaceutical product authorization as a drastically reduced network comprising the EMEA and a few national agencies. No longer will forty-one agencies in twenty-seven member-states participate in European procedures as EMEA partners, but in their place a small number of efficient, fast and scientifically excellent authorities. The German licensing authority is to undergo a fundamental institutional reform to equip it for inter-agency competition (Bundesregierung 2007).

The core features of the restructuring process since 2004 relate to:

- *Organizational Streamlining:* Efficiency gains are to be achieved by changing competences and responsibilities within the agency. A reduction in the number of departments and organizational units and the formation of project teams is designed to accelerate the authorization procedure.

- *Benchmarking and Change Management:* In future, the work of the Institute will undergo continuous review and any necessary changes in organization, control and planning will be implemented speedily. Senior management is to be enabled to take rapid, flexible decisions.
- *Professional Competence:* The scientific know-how of the BfArM has been expanded. The Institute's own laboratory work has been expanded and cooperation with universities has been consolidated. The idea is that concentrating specialists in a variety of interdisciplinary teams will make decision-making processes more effective.
- *Improved Access for Applicants:* Pharmaceutical companies, or applicants, have been given better access facilities to the licensing agency. For the first time, companies will be given the telephone numbers of the employees responsible for dealing with their application and will be able to contact them directly.

The German government's draft bill makes provision for further steps in future:

- *Greater Autonomy for the Institute:* The Institute's legal form is to be changed (from an independent higher federal authority to a public-law corporation directly under federal government control). The aim is to enable it to act with greater autonomy from the Federal Health Ministry and to get it to abandon its previous "typical civil-service" ethos in favour of a "market-oriented" orientation. The Federal Health Ministry will still be responsible for legal and technical oversight, but its authority to issue instructions will be reduced.
- *New Senior Management:* The DAMA is to be headed by a two-person board of management appointed for a fixed term. Their remuneration will be performance-related and based on annual targets agreed with the Health Ministry. The board is to have organizational, staffing and financial autonomy.
- *Pharmaceutical Product Authorization to be Financed by Fees:* After a transitional phase, pharmaceutical product authorization is to be wholly financed by fees from industry. The present system of mixed financing by taxes and fees is to be discontinued in the medium term.
- *Improvement in Scientific Expertise:* The board's greater organizational and financial scope for action is to be utilized to improve its access to scientific experts. The

DAMA is to be given the option to pay employees outside collectively agreed pay scales to make it easier for it to recruit highly qualified specialists (Bundesregierung 2007).

Since the establishing of the EMEA and the reform of the European authorization procedure, the Europeanization of pharmaceutical product authorization has unleashed a new dynamic in German pharmaceutical policy. The present changes in the German system are not happening because of the need to implement European law, but rather as a result of the changed economic, legal and institutional context. This is an indirect form of Europeanization and its consequences for pharmaceutical safety are a hot topic of discussion.

3. Competition-orientated Restructuring of the Authorization System

The first two phases of Europeanization in pharmaceutical product authorization had the result of raising pharmaceutical safety standards in Germany. The introduction of compulsory state authorization in 1976 was essentially based on the precepts in Directives 65/65/EEC and 75/319/EEC. During this period, Europeanization led to the seemingly contradictory outcome that national authorities had to cede the power to issue directives and norms to European institutions, while in return member-states' powers to issue marketing authorization were strengthened on the basis of European law. The requirement for state approval and the fundamental authorization criteria of efficacy, quality and safety were agreed by the European Community prior to their translation into German law. In the case of Germany one can record that the Europeanization of safety standards in the pharmaceuticals sector had the effect of strengthening government regulation of risks. However, this assessment is not transferable to other countries. For countries such as Sweden and Norway which had a fully-fledged system of state authorization prior to 1965, Europeanization meant a partial dismantling of state regulatory powers (Norris 1998, Rehnberg 2002).

Nonetheless, the character of Europeanization underwent a marked change in 1993. The introduction of binding European authorization procedures and the formation of the EMEA placed the institutional structure of pharmaceutical product authorization in the EC on a new footing. From now on, there was an elaborate, multi-layered European system of pharmaceutical product authorization in which the participating actors had experienced a reallocation of tasks. At the EC level, there was a change from a weak to a strong "regula-

tory state" (Abraham/Lewis 2003). The integration of national authorities into a European authorization system resulted in a distinct loss of powers at the national level. Subsequently, national authorization procedures played a subordinate role, both economically and medically. National regulatory authorities began to compete for commissions from industry (as the RMS in mutual recognition procedures) or the EMEA (as rapporteurs in the centralized authorization procedure).

The changes in pharmaceutical product authorization are embedded in a competition-oriented political strategy, the aim of which was to make the EU the "most dynamic and most competitive economic zone on earth" (the Lisbon Strategy), and in which the pharmaceutical and biotech industry plays an important role (European Council 2000, Commission 2002, Commission 2003). As an innovative, forward-looking sector, it is attributed with considerable growth and employment potential. To encourage this potential, the aim is to place new pharmaceuticals quickly on the market. Now, state supervision of pharmaceutical safety is increasingly regarded as a part of the pharmaceutical value chain (Boston Consulting Group 2001).

The formation of the EMEA and the establishing of the European authorization procedure required no direct implementing legislation in member-states. This distinguishes the third phase of Europeanization from the previous two, when standards were specified for legislation on pharmaceuticals. Nonetheless, recent developments elicited a response from German politicians that consists making the national licensing authority more competitive. The German government is keen for the procedure for authorizing pharmaceuticals to be faster and more efficient in future, and carried out in a manner that is more responsive toward the industry (Task Force 2004, 2005). The licensing authority should see itself increasingly as a Europe-oriented service and to distinguish itself to its "customers" in the industry by its cooperative, fast and efficient way of working. This change in the regulatory system tends to make the authority and applicants "virtual allies" with at least partially identical interests (Abraham/Lewis 1999).

Although safety standards have not been lowered, there is cause for concern that the changes in the institutional framework of pharmaceutical product authorization in the EC and its consequences in the German system will have a negative impact on pharmaceutical safety (ISDB 2005, Kiewel 2003). This is because of the special nature of the decisions to be taken. The safety of a new pharmaceutical is evaluated on the basis of previous clinical trials conducted by the applicant. Since the tests involve a limited number of

subjects, there are limits to the certainty of statements about the risks that using that product entails. Scientists in the licensing agencies weigh up the benefits and risks on the basis of information submitted. In many cases they have some scope for discretion. How they exercise this discretion is connected not least with the regulators' institutional framework and the way they see their role. If there is mounting (economic) pressure on the licensing authority and its employees to process authorization applications quickly and successfully, decision-makers may become more willing to take risks (Lexchin 1994). Many political decision-makers share this concern. The German government's proposals for further-reaching changes in pharmaceutical product authorization (Bundesregierung 2005; BMGS 2005), which include funding the licensing agency entirely from applicants' fees, have come to nothing for the time being due to resistance from both the parliamentary opposition and the parties of government. However, this does not mark the end of re-engineering of the regulatory system for pharmaceutical safety. Against the background of the European developments outlined, competition-oriented restructuring of the German marketing authorization system is still on the political agenda (Zöller/Straubinger 2007).

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Tables

Table 1: List of European and German Legal Instruments Analysed

Year	Legal Instrument	Object of Regulation	Regulatory level
1961	Medicines Act 1961	Definitions, prohibitions, registration. etc.	National (law)
1964	Medicines Act (Second Amendment Act)	More stringent testing requirements, prescription drugs	National (law)
1965	Directive 65/65/EEC	Authorization on the basis of the criteria of efficacy, quality, safety	European
1971	Medicines Testing Directive	Pharmaco-toxicological tests and clinical trials	National (ordinance)
1975	Directive 75/318/EEC	Analytical and pharmaco-toxicological tests and clinical trials	European
1975	Directive 75/319/EEC	Extension of Directive 65/65/EEC; CPMP, multi-state procedure	European
1976	Medicines Act 1976	Authorization procedure	National (law)
1983	Directive 83/570/EEC	Reform of multi-state procedure	European
1986	Medicines Act	Second Amendment Act to the Medicines Act	National (law)
1987	Directive 87/22/EEC	Concertation process	European
1988	Operational ordinance	First amending ordinance to the operational ordinance for pharmaceutical entrepreneurs	National (ordinance)
1989	Directive 89/341/EEC	Amends Directives 65/65, 75/318, 75/319	European
1989	Directive 89/342/EEC	Immunological medicines	European
1989	Directive 89/343/EEC	Radioactive medicines	European
1989	Directive 89/381/EEC	Medicines made from human blood or plasma	European
1989	Directive 89/552/EEC	Ban on TV advertising of prescription medicines	European
1991	Directive 91/356/EEC	Good manufacturing practice	European
1991	Directive 91/507/EEC	Approximation of legal and administrative regulations for testing pharmaceuticals	European
1992	Directive 92/26/EEC	Regulations concerning prescription medicines	European
1992	Directive 92/27/EEC	Labelling and package leaflet	European
1992	Directive 92/28/EEC	Ban on advertising medicines available only on prescription to the general public	European
1992	Directive 92/73/EEC	Registration procedure for homoeopathic medicines	European
1993	Regulation 2309/93/EEC	EMEA and centralized authorization procedure	European
1993	Directive 93/39/EEC	Mutual recognition process; European conciliation procedure; European pharmaco-vigilance system	European
1994	Medicines Act (Fifth Amendment Act)	Implementation of European Directives of the years 1989 to 1991	National (law)
2001	Directive 2001/83/EC	Common code for pharmaceuticals for human use	European
2004	Regulation 726/2004/EC	EMEA and centralized authorization procedure	European
2004	Directive 2004/27/EC	Mutual recognition process and decentralized procedure	European
2005	First draft of the law to establish DAMA	Transformation of the BfArM into a German Drugs Agency	National (draft law)
2007	Second draft of the law to establish DAMA	Transformation of the BfArM into a German Drugs Agency	National (draft law)

Table 2: Pharmaceutical Testing Requirements for Manufacturers 1961–1976

Drug Registration and Administration Act, 1961	"… pharmacological and medical testing of the proprietary pharmaceutical" (§ 21 Para. 1 Item 4)
Drug Registration and Administration Act, 1964	"… pharmacological and clinical and in special cases other medical testing" § 21 Para. 1a)
Directive 65/65/EEC	"… physico-chemical, biological or microbiological tests; pharmacological and toxicological tests; clinical trials" (Article 4 Number 8)
European Commission Proposal, 1970	Detailed guidelines for analytical, pharmacological and toxicological tests and clinical trials
Drug Testing Directive, 1971 (FRG)	Detailed guidelines for pharmaco-toxicological tests and clinical trials
Directive 75/318/EEC	Detailed guidelines for analytical and pharmaco-toxicological tests and clinical trials
Drug Registration and Administration Act, 1976	Necessity of analytical and pharmaco-toxicological tests and clinical or other medical trials (§ 22 Para. 2) Issuing of detailed guidance for testing pharmaceuticals by the relevant federal ministry (§ 26 Para. 1)

Table 3: Regulation of Placement of Pharmaceuticals on the Market

	Drug Registration and Administration Act 1961 (FRG)	Directive 65/65/EEC	Drug Registration and Administration Act 1976 (FRG)
Mechanism for placing on the market	Registration	Authorization	Authorization
Criteria for placing on the market	- Material composition according to German Pharmacopoeia (DAB) (§ 5 Para. 1) - No damage to health beyond a "justifiable extent" (§ 6)	- Harmlessness, therapeutic efficacy, quality of composition (Art. 5)	Quality, efficacy, safety (§ 1)
Withholding of authorization to place on the market	- No registration if documentation required under § 21 is incomplete - Authorization to place on the market will be withheld if the pharmaceuticals "when used as directed cause harmful effects that exceed a degree that is justifiable in accordance with the findings of medical science", or if they "when used as directed because of their nature" are harmful to health (§ 6) - When placed on the market by regional authorities, if medicines fail to comply with the regulations on dealings in pharmaceuticals and administering them could "put the general public at risk" (§ 42).	- Approval will be withheld if the pharmaceutical is harmful, not therapeutically efficacious or incorrectly composed (Article 5) - Approval will be withheld if documentation submitted does not comply with guidelines (Art. 5)	- Approval will be withheld if documentation is incomplete - Documentation will be withheld if the pharmaceutical was inadequately tested - Approval will be withheld if the pharmaceutical possesses no appropriate quality - Approval will be withheld if not therapeutically efficacious of if insufficient evidence of efficacy - Approval will be withheld if there is good cause to suspect that a pharmaceutical "when used as directed causes harmful effects that exceed a degree that is justifiable in accordance with the findings of medical science" (§ 25 Para. 2)
Suspension, Withdrawal, Revocation of Placement on the Market	- Register entry will be deleted if the proprietor of the registration number applies for this to be done (§ 25 Para. 2 Number 1) - Register entry will be deleted if the proprietor fails to comply with a condition imposed by the authority in respect of complete and accurate information on the receptacle and outer wrapping of the proprietary pharmaceutical (§ 25 Para. 2 Number 2)	- Approval will be withheld, suspended or revoked if the pharmaceutical is harmful, lacking in therapeutic efficacy or incorrectly composed - Approval will be withheld or revoked if the information in the documentation is incorrect - Approval will be suspended or revoked if the required monitoring of the pharmaceuticals is not carried out (Article 11)	- Approval will be withdrawn if it subsequently becomes known that there was a reason to refuse approval when approval was issued, or if such reason arose subsequently (§ 30 Para. 1) - Approval will be withdrawn if it turns out that the pharmaceutical is not therapeutically efficacious, (§ 30 Para. 1) - Approval will be withdrawn if information provided is incorrect - Approval will be withdrawn if conditions imposed are not complied with - Approval will be withdrawn if quality tests are not carried out (§ 30 Para. 2)

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