Regulatory Europeanization, National Autonomy and Regulatory Effectiveness: Marketing Authorization for Pharmaceuticals

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Abstract

The EC harmonized market entry regulation for pharmaceuticals from the early sixties on, but it achieved neither its goal of uniform national regulatory decisions nor that of automatic mutual recognition. Subsequent attempts to Europeanize the procedures themselves resulted in two alternatives in 1995: a Centralized Procedure for innovative pharmaceutical products implemented at the EU level, and a Decentralized Procedure which tries to assure mutual recognition. First, the paper analyzes the distinctive modes of Europeanization employed in these regulatory alternatives, examining both their impact on the effectiveness of European governing and the balance they strike between European interventionism, national participation and national autonomy. Second, it tries to assess whether Europeanization furthers the goals of pharmaceutical market entry policy as defined in European regulations – public health protection, creation of a single market and the reduction of regulatory costs to industry. There is little evidence that the public's health is less well protected when regulation is Europeanized. Only the Centralized Procedure contributes significantly to the goal of establishing a single market. Regulatory costs in terms of approval time did go down especially for pharmaceutical firms using the Centralized Procedure, mainly because of efficiency-enhancing legal provisions and institutionally induced regulatory competition between national authorities.

Zusammenfassung

Seit Anfang der sechziger Jahre hat die EG das Zulassungsrecht für Arzneimittel harmonisiert, ohne damit das Ziel uniformer nationaler Zulassungsentscheidungen bzw. die gegenseitige Anerkennung derselben zu erreichen. In einer zweiten Stufe kam es zu Versuchen, die Verfahren selbst zu europäisieren, was 1995 in die Einführung von zwei europäischen Zulassungsverfahren mündete – eines zentralisierten mit europäischer Implementationsstruktur für innovative Medikamente und eines dezentralen, das die gegenseitige Anerkennung nationaler Entscheidungen prozedural durchsetzen soll. In diesem Papier werden zunächst die in diesen Verfahren verwirklichten Formvarianten regulativer Europäisierung und das je charakteristische Verhältnis zwischen europäischer Intervention, nationaler Partizipation und nationaler Autonomie analysiert sowie nach der Effektivität europäischen Regierens gefragt. In einem weiteren Schritt wird abzuschätzen versucht, wie sich diese Europäisierungsstrategien auf die in der europäischen Regulierung verankerten Ziele des öffentlichen Gesundheitsschutzes, der Binnenmarktetablierung und der Industrieförderung auswirken. Es spricht wenig dafür, dass die Europäisierung des Zulassungsverfahrens den Gesundheitsschutz systematisch vernachlässigt. Zur Verwirklichung des Binnenmarkts bei Arzneimitteln trägt bislang eindeutig nur das zentralisierte Verfahren bei. Schließlich: Insbesondere durch rechtliche Vorgaben und einen institutionell induzierten regulativen Wettbewerb zwischen nationalen Behörden wurden die regulativen Kosten – gemessen in Zulassungszeiten – speziell für die Unternehmen reduziert, die das zentralisierte Verfahren nutzen können.

Contents

1 Introduction

This paper[1] is about product regulation in an intensely regulated policy field in which the regulatory landscape in the European Community (EC) has reached a high degree of institutional variation and sophistication. It is about marketing authorizations for pharmaceutical products for human use, and will focus on two major blocks of questions. The first one has to do with the tension between regulatory supranationalization – be it central or hierarchical – and national autonomy (Scharpf 1994), the second one with the efficacy and efficiency of regulatory Europeanization. Both questions are connected to the wider topic of governing in the EC (Scharpf 1999) – here by means of regulatory policies – with the aim of correcting market behavior while simultaneously enabling the creation of a larger market and also furthering the policy goals of industrial innovation and competitiveness. The paper focuses mainly on implementation. Policy-making in the European multi-level system has received most of the attention in the last decades. But when inquiring into the governing capacity of the EC, the complicated relationships between European and national institutions, and the impact of regulatory decision-making, it is no less important to analyze what happens after regulatory law has been passed. Or, as Martin Shapiro puts it: "the crucial problem for the Union is now … implementing the regulatory statutes it has enacted" (Shapiro 2001: 95).

The policy problem of market entry regulation for pharmaceuticals has been on the agenda of the EC, the Member States and other industrialized countries since the early sixties, after the thalidomide catastrophe had surfaced with thousands of fetal deformities and children born with phocomelia. The United States reacted first, amending already existing, comparably strict market entry regulation. During these years intensive international regulatory discussions took place among many national governments, parliaments and regulatory authorities as to the appropriate policy solutions. A specific motive behind the EC's early involvement in these exchanges on regulatory design was to remove already existing regulatory trade barriers and to avoid new ones. After thirty years of trials and relative successes in harmonizing national legislation – the first legislative guideline

1 I would like to thank S. Schmidt and P. Bouwen for their reviews of preceding versions and very helpful suggestions, F. Scharpf for early discussions about the perspective of this paper, P. Urfalino and B. Hauray for their comments on French regulatory behavior, and G. Abels for useful questions and remarks especially concerning the biotech sector. I would especially like to thank many interviewees in public institutions at different levels, in industrial and professional associations and in operational organizations of the health care sector for helping me to understand the issues discussed in the paper. F. Pfeffer was also extremely helpful in preparing the graphs and tables.

coming out as early as 1965 – and of failures in attempting to achieve mutual recognition through legal harmonization and soft policies of communication requirements and procedural coordination (1975, 1983, 1987), the EC finally introduced two ostensibly European procedures for marketing authorization in 1995, backed by new regulatory implementation structures. These two European procedures – a purely national alternative having been retained – obey different institutional logics, reflecting in their design and allowing in their application the intrusion of specific national and industrial preferences and interests. It is the still rather brief experience with these new procedures which provides the empirical basis of this paper.

Empirical information stems from a variety of sources. Primary information includes official documents such as legal provisions, administrative guidelines and the written positions of crucial actors, oral information provided by participating actors in different agencies and administrations, stakeholders and interested parties, and also process-produced data such as statistics on the procedures and their outcomes. Secondary information contains statistical data provided by third parties, quantitative and qualitative survey data as well as secondary literature. It should be noted that in this regulatory area the European tradition is one of extreme secrecy and, furthermore, shows a lack of consistent data collection. This means that often even seemingly hard data have to be interpreted with great care. In the literature certain data are often cited – such as national counts of authorized or marketed pharmaceuticals – which lack comparability due to differing, changing or obscured definitions. Where it seems advisable the reader will find notes of caution.

In the spectrum of EU research[2] this paper's general interest is on the capacity of the EU to cope with perceived policy problems, to institutionalize a viable regulatory implementation structure and to reconcile potential tensions between European centralization and the autonomy of national authorities. From a policy-process perspective we are dealing with the output of policy-making, the throughput system of implementation, and the outcome-related effectiveness of implementation.[3] Analytically the institutionalized regulatory procedures are the primary focus, because it is the institutional context which prescribes the way decisions have to be taken and provides options as well as restrictions for involved actors to bring both their cognitive and their normative orientations to bear.[4] Furthermore, the different institutional procedures develop their own logic, making the functionality of the decision-making procedures and any possible outcomes more or less probable. Although market entry regulation for pharma-

2 For overviews see Wolf (1999), Giering (1997) and Jachtenfuchs / Kohler-Koch (1996).
3 See Scharpf (2001a, 1970, 1999).
4 See Mayntz / Scharpf (1995: 43).

ceuticals is only a rather limited field and probably not even approximately representative of EU policy-making and implementation in general, it is nevertheless an interesting case for different reasons:

– its regulatory history has traversed practically all approaches to European integration;

– its current regulatory state offers two radically different European regimes, together with a purely national option, for basically the same regulatory task;

– it is one of the rare governmental intervention fields in which a genuine European implementation structure has been institutionalized for the most Europeanized procedural alternative.

J. Weiler's remark on the EU's "stunningly small bureaucracy … and … laughably small budget" (Weiler 2000: 235) reminds us of its resource scarcity, which is one of the reasons why the EU has been confined mainly to regulatory instead of distributive policies (Majone 1996a) – except in agricultural and, to a lesser degree, structural policies – and has to rely on Member State administrations for implementation in a "two-tiered system" leaving the Commission with the problem of "regulating the regulators" (McGowan / Wallace 1996). The European Commission generally does not possess the necessary administrative infrastructure (Scharpf 1994: 91) and Member States have been reluctant to furnish the Commission with it. Pharmaceuticals regulation for market entry is one of the rare policy sectors where, finally and selectively, the EU has not only introduced a positive regulatory policy regime but also a genuine European implementation structure for parts of the market. Such a regulatory policy-making output was unexpected, because the Treaty of the European Communities (TEC) explicitly preserves national intervention autonomy in public health matters (Art. 30 – formerly 36 – TEC). Almost ironically, it is this explicit preservation of national intervention rights in the health sector which required rather strong steps being taken towards Europeanization if other goals were to be achieved, namely the establishment of a Single Market and the provision of a competitive and innovative regulatory environment for industrial development. Because of this initial national autonomy in health matters and the complexity of assessing the medical risks and benefits of pharmaceuticals, the so-called "new approach" to harmonization could not be applied to medicinal products (Kommission der Europäischen Gemeinschaften 1985). Based on the European Court of Justice's Cassis de Dijon decision, this "new approach" of 1985 regarded a minimal degree of legal harmonization as sufficient to oblige Member States to mutually recognize one another's regulatory controls whenever these could be regarded as equivalent measures of protection. Initially, the European Commission had tried to apply this strategy to the marketing authorization for pharmaceuticals, too, but very

quickly it became clear that in this regulatory sector "the old approach" of "total sectoral harmonization" (Dinan 1999: 356–358) was advised if mutual recognition should have a chance at all in face of the mutual distrust of national authorities in each other's implementation. Eventually, it was the failure to translate even this extensive legal harmonization into the practice of mutual recognition which finally brought about what Abraham and Lewis call a "strong European regulatory state" (Abraham / Lewis 2000: 113) in this domain: the introduction of a centralized European procedure for at least parts of the market in order to facilitate the uniform application of European legislation. Such a policy output becomes possible or advisable – even in the institutionally difficult setting of multi-level policy-making – whenever there is consensus about the general policy goals. In this case, this meant the guarantee of specific market-correcting product standards, the creation of a larger, more easily accessible transnational market (Scharpf 1999: 106–107, 110), and the improvement of the international standing of the EC-based pharmaceutical industry.[5]

The regulation of market entry in the pharmaceuticals sector with its peculiar procedural differentiation is the result of decades of negotiated policy-making. The policy output in the form of three different institutionalized procedures incorporates problem or product-specific exigencies and takes into account actor-related orientations, interests and resources. At the same time the procedures provide the gates and channels through which actors may pursue their specific interests in the implementation process. Thus, it depends in large measure on the characteristics of these distinguishable institutional structures and procedures whether they are likely to contribute to the Europeanization of regulatory decision-making or are protective of national regulatory autonomy, whether they tend to support the development of market uniformity or market diversity, and whether or not they make a difference as regulatory environments for firms with respect to regulatory efficiency.

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5 Majone makes the point that in certain situations centralization of regulatory decision-making can be a viable means to counter distrustful national implementing authorities by forcing them into an integrated, uniform procedure: "Until regulators can trust each other to avoid … selfish strategies, centralisation of regulatory authority is the only practical way of correcting transboundary externalities, or preventing the local regulation of a local market failure from becoming a trade barrier" (Majone 1998: 32). In the case of pharmaceuticals one may, indeed, argue that centralized implementation does succeed in integrating otherwise non-cooperative national authorities into a collective decision making process as long as there are no veto positions or exit opportunities (Majone 1996b: 279–280). But one should also note that even centralized transnational regulation requires a minimum of mutual understanding and trustworthy cooperation as can be seen in pharmaceuticals regulation.

2 Context and Goals of European Market Entry Regulation for Pharmaceuticals

2.1 The Context

The EEC was still in its infancy when the thalidomide catastrophe hit several countries in which the medicine had been marketed in Europe and around the world.[6] By 1961 at the latest, it had become evident that taking this drug, which was supposedly "one of the safest sedatives ever discovered," (Silverman / Lee 1974: 94) could lead to fetal deformation in pregnant women. The country most affected was Germany but, except for France and the USA,[7] there have been victims in almost all highly developed societies. The thalidomide affair, though not the only one during these decades, was classified as "the single most important event to influence our attitudes to the unwanted effects of medicines" (McEwen 1999: 269). These revelations had immediate impact on policy discussions. For practically all European countries it had become evident that effective pharmaceuticals regulation, able to protect the public from health hazards, was by and large lacking. And, where a potentially adequate legal framework existed, as in France, implementation deficits prevented it from being much more than an instrument to protect the home market. These events and the public discussions they initiated shed light on the following characteristics of the policy problem and its context:

– Due to scientific progress in pharmaceuticals research, the industrialization of production and increasing internationalization of trade, different countries were facing increasingly great and widespread risks at the same time.

– Voluntary intra-industry schemes of medicines control had failed, while public pre-marketing controls were mostly absent, ineffectively designed or insufficiently implemented.

– While the internationalization of information through worldwide media coverage was able to arouse suspicion and even panic for fear of dramatic negative events, the lack in international regulatory communication and cooperation became even more evident.

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6 Descriptions of the events, their pharmacological background and the reaction of different actors in this policy domain are provided by Kirk (1999) for Germany and by Silverman / Lee (1974) and Abraham (1995) mainly for the Anglo-Saxon world.

7 For quite different reasons the medicine had not been approved in both countries, which were among the few that enjoyed a formal public approval procedure for pharmaceuticals at that time. Nevertheless, some babies were affected in the USA because their mothers had taken thalidomide during pregnancy while travelling abroad, through access to Canadian pharmacies or through doctors' samples widely distributed by the American company Merrell, which marketed the medicine in Canada and was preparing market entrance in the USA (Silverman / Lee 1974: 96).

At the same time, policies to cope with the perceived problems were available:

– Technologically the same scientific and technical knowledge and tools which facilitated an increasingly systematized development of medicinal products could also be used for regulatory controls of their quality, toxicity and efficacy.

– Successful national policy models existed which could inspire policy-making.[8]

Problem pressure was high enough – and viable solutions obviously available – to prevent the handling of the situation by way of non-decisions or purely symbolic politics.[9] Risk-averse politicians had every incentive to create regulatory regimes and systems which would not only increase the safety for patients but also make it possible for governments to avoid blame if accidents should occur despite regulatory precautions.[10]

It was in this context that the EEC – or more precisely the Commission – started discussions about developing a harmonization strategy for pharmaceuticals regulation in the early 1960s, as an attempt to standardize regulatory assessments and evaluations in order to assure that equivalent national regulatory procedures and decisions were in place. The thalidomide scandal actually marked a regulatory starting point for both the EC and the Member States. Therefore, one might have expected a more unified approach from the very beginning. However, the lack of rigorous regulatory legislation or implementation in the single Member States did not signify the absence of nationally diverging conditions – be they economic, political, legal, administrative or medical – when it came to the design of a regulatory framework which would control the behavior of the pharmaceutical industry, prescribe regulatory action to be taken by implementing administrations and influence the availability of pharmaceuticals for medical therapies. In fact, the Commission was well aware from the outset that differences in administrative practice could always jeopardize the desired effects of legal harmonization.[11]

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8 In the thirties the US had institutionalized quality- and safety-oriented marketing authorization procedures entrusted to the Food and Drug Administration (FDA). These controls were tightened and extended to efficacy standards by the Kefauver-Harris Amendments of 1962 as a reaction to the thalidomide scandal (Silverman / Lee 1974: 96). In Scandinavia, some rather strict licensing regulations had long been in force – in Norway, for example, since 1928 and in Sweden since 1934 (Abraham / Lewis 2000: 55; Dukes 1985).

9 It took some years, though, until effective control systems were installed in the different countries. For differences in policy-making speed, see Mayntz / Feick (1982) and Feick (2000).

10 For a systematic discussion on strategies to avoid or to shift blame, see Hood (2002).

11 The European Commission expressed its skepticism about a purely legal harmonization strategy only one year after the Council had adopted the General Programme on

2.2 The Goals

The general goals of European pharmaceuticals regulation are straightforward. In the words of the Pharmaceuticals Unit of the Enterprise Directorate-General, all regulatory measures are supposed to ensure a high level of public health protection, to establish a single market and to provide a stable and predictable environment for pharmaceutical innovation (DG Enterprise 2000b: 4). These goals are mirrored in the different Council Directives and Regulations as well as in Commission Communications, starting with the first harmonization directive of 1965 "on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products." This states: "… the primary purpose … must be to safeguard public health," adding that this objective has to be achieved without hindering "the development of the pharmaceutical industry or trade in medicinal products within the Community." The abolition of national regulatory disparities through the "… approximation of the relevant provisions" was meant to lead to "the establishment and functioning of the common market" (European Council 1965: preamble).

While patients' safety, public health protection, and industrial policy goals have been common concerns of European and national policy-making alike, the specific European goal is linked to the creation of a Common Market (Art. 2 of the Treaty establishing the European Community of 1957, as amended). Guaranteeing free trade among Member States and thus enabling the efficiencies of a larger market (Cecchini et al. 1988: 5, 27), as well as contributing to the rationalization of regulatory practice and the reduction of regulatory costs to industry (Deboyser 1995: 33) through substantive harmonization, procedural coordination and even centralization were meant to maintain or strengthen the EU region as a competitive research, development and production site especially vis-à-vis an increasingly dominant US-American industry and rising Japanese industrial competition.[12] The partly conflicting policy goals may be summed up as follows:

– *Patient protection and public health* contain two interrelated, in practice potentially conflicting, goals. One goal is protective, namely to avoid or limit the risk of distributing qualitatively inferior drugs, those with unacceptably severe side effects and those with non-existing or unacceptably low therapeutic efficacy. The complementary health goal is promotive and linked to the therapeu-

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legal harmonization with the goal of automatic mutual recognition (May 28, 1969). Acknowledging that the Programme was a historical turning point with respect to technical trade barriers, it made clear that their complete abolition might necessitate EC implementation measures (Kommission und Gemeinschaften 1970: 127).

12 See a recent speech by the EU Commissioner for Enterprise and the Information Society, Eric Liikanen (Liikanen 2002).

tic efficacy objective, namely to allow market entry for promising medicinal treatments as fast as possible.

– The *creation of an internal market* is targeted at two groups. From the point of view of the pharmaceuticals industry this means potential access to all Member State markets for a medicine authorized within the EC, and from the point of view of potential patients it means access to all pharmaceuticals available within the EC.

– The *industrial policy aim* of supporting an innovative and competitive European pharmaceuticals industry is twofold. Market entry regulation is intended to promote the development of a larger-scale internal market and, thus, economies of scale. And the rationalization of regulatory procedures aims at reducing direct and indirect regulatory costs to industry and thereby providing incentives for research, development and production in Europe.

3 The Regulatory Development and the Changes in 1993

European market authorization for pharmaceuticals has traversed practically all market integration strategies employed in the EC and, today, there co-exists a regulatory policy-mix of different procedural solutions for the same basic task within a harmonized legal framework. Up to the late 1980s, all attempts to provide for uniform marketing authorizations in the EC had, by and large, failed – be it through an increasingly extensive and detailed harmonization of national legislations in the hope that mutual recognition of national regulatory decisions would come about, or through the subsequent introduction of cooperative or concerted measures. National regulatory decision-making behavior differed too much, revealing "that differences of opinion [in assessing and evaluating medicinal products] do exist" (DG Employment 1989: 5–6) and demonstrating the limits of legal harmonization (Glaeske et al. 1988: 13–20). Those who would have preferred to cut the Gordian knot by a radical approach, namely the centralization of marketing authorization at the European level,[13] were convinced that the idea was not realistic under the prevailing political conditions (Merkel 1988, in: Glaeske et al.: 80). However, five years later the European Council opted for just such a step, even though this was limited to the category of especially innovative medicinal products.

13 This policy idea had been brought up often since the first harmonization discussions in the early sixties but it had always been abandoned as politically unacceptable – to most of the Member States – and administratively unfeasible due to the lack of administrative capacity with the Commission.

3.1 The New Procedures of 1995/1998

In 1993, after two years of discussions, the European Council adopted three pieces of legislation which introduced two new European authorization procedures for the marketing of medicinal products for human use[14]: the Centralized (CP) and the Mutual Recognition Procedures (MRP). These legislative reforms were further developments of already existing "European" procedures which introduced some radical structural changes. The new CP replaced the Concertation Procedure, which had come into effect in 1987 (Council Directive 87/22/EEC) and required European-level pre-assessments and pre-evaluations for specific categories of pharmaceuticals – the same categories still applicable in the CP – before the single national authories made their nationally valid regulatory decisions. But the national regulators were not obliged to follow the European recommendations. The MRP[15] replaced the Multi-state Procedure introduced in 1975 and revised in 1983, which involved a regime of sequential or parallel reviews of national applications by national regulatory authorities and called for some inter-agency communication and cooperation but led to little convergence concerning the final national marketing authorization decisions. Thus, both preceding "European" procedures somehow accompanied national regulatory decision-making but did not replace it.[16] The result of the reform legislation of 1995 is the remarkable range of three alternative regulatory routes for pharmaceuticals' marketing authorization in the EC:

1. the different *national procedures* (NP) for marketing in one country only (exception: medicinal products for which alternative 3 is obligatory);

2. a *Decentralized* or *Mutual Recognition Procedure* (MRP) whenever a pharmaceutical product is to be marketed in more than one Member State (exception: medicines for which alternative 3 is obligatory);

3. an integrated *Centralized Procedure* (CP) for specific categories of pharmaceuticals – obligatory for category A pharmaceuticals (derived from biotechnologi-

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14 The three texts are Council Regulation (EEC) No. 2309 / 93 of July 22, 1993, Council Directive 93 / 39 / EEC and Council Directive 93 / 41 EEC, adopted on June 14, 1993 and in force since January 1, 1995 and 1998 respectively.

15 This introduction of the MRP included a transition phase from January 1, 1995, to December 31, 1997, during which multiple national procedures co-existed alongside the MRP.

16 However, it seems fair to say that both preceding procedures contributed quite a lot in terms of mutual inter-agency understanding and the Europeanization of a professional and regulatory dialog. Without these advances in discourse capability over several decades, Europeanized regulatory procedures could not have been expected to work at all.

cal research and production), optional for category B pharmaceuticals (innovative medicines – mainly new active substances – outside category A). [17]

While surprising at first sight, this variety of regulatory options for the same task does take into account the multitude of orientations and interests which have had to be accommodated:

A variety of interests within the *pharmaceutical industry* are accounted for by the different procedural options. Internationally oriented and research-intensive pharmaceutical companies are prepared to face fairly strict control measures on the basis of contemporary scientific evidence. They are best served by a uniform centralized procedure that opens up the large Common Market in one regulatory step, thus reducing regulatory costs and speeding up market access. Companies producing more traditional medicines, targeting smaller, sometimes only national, markets and, to a certain extent, less prepared to fulfill strictly implemented harmonized regulatory requirements are better served by the NP or MRP, where the peculiarities of national regulatory environments – including traditional therapeutic traditions and specialties – have a greater chance of being respected.

A similar distinction of interests can be made with respect to *health care professionals* and *patient groups*, depending largely on their therapeutic convictions. The available regulatory procedures allow for a variety of therapeutic options, including what might be called traditional or alternative medicinal therapies, which are often only of regional interest. The risks of these kinds of products failing a centralized assessment and evaluation procedure are higher, since such a procedure is biased towards stricter scientific evidence.

The regulatory orientations and preferences of *national authorities* vary also with respect to pharmaceutical, medical or regulatory traditions. There is nevertheless a common institutional interest in organizational influence and survival in the face of potentially menacing institutional centralization. The NP and the MRP allow a high degree of national autonomy to be maintained in regulatory decision-making. And even the uniform CP is designed in a way that integrates the national authorities as indispensable providers of assessments and evaluations. Autonomy, on the one hand, and participatory inclusion, on the other, preserve the existence and regulatory autonomy or influence of national authorities.

Less well served within this institutional structure are the “interests” of those specialized patient or consumer protection groups or individual professionals

17 For the definition of the two categories, see ANNEX to Council Regulation (EEC) No. 2309 / 93 of July 22, 1993.

who regard themselves as watchdogs of a regulatory power structure which, in their view, is biased towards the preferences of industry (Abbasi / Herxheimer 1998; Abraham / Sheppard / Reed 1999; Abraham / Lewis 2000). Their demand for greater transparency in assessment and evaluation procedures, including the documents underlying them (test results etc.), has been, by and large, ignored. Transparency, so their criticism, has generally been sacrificed in Europe on the altar of industrial and administrative secrecy.

3.2 The Main Characteristics of the Two European Procedures

The Centralized Procedure

Where the Centralized Procedure (Figure 1) applies,[18] regulatory decisions have to be taken at the European level and are valid in all Member States. There is no way for either applicants or national authorities to circumvent this decision-making process if an EC-wide application is obligatory or optionally sought. Within a certain, relatively calculable time span, a final decision has to be produced and directly presented to the individual applicant. The latter may withdraw during the procedure, but then the only remaining option is to re-apply later on in the framework of the CP. Member States have no exit option and must participate actively if they want to influence the collective decision. Singular veto positions do not exist.[19]

Formally the regulatory procedure is divided into a scientific assessment and evaluation (EMEA / CPMP and external experts) and an administrative / political decision process (European Commission and comitology procedure) very much along the analytical lines drawn by S. Breyer's distinction between scientific regulatory "assessment" and administrative regulatory "management" (Breyer 1993). The function of the first part is to provide a decision recommendation based on scientific evidence and professional logic. This is supposed to establish

18 The Centralized Procedure is obligatory for Part A pharmaceuticals (medicinal products developed by means of specific biotechnical processes such as recombinant DNA technology) and optional for Part B pharmaceuticals (medicinal products that are innovative in some other significant way such as the type of therapy, delivery systems or manufacturing, or the novelty of the active substance). See Annex to Council Regulation (EEC) 2309 / 93, 22 July 1993.

19 Once a centrally approved medicinal product is on the market, a Member State may recall it individually as a measure of pharmacovigilance based on Art. 30 (former Art. 36) TEC. But such a national measure to protect public health is valid only temporarily. It must be reviewed by the European institutions (EMEA / CPMP, Commission) and finally decided upon within this institutional framework.

the basis for the regulatory decision to be taken in Brussels since the Commission is legally prohibited from delegating regulatory decision-making power.

A first decision draft – based on the opinion delivered by EMEA – is prepared by the Pharmaceuticals Unit of the Directorate-General (DG) Enterprise and circulated within the Commission among the other relevant DGs. The Commission's draft is then communicated to the Member States represented on the Standing Committee. The acceptance of this draft depends on the approval of the Standing Committee, which decides by qualified majority vote. If this Committee does not approve, the Council becomes involved – which has never happened to date – and can either not respond (the Commission's proposal would then be implemented) or adopt or modify the proposal by qualified majority, or refuse it by simple majority (a practice which is likely to change to qualified majority as a result of the ongoing review).

In between these procedural steps, specific scientific / technical questions might again be addressed to the scientific committee (CPMP) at the newly established European Agency for the Evaluation of Medicinal Products via the Commission, which would eventually change its decision draft on the basis of new or additional recommendations. Only in very rare cases – two were mentioned in interviews – has the Standing Committee asked for further clarifying discussions in the CPMP at EMEA. In these cases, the final results upheld the CPMP's former position.[20]

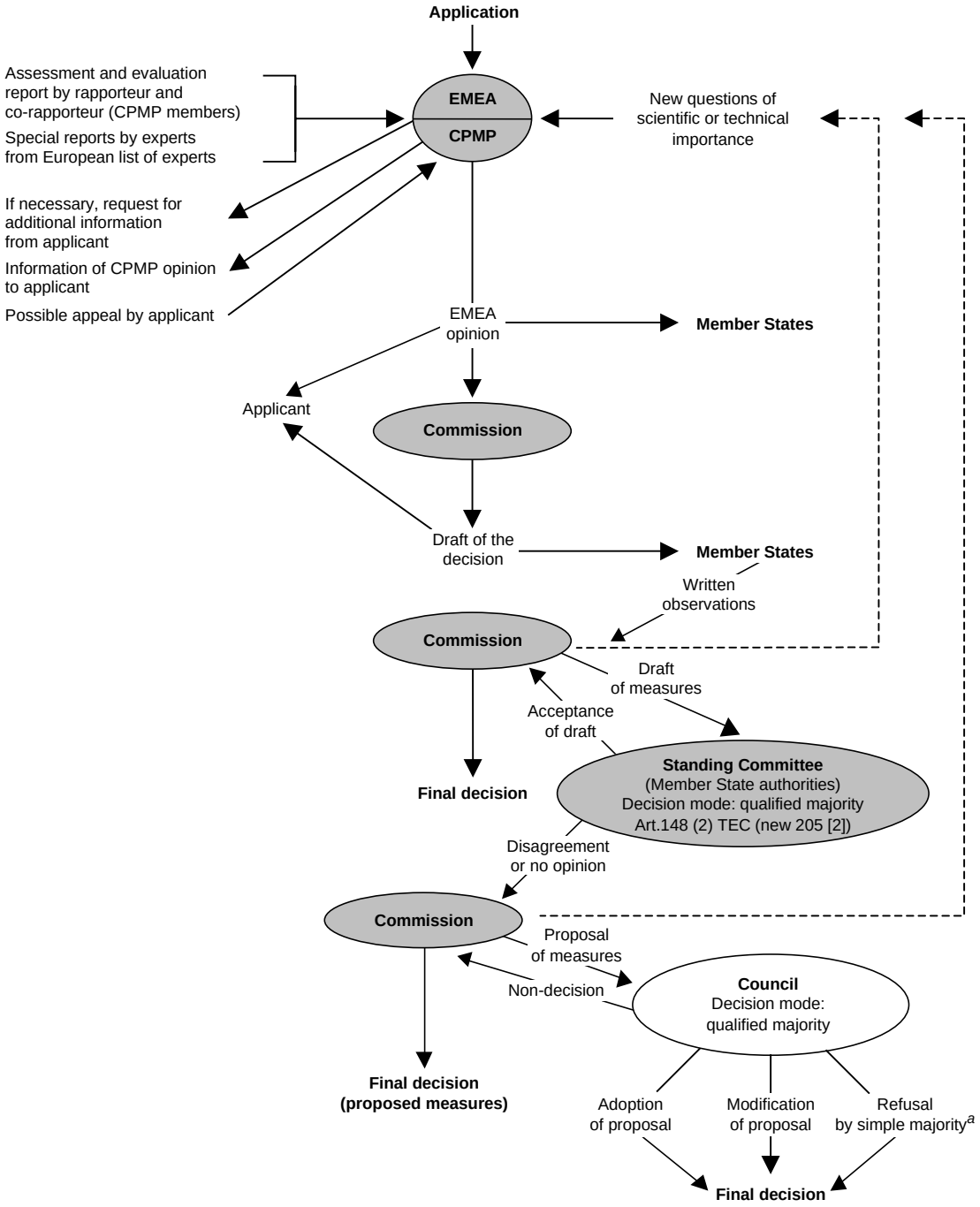
EMEA is of central importance in this framework since it is responsible for coordinating the scientific assessment and evaluation process and delivering an opinion to the Commission and the Member States. EMEA's Committee for Proprietary Medicinal Products performs the scientific assessments and professional evaluations, and is formally independent in its deliberations from both European and national administrations. Although the authorization decision is taken in Brussels, it is actually the CPMP's evaluation which pre-determines the final outcome. Thus, informally, centralization is even stronger in this regulatory procedure than seems to be the case from looking at the legal framework.

The Centralized Procedure can be regarded as a joint decision-making process[21] orchestrated by the European Commission, but containing especially strong centralizing elements which tend to dominate the whole procedure (see below). The restriction of the CP to the most innovative medicines facilitates consensus-build-

20 It is interesting that these two questions arose after the CPMP had arrived at its opinion by majority vote, not by consensus, which is normally sought and attained.

21 For a classification of decision-making modes in European integration, see Scharpf (2001b).

Figure 1 Centralized Procedure: Supranational and Intergovernmental



MEA European Agency for the Evaluation of Medicinal Products
PMP Committee for Proprietary Medicinal Products

Refusal by qualified majority is proposed for the legislative review of 2001/2002.

egal basis: Council regulation (ECC) No 2309/93; Commission Regulation (EC) No. 1662/95.

ing in the CPMP, a consensus which is difficult to challenge since it is founded on the expertise and collective deliberations of national regulators. The sophisticated structure of this Europeanized procedure provides ample opportunities for national experts and national authorities' representatives to bring their specific assessment and evaluation views to bear at different points. But in the end it is European decisions that have to be taken – scientific assessments by consensus or absolute majority (CPMP) and regulatory decisions by qualified majority (Standing Committee, Council).

Some of the institutions and committees that have been created function more like supranational bodies (CPMP / EMEA, Commission), others more like intergovernmental ones (Standing Committee, Council).[22] The way they deal with the issues resembles in one regulatory context more deliberative problem-solving (CPMP), in others it is closer to a negotiating attitude (Standing Committee, Council). Empirically, it is rather difficult to distinguish deliberative from negotiative interactions (Joerges 2000). Participants will readily agree that even in such a scientifically oriented body as the CPMP negotiations can be necessary when it comes to the precise wording of regulatory recommendations such as the Summaries of Product Characteristics. They are well aware that their collective recommendation has to pass the qualified majority gate of administrative regulatory decision-making in Brussels.

The Centralized Procedure has been restricted to the most innovative pharmaceutical products for several reasons.[23] Administratively this new Centralized Procedure was a considerable challenge to the Commission. Nobody wanted the procedure to fail due to work overload, which would strangle the new agency (EMEA). It was also a challenge to the consensus-building capacity of the collective bodies involved. Nobody wanted the deliberations and negotiations to be driven into highly controversial pharmacological, medical and administrative issues. With the technologically and medically most innovative medicines, the chances of reaching scientific and professional consensus have been higher[24] and the risks that national regulatory traditions would obstruct intended Europeanization have been lower.

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22 In practice, it is difficult to make empirically meaningful distinctions between supranationally or intergovernmentally oriented institutional interactions (Schmidt 1996).

23 The legal amendments under way in the legislative review will probably open the CP for a wider spectrum of pharmaceuticals, e.g. for all new active substances.

24 In fact, the CPMP, which may decide by absolute majority vote, normally reaches opinions by consensus: Of the 123 positive opinions in the years 1995 to 1999 (during which time there were only 7 negative opinions), 107 were consensual (Sauer 2000: 4).

The Mutual Recognition Procedure – Really European?

In contrast to the Centralized Procedure, the Mutual Recognition Procedure (Figure 2) is the "weaker" form of regulatory Europeanization although some supranational elements distinguish it from its predecessor, the so-called Multi-state Procedure introduced in 1975 and amended in 1983. The national level still dominates regulatory decision-making even though this procedure formally allows for a supranational, European stage, which is rarely attained in practice. The Commission and industry alike had hoped that the newly designed procedure would assure mutual recognition, i.e. the adoption of the Reference Member State's (RMS) initial evaluation and regulatory decision by the Concerned Member State(s) (CMS) where the applicant had additionally applied for marketing authorization. Mutual recognition or uniformity of national regulatory decisions with respect to the same medicinal product was to be facilitated by a two-stage process.

At the first stage the dissenting CMS(s) will communicate the issues hindering mutual recognition, followed by a so-called "breakout" session.[25] In such a meeting, in which the RMS and the CMS(s) are supposed to participate[26] and which is headed by the RMS's authority, the disputed parts of the assessment and evaluation are meant to be resolved. In practice, however, this is a rather complicated undertaking since the RMS's regulatory authority has already made its decision.

It is difficult for a dissenting CMS to retract its opinion and adopt the RMS's position once it has refused automatic mutual recognition because of "serious concerns"[27] to public health in their countries. The other possibility of finding a compromise position would require a change in the RMS's initial authorization. This is no less complicated since a legally valid national authorization already exists furnishing the authorization holder with a right to market in the RMS. The latter's cooperation would be necessary in this case. Additionally, this approach would also require changes in the position of all those CMSs which are prepared to mutually recognize the RMS's initial decision.[28]

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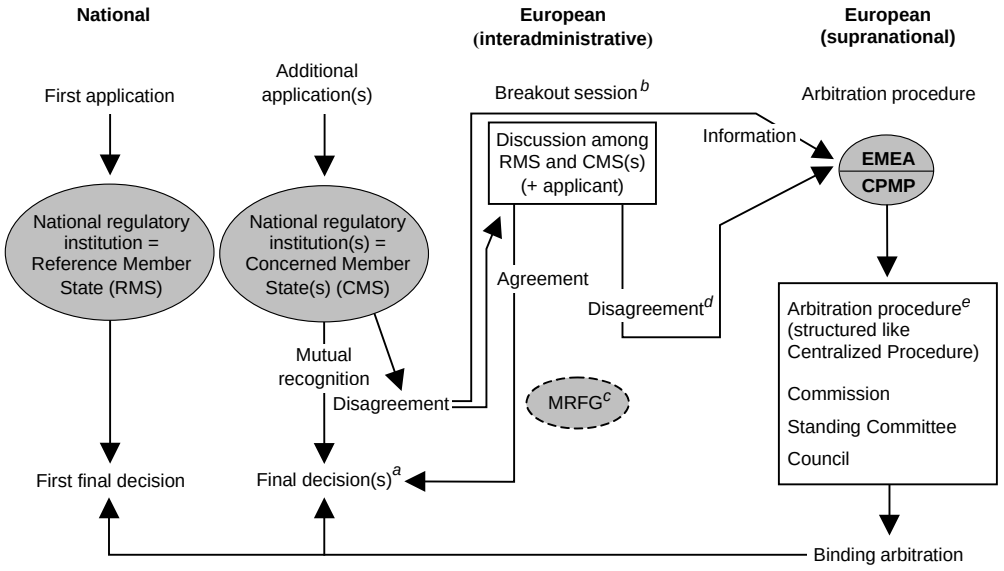
25 These take place monthly on the premises of the EMEA, parallel to the meetings of the CPMP and the so-called Mutual Recognition Facilitation Group (see below).

26 Participation often does not turn out as expected. Consenting CMS authorities which support the RMS's position are generally absent, and even dissenting CMSs do not always attend, partly due to lacking resources, especially on the part of the smaller authorities.

27 These are the only grounds on which mutual recognition may be refused.

28 The ongoing legislative review is heading for a change in the following direction: Whenever applications are made in the RMS and the CMS(s) at the same time, the RMS's regulatory authority will not make its final decision until it has discussed its assessment and evaluation with the CMS(s)'s authorities.

Figure 2 Mutual Recognition Procedure: National, Interadministrative and Supranational



Pharmaceutical products for human use; EMEA: European Agency for the Evaluation of Medicinal Products; CPMP: Committee for Proprietary Medicinal Products; MRFG: Mutual Recognition Facilitation Group.

a All final decisions in MRP are national decisions.
b Breakout sessions are organized by the RMS to discuss and resolve conflicting positions (scientific assessment and evaluation) with CMS(s).
c The MRFG is an informal group of representatives of the national authorities set up to discuss general issues of the procedure and to provide overall monitoring (attendance by Commission); meetings are also held with industry associations.
d An applicant may withdraw his application from selective countries to avoid binding arbitration.
e Arbitration procedures are conducted on the basis of referrals by Member State(s), Commission or applicant.

Legal basis: Council Directive 75/319/EEC as amended.

If this interadministrative phase does not lead to an agreement between the RMS and the dissenting CMS(s), the second stage of the MRP comes into play, a supranational arbitration procedure involving the EMEA / CPMP. This opens the door to a regulatory decision-making process, which then functions in the same way as the Centralized Procedure except that the final regulatory decisions would still be national ones, at least formally. However, these national "decisions" would have to apply the results of the centralized arbitration. From a Europeanization perspective, the problem with the MRP is that it rarely arrives at this supranational second stage. Since the decisions are nationally based and since the applicant has the legal option to withdraw his application selectively from single Member States without jeopardizing the authorization in the Reference Member State and the mutually recognizing Concerned Member States, he will generally withdraw from the dissenting CMS(s). Withdrawal from one or several – maybe even minor – potential markets is generally more advantageous than losing marketing time on more profitable markets until the arbitration procedure has been concluded.

Furthermore, the applicant would also run the risk of an unfavorable arbitration result at the European level, which would then be binding for all national authorities to which he has applied.[29]

The MRP contains two different types of attempts to arrive at regulatory Europeanization. At the *first stage*, independent national authorities discuss their assessments and evaluations in order to try to find a common position. Ideally, this can be understood as a problem-solving attempt to find the best answer to the assessment and evaluation problem without obliging the national authorities to accept or apply any proposal.[30] These discussions nevertheless take place in the framework of maximally harmonized regulatory legislation and on the basis of legal communication and interaction requirements. The *second stage* in this regulatory procedure is meant to lead to binding arbitration at the supranational level, which in practice means a harmonization of national regulatory decisions. The conflicting issues following national assessments and evaluations would be resolved through formulating a single European position which has to be adopted by the national authorities. The Commission, a Member State or the applicant can all request binding arbitration. As mentioned above, applications rarely reach this second stage due to the withdrawal behavior of applicant firms. This behavior of firms actually facilitates the national authorities' dominance in this procedure. Given its quantitative importance at the European level (see Table 5), it provides many options for national authorities and applying firms to deprive it of its Europeanization potential, whose realization depends on the combined voluntarism (Streeck 1995) of the national authorities and the applying firms.

4 European Governing and National Autonomy

The following part of this paper deals with questions of European governing in market entry regulation for pharmaceuticals and the balance struck between European regulatory uniformity and national autonomy by and in the different

29 The so-called Mutual Recognition Facilitation Group (MRFG), informally established by the heads of the national regulatory authorities and made up of representatives from the national regulatory authorities, meets quasi-officially every month alongside the CPMP at the EMEA; a Commission representative also attends the meetings. The MRFG tries to smooth out procedural difficulties and discusses more general problems of mutual recognition. It does not deal with individual procedures.

30 Here, of course, the interactions of committees and authorities are similar to those in the CP: the reasons for disagreement may not only be of a scientific or technical nature but also administrative or political in a wider sense, and the interactions can contain deliberations as well as negotiations.

regulatory regimes. First, the different procedures will be discussed on the basis of process-produced data and observations by participating actors. Together with the institutional insights gained above, this discussion will lead us, in the second part, to an interpretation of the available procedural regimes in terms of the opportunities open to actors and the constraints imposed on them in pursuing strategies which foster or hinder the effective Europeanization of governance functions, on the one hand, and preserve or limit national regulatory autonomy, on the other.

4.1 Implementation: How the Procedures Are Utilized and Perceived

The Centralized Procedure

Since its inauguration in 1995 there has been an overall increase in the utilization of the Centralized Procedure in terms of annual applications (see Table 1). Applications for category A pharmaceuticals are quantitatively, but – due to their innovativeness – not qualitatively, less important than those for category B pharmaceuticals. The application figures for category B are indicative of the general acceptance of this procedure since the firms applying could have chosen the Mutual Recognition Procedure instead.

Some data in this table point at significant differences between the two product categories. Applications for A pharmaceuticals (obligatory) display a more steady development; larger fluctuations can be observed for the B category (optional). These fluctuations are not surprising,[31] since companies might have experimented with the CP in choosing purposefully between the two European procedures and reacting to their specific procedural experiences. They might also have been trying out the CP for products whose "dossier" has not been adequate for this potentially more demanding procedure (see the high number of withdrawals). Application fluctuations can, of course, also depend on fluctuations in the development pipeline of pharmaceutical companies.[32]

Part A pharmaceuticals are much less prone to be withdrawn by an applicant and much less frequently receive a negative opinion by the CPMP than Part B medicinal products. Here, too, it seems plausible that the specific characteristics of category B medicines (not as innovative) and of the applying firms (on average not as well adapted to the exigencies of the CP) might account for the greater degree of withdrawals and negative assessments.[33]

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31 Unfortunately there are no separate data available for Part B pharmaceuticals as to the utilization of the different regulatory options open to applicants (CR, MRP or national).

32 Interview D–2002 –1a.

33 Regulatory authorities see the main reason for withdrawals in premature applica-

Table 1 European Centralized Procedure: Part A and B Pharmaceuticals (new applications only)

		1995	1996	1997	1998	1999	2000	2001	1995–2001
Applications received	Part A	15	14	19	14	18	17	23	120
	Part B	19	23	43	30	29	38	33	215
Withdrawals of applications	Part A	0	0	3	8	1	0	3	15
	Part B	1	5	2	11	7	11	8	45
Withdrawals in % of applications	Part A								12.50%
	Part B								20.93%
Negative opinions by CPMP	Part A	0	0	0	1	0	0	0	1
	Part B	0	0	0	2	4	0	1	7
Marketing authorizations	Part A	2	10	13	3	12	16	15	71
	Part B	0	15	12	33	18	17	28	123

Pharmaceutical products for human use only. Applications in one year might not have been withdrawn or processed in the same year. Negative opinions are only counted for procedures finalized at EMEA, i.e. the numbers of withdrawals are hiding expected negative opinions.

Sources: EMEA annual reports; EMEA press releases and monthly reports; personal communication with EMEA.

The Mutual Recognition Procedure

Data for the Mutual Recognition Procedure (see Table 2) are more difficult to obtain since the procedure itself lacks an official coordinating center. Most data are assembled by the informal, though quasi-official, Mutual Recognition Facilitation Group. Quantitatively, the MRP is the more important of the two European marketing authorization procedures and its number also shows gradual yearly increases. Yet, at the same time, the data signify to what extent the procedure does not work as intended. What has been criticized with respect to the preceding multi-state procedure is still valid today: “la reconnaissance mutuelle automatique est une utopie dans ce secteur” (Deboyser 1991: 127).

The relatively high number of “breakout sessions” (cf. Figure 2), organized in order to resolve deviations in scientific assessment and professional evaluation between the Reference Member State and one or several Concerned Member States, and the high number of withdrawals by applicants despite these attempts are regarded as a matter of concern. They indicate the degree to which national

tions (DG Enterprise 2000a: 114–115). It should be noted that negative opinions by the CPMP are counted as such only when the procedure has been finalized at EMEA. Since companies generally withdraw when expecting a negative opinion, this figure should be higher.

Table 2 The Decentralized Procedure: Mutual Recognition (new applications only)

	1995–1997	1998	1999	2000	2001	1995–2001
Procedures submitted (total)	361	183	275	373	484	1676
Arbitration referrals	3	1	2	3	1	10
Breakout sessions	84	64	48	52	36	284
Procedures finalized	240	182	228	306	443	1399
Procedures finalized with at least one CMS withdrawn[a]	46%	47%	28%	30.5%		
% of withdrawn national applications related to all CMSs[a]	12%	16.5%	8.2%	7.6%		

Pharmaceutical products for human use. Applications in one year might not have been processed or withdrawn in the same year.

a MRFG (2001).

Sources: EMEA annual reports; MRFG (2002); own calculations.

regulators raise "serious concerns" about public health regarding the RMS's preceding regulatory decision. The low number of arbitration referrals leading to binding assessments and evaluations at the European level is also revealing. Applying companies avoid binding arbitration procedures by choosing the exit option: withdrawal of the application from the CMS that remains unwilling to mutually recognize the RMS's regulatory decision even after breakout sessions. Some would argue that the figures on withdrawals have shown signs of improvement since 1999; still, this is not what one might call an effectively Europeanized regulatory procedure.

The MRFG has undertaken a detailed study of MRPs finalized between April 1 and September 30, 2000, in order to unveil the causes for the high number of withdrawals in this procedure (MRFG 2001). As Table 2 shows, an application was withdrawn in at least one Concerned Member State in more than 30% of all MRPs in the year 2000. The MRFG's analysis reveals the following, interesting details:

– *One country* alone, France, has been responsible for almost half of the withdrawals.

– *One group of pharmaceuticals*, generics, has been affected by almost half of the withdrawals.

– In more than half of the cases *the reason for withdrawal* has been differences of opinion between a Reference Member State and Concerned Member State(s) with respect to the SPC (Summary of Product Characteristics).[34]

34 SPCs are an integral part of a marketing authorization "which is granted only pro-

These three observations are interrelated. SPCs for generic pharmaceutical products often deviate from SPCs of the original or reference product, especially if the product was authorized years ago, and the French authority pursues the strict policy of not accepting differing SPC contents for medicines that are basically the same.[35]

The in-depth analysis also revealed that whenever a new chemical entity was subject to the MRP, similar assessments and evaluations by national authorities and, as a consequence, mutual recognition were much more likely. New chemical entities have been involved in withdrawals in only 10% of the cases. Here, again, it seems that the novelty of a medicine is an important factor for regulatory convergence.

General Perception of the Two Procedures

The Centralized Procedure is perceived as functioning more or less as expected and as being utilized more than was expected. Table 3 shows a very high level of general satisfaction with the CP, the regulators' positive reaction being even more pronounced than that of marketing authorization holders (pharmaceutical companies). As a rule of thumb, the companies' level of satisfaction "tended to be lower if they had experience of withdrawing a product" (DG Enterprise 2000a: 72).

For the MRP the picture is not as bright and not as uniform. While a large majority of regulatory administrations approve of this procedure, the responses of market-authorization holding companies tends to be split between those who are dissatisfied and a smaller, though still substantial, group of positive respondents. The national authorities' generally positive view of the MRP can be easily explained by the fact that it preserves the national authorities' autonomy. The split within industry is related to company-specific regulatory needs and experiences. Most companies would not like to be without the MRP because it adds to the freedom of choice between alternative regulatory regimes. It provides flexibility

vided the indications, conditions for use, composition of the medicinal product, etc. strictly comply with the corresponding description" (Brunet 1999: 160).

35 The reasons for this especially strict national position are not just related to evaluation issues concerning marketing authorization. Socio-economic regulations in the health insurance field that deal with prescriptions, i.e. aut-idem (substitution of similar medicines by pharmacists) and reimbursement rules seem to play an important role, too (personal communication by P. Urfalino and B. Hauray). The French regulation that allows pharmacists to substitute a generic for a prescribed brand of a medicinal product could become impracticable if the SPCs and package leaflets for basically the same products vary with respect to indications, contraindications, side effects, etc. There are efforts under way to have national SPCs harmonized by the CPMP, a task which would probably take many years to accomplish.

Table 3 Overall Satisfaction with the European Procedures (number and percentages of respondents)

	Centralized procedure			Decentralized procedure		
	Dissatisfied/ very dissatisfied	Satisfied	Very satisfied	Dissatisfied/ very dissatisfied	Satisfied	Very satisfied
Marketing authorization holders	3 (9%)	28 (88%)	1 (3%)	29 (56%)	22 (42%)	1 (2%)
Regulatory authorities in the EU	0	12 (75%)	4 (25%)	3 (20%)	12 (80%)	0

Pharmaceutical products for human use.

Source: DG Enterprise (2000a: 72–73, 122).

with respect to the choice of countries targeted for marketing and, also, the choice of the Reference Member State providing the lead assessment and evaluation. But there is dissatisfaction with the malfunctioning of mutual recognition and the inefficiencies of the procedure whenever an agreement cannot be obtained between the Reference Member State and dissenting Concerned Member States.

4.2 Europeanization, National Authorities, and Applicants

The regulation of marketing authorizations for pharmaceuticals in the EC with its mix of regulatory procedures may be taken as a sector-specific example of how a balance is being struck between the centralization of regulatory decision-making power at the European level and the preservation of national autonomy and / or influence. The difficulties of developing positive European policies to offset, on the one hand, decreasing Member State control capacities in an increasingly transnational market or to establish, on the other hand, such a transnational Single Market initially in certain sectors such as pharmaceuticals, have been widely described (see, for example, Scharpf 1992: 24–26). Consensus in the European Council – legislation in public health matters requires unanimity – is especially difficult to obtain if European interventions have or are expected to have important distributive effects, and / or if they necessitate changes in established national implementation structures and practices (Scharpf 1992: 26). If European regulation in this field is supposed to be effective, then its implementation has to overcome or influence national regulatory traditions, including implementation structures, and its outcomes risk having an impact on the competitive situation of national pharmaceutical industries and, more indirectly, on the national provi-

sion of medicinal health care as a whole. Scharpf's judgement that the regulation of product standards should be the easier task for European intervention and even be a candidate for the most invasive mode of European integration – that of hierarchical direction – certainly contains an element of truth. But his assumption that institutional as well as cultural national differences should be less of an obstacle (Scharpf 1995: 94) somehow gainsays the decades of European experience in pharmaceuticals control. In the end, policy mixes have had to be allowed for and complex implementation procedures have had to be set in place which are heedful of the political and institutional autonomy and / or influence of national polities while at the same time providing for more European uniformity in regulatory implementation or even introducing a completely Europeanized procedure (Scharpf 1994).[36]

The following analysis will concentrate on the two European procedures, leaving the purely national procedure aside, since this is the one in which national autonomy clearly dominates implementation within an otherwise extensively harmonized legal framework. Two analytical concepts will be applied: Scharpf's distinctions between different modes of European integration and Hirschman's notion of "exit" and "voice" in the sense of institutionalized behavioral alternatives in a collective setting.

Scharpf's Europeanization modes allow us to distinguish the regulatory procedures or elements thereof with respect to supranational European integration, on the one hand, and national autonomy on the other (Scharpf 2001b: 6–19). They can be ranked according to their invasive strength, starting with the weakest mode:

– *Mutual adjustment* presupposes completely independent national governments deciding on their own, while being aware of mutually interdependent effects.

– In the *open coordination* mode, governments would also be independent in their decisions but embedded in collective evaluatory discussions at the European level, without formal obligations but with a certain self-binding commitment.

– *Intergovernmental negotiations* are conducted by independent governments acting within well-defined institutional structures (participation, voting rules) in order to arrive at collectively binding decisions.

– *Joint decision-making* is a combination of two pure models – of intergovernmental negotiations and of hierarchical direction: Centralizing elements coexist alongside negotiation processes, and the success of the whole procedure de-

36 For further elaborations of different modes of integration in the context of European multi-level governing, see Scharpf (1996, 2001b, 2002).

pends on the functioning of the center's coordination capacities and on the readiness of participating national authorities to converge their preferences.

– In the *hierarchical/central direction* mode, decision-making competencies are centralized at the supranational level, and national governments are not in a position to prevent them from being exercised.

The other analytical categories applied are Hirschman's notion of "exit" and "voice." In this analysis "exit" relates to the autonomy of actors to leave a given situation of collective decision-making and to (re)gain an autonomous regulatory position. "Voice," on the other hand, is related to integrative Europeanization or, in Hirschman's perspective: "Integration can … be considered as an arrangement, not for suppressing voice through hierarchy, but rather institutionalizing and routinizing it" (Hirschman 1981 [1974]: 222–223).

In contrast to the analyses from which Scharpf has derived his analytical categorization, which are mainly policy-making processes, we focus here on policy output in terms of institutionalized regulatory procedures, and on the way in which both their institutional design and their utilization determine the functioning of the procedures as means of European governing. Having highlighted the crucial differences between the two European regulatory regimes of marketing authorization above, we can now concentrate on a more focused analytical discussion.

The Centralized Procedure – Hierarchy, Voice and Negotiations

At first sight the Centralized Procedure (Figure 1) might be regarded as an example of the *central direction* mode. The procedure is institutionalized at the central European level, obligatory for certain medicinal products and conducive to genuinely European regulatory decisions, which are directed at individual applicants and binding in all Member States. Neither national governments, nor their regulatory authorities, nor applicants can evade this regulatory frame. National autonomy seems to be non-existent. For a more precise analysis it is necessary to look at the different phases and the distinctive institutional elements.

In the *first phase* scientific-professional assessment and evaluation is conducted in a centralized institutional setting. This work is coordinated by an independent European agency (EMEA), executed by the formally independent, scientific committee of this agency, the CPMP, and addressed to the Commission via an opinion which contains a recommendation for the regulatory decision to be taken. As these recommendations in almost all cases predetermine the decisions taken within a comitology procedure in Brussels, this centralized institutional element of the first phase is much more important than the term "recommendation"

might indicate. This institutional asymmetry between European and national institutions is – at least partly – counterbalanced by participatory opportunities. The CPMP is composed of nationally based experts from all the national regulatory authorities. Furthermore, for every single application, two "rapporteurs" are chosen by the CPMP to prepare and deliver detailed assessment reports to be discussed in plenary sessions. Since the assessments of the rapporteurs are produced mainly in the respective national regulatory authorities, these national institutions still have an important, though not decisive part to play in this phase. Decisions in the CPMP are collectively taken – discussions leading to consensus or, in rare cases, to majority voting –, but this first phase provides for multiple opportunities to introduce and discuss national assessment and evaluation positions. Nevertheless, on the whole, European integration is at a maximum in this phase, whereas national autonomy is at a minimum, though compensated for by participatory means ("voice").

The *second phase* leads to the administrative regulatory decision and is coordinated by the European Commission at the center. The latter transforms the recommendations into regulatory decision drafts. To become valid administrative acts, at least one additional committee – the Standing Committee on Medicinal Products for Human Use – becomes involved, the logic of whose interactions inclines towards the negotiative rather than the deliberative pole. The involvement of this Committee, whose members are representatives of national authorities, provides the opportunity to (re)introduce clearly national points of view. A qualified majority, with votes weighed according to Art. 205 (2) TEC (new), is necessary for a positive decision to be taken; anything else would lead to the involvement of the Council – a situation which has not yet occurred. The Council would also decide by qualified majority if it adopts or alters the decision proposal; plain refusal would be possible by simple majority.[37] In any event, no single national authority or Member State is in a strong veto position. The Commission's decision proposal can only be modified or rejected by a rather large coalition.

Looking at the whole procedure, this second phase formally turns the mode of integration into that of *joint decision-making*, though without the opportunity for single Member States to block a decision. The further the decision process moves along the different phases and up the institutional ladder, the more it becomes

37 According to the new comitology procedure (Council Decision 1999468 / EC of 28 June 1999) the Council now can oppose Commission proposals only by qualified majority (whereas, before, a simple majority was required). Furthermore, the European Parliament will be informed of the Commission's proposal and may confront the Council with an opinion that the Commission has exceeded its implementing powers. The Council has to respond decisively to such an opinion expressed by the European Parliament.

"administrative" or "political," and the more the potential for intergovernmental or interadministrative negotiations increases. However, since the Commission's decision draft – generally identical with the regulatory agency's centrally determined opinion – will only be overturned under exceptional circumstances, the whole Centralized Procedure might be classified as an integration or Europeanization mode where, in practice, *hierarchical* – or, better still, *central – direction* dominates. But this central direction is complemented and, thus, cushioned by opportunities for nationally oriented experts to provide an input and for authorities to raise their voice, on the one hand. On the other, this central direction is taking place "in the shadow"of the "threat" that national authorities might fall back upon interadministrative or intergovernmental negotiations whenever administrative or political bodies like the Standing Committee or the Council – or, within the new comitology procedure, the Parliament – come to the conclusion that the Commission, in drafting its decision, has exceeded its implementation competencies (European Parliament) or arrived at positions which are unacceptable to a large enough group of countries (Standing Committee, Council).

The Mutual Recognition Procedure – Missed Europeanization Potential

The Mutual Recognition Procedure (see Figure 2) represents two opposite logics. One of them is based on the mutual recognition of national regulatory decisions which, themselves, should be an implementation of the extensively harmonized legislation. The other – and this is the main innovation in comparison with the preceding multi-state procedure – is the potential to include a genuinely Europeanized decision process whenever the mutual recognition mechanism does not work as intended. These two logics correspond with the procedural distinction of two phases.

The *first phase* comes close to an *open coordination* process in which different national regulatory authorities are supposed to cooperate in a way that produces a uniform implementation decision on the basis of the existing harmonized legislation. Concerned Member States are supposed to recognize, but have the exceptional right to oppose, the Reference Member State's initial regulatory decision if serious concerns about public health can be advanced by the opposing national authority (Council 1975: Art. 10, 1).[38] Such a challenge has to be discussed among the Member State authorities with the aim, but not the obligation, to come to an agreement. Although the procedure has been designed to arrive at identical decisions in all Member States targeted by the applicant, the legal obligation to coop-

38 This leads to the much-criticized practice that national authorities claim this exceptional reason even in the case of minor objections. Up to now, attempts to define exactly just what constitutes a "serious concern" have failed.

erate and the institutional support for cooperation are so weak that national authorities can easily choose between "exit" and "voice" or, more correctly, opt to "exit" if "voice" has gone unheeded. The MRP even contains a kind of self-defeating mechanism: although the national authorities of the CMSs are not supposed to carry out intensive assessments of the applications, this being the RMS's task, they are practically obliged to do so in order to identify reasons for serious concern. And this practice, in turn, increases the chances of identifying discrepancies between the RMS's and CMSs' positions.

The *second phase* is the sequence which should follow if the open coordination attempt fails. This would turn the MRP into a real European regulatory procedure. If implementation moves on to this second stage of centralized binding arbitration, then the same integration modes would prevail which characterize the Centralized Procedure – that of *hierarchical (central) direction* and *joint decision-making* (see above, 4.2.1). The marketing authorizations delivered to the applicants would still be national ones, but their content would be made uniform through binding arbitration by European institutions. Yet as we have seen above, the process only very rarely moves into the second phase even when mutual recognition is not attained in all CMSs.

Implementation practice shows that this potentially European procedure remains very much in the *open coordination mode*. The reason for this is the strategic behavior of those applying companies for whom it is generally economically advantageous to withdraw their application from dissenting national authorities in order to avoid time-consuming and potentially risky arbitration (DG Enterprise 2000a: 135, 144). Thus, in the case of the MRP, effective Europeanization depends on the voluntarism of national authorities to cooperate and adjust in regulatory implementation and of pharmaceutical companies to accept arbitration. The MRP's institutional set-up invites strategic use by the "non-integrative" actors. The flexibility built into this procedure and welcomed by national authorities and industry alike – albeit for different reasons – protects the dominance of national autonomy and adjustments to national preferences to the detriment of uniform Europe-wide implementation of European standards.

Procedural Variety: Constraints, Opportunities and Interests

Although, both the Centralized Procedure and the Mutual Recognition Procedure have been designed as Europeanized regulatory procedures, their general institutional logics work in opposite directions. Furthermore, even within the single procedures, phases can be distinguished which provide institutional options that again follow different modes of Europeanization. And finally it is the preferences of participating actors and the constraints and opportunities provided by the in-

stitutionalized procedures on which the realization of the different Europeanization modes depends.

The main general institutional difference between the two procedures is that the CP necessarily arrives at a European regulatory decision taken by European bodies whose decision output is directed at individual applicants, while in the MRP the national level's regulatory decisions are relevant for the individual applicants.

The CP contains two phase-dependent modes, one leaning towards central direction, the other towards joint decision-making. Owing to the informal weight of the centrally established scientific assessment and evaluation and the succeeding regulatory recommendation as well as the institutional hurdles to decisive national opposition in the second phase, the CP as a whole resembles hierarchical or central direction. It is the most invasive mode of European integration, leaving practically no space for nationally autonomous regulation. Effective European governing is assured in an almost state-like sense. The loss of national autonomy in this procedure is substituted by participatory channels which offer the option of "voice" in a highly integrated structure. And there is also a kind of "emergency route" in case enough Member States should agree to challenge the proposed regulatory decision – which would push the CP into a joint decision-making framework re-opening the procedure to interadministrative / intergovernmental negotiations.

In the MRP, the first phase mode of open coordination dominates the whole procedure due to the fact that it is in the interest of the applicants to avoid the binding arbitration that is called for in the second phase, which would oblige the national authorities to adopt a uniform European decision. Thus, in this procedure, national autonomy can be maintained because exit options are held open. "Europeanization" in the sense of the application of harmonized standards takes place only within the group of those national authorities which is prepared to agree on a common regulatory decision. The national authorities which choose to "exit" from the mutual recognition path are an indicator of the non-functioning of harmonization in this specific case and the relative ineffectiveness of European governing. But, as we have seen above, the national authorities that want to protect their national autonomy are dependent on the pharmaceutical applicant's choice to avoid binding arbitration.

An explanation for these differences has to go beyond institutional opportunity structures or the institutionally defined difficulties in overcoming institutional hurdles – such as majority requirements – and to account for the actors' preferences in not taking certain opportunities as well as for the factors which might account for specific behavioral preferences. One important differentiator seems to

be the type of pharmaceutical product at stake, which is related to the specific interest structures of applying companies, national governments and also more widely defined actors in health care systems.

The Centralized Procedure is reserved for the *most innovative pharmaceutical products*. They are the ones with little or no legacy concerning preceding regulatory assessments and decisions. Differences in national *cognitive perception*, if they occur, are therefore likely to be resolved through professional deliberations, and European assessments and evaluations, once established, are less likely to be challenged by an institutionally necessary quorum of national authorities. Because of these products' novelty, the chances are also lower that marketing authorization will be influenced by considerations relating to national health-care delivery regulations. If such considerations do come into play, discussions even in scientifically based committees risk developing into interest-related negotiations.

Turning to the *interests of actors* directly involved or indirectly concerned, the argument can also be made that they are generally very much in favor of an extensive Europeanization of marketing authorization with respect to this category of pharmaceuticals. *Applicant companies* overwhelmingly belong to the research-intensive, internationally oriented large companies. Their aim is to get their products as fast as possible onto the largest possible market via a single, cost-saving procedure. In general, they are the direct beneficiaries of the Centralized Procedure. *National governments* as well, at least those representing countries with a considerable pharmaceutical industry, regard companies which are researching and producing these innovative pharmaceuticals as a necessary industrial and technological basis for future growth. They have an industrial-policy interest in presenting the EC as an attractive site for research and industrial investment in competition mainly with the USA and Japan. National governments share this interest with the *European Commission*. And a well-functioning European CP is regarded as the competitive regulatory answer to a situation large companies encounter in the USA: a single procedure providing access to a large medicinal market. There is also a kind of background interest and potential pressure for a Europe-wide, efficient way to provide access to the most advanced medicines. Since medical knowledge is a public good and communicated quickly in the medical community, national boundaries are regarded as anachronistic when it comes to medicines required for the most advanced therapies. *Health care providers and their patients*, very often in coalition with the concerned industry, represent another more or less visible and more or less organized interest demanding access, which cannot be ignored by governments and national regulatory authorities.

Beside these more product and industry-oriented interests, another interest should be mentioned which concerns the functioning of this procedure as such. It

is mainly the European Commission, the regulatory authority, EMEA, and its scientific committee, the CPMP, but also most of the national authorities participating in this procedure that have a *high motivation as regulators* to prove that this European regulatory procedure can work. When mentioning this facilitating factor for successful Europeanization, one is also reminded again of the type of companies mainly involved in the CP. They are the ones not only with a high interest in this procedure but also with the resources and the capacity to adapt to and to be successful in a more demanding transnational regulatory environment.

The world of the Mutual Recognition Procedure is a different one. Unlike the more international pharmaceuticals of the CP which transcend national medical, pharmaceutical and regulatory traditions, the pharmaceuticals of the MRP are generally the less innovative products which are embedded in an existing national medical and regulatory tradition. On the *cognitive level* it is much more difficult to find cross-national consensus in assessments and evaluations, and the impact of national health care regulations can be felt as well. Therefore it is not surprising when one national regulatory agency challenges the assessment of the other. That this does not occur more often has to do with the fact that applying companies can select their target countries in this still nationally based procedure.

Turning to the underlying *interest structure* supporting this regulatory procedure, one can say that it is in the interest of important actor groups – largely the same as above – to preserve this procedural alternative also. These less innovative products are most often produced by *medium-sized and smaller pharmaceutical companies*, which are not very strong in research, whose resources are very limited – including those devoted to regulatory affairs – and who tend to be present only in a few national markets. For regulatory success, the proximity of and the acquaintance with their national regulatory authorities and environments are instrumental. A procedure like the CP is not only unnecessary and too costly for them, it can also be too demanding in the implementation of the requirements and too far removed from the specific "needs" of a national medicinal market. *National authorities* have a specific interest in this procedure since they are still the main regulatory actors involved, safeguarding their autonomy. From an industrial policy standpoint, *national governments* have an interest to protect this kind of industry, too, which might not be an especially innovative one,[39] but which employs a considerable workforce and which, additionally, provides categories of medicinal products demanded by a considerable proportion of national *medical health care providers and patients*, whose therapeutic needs rely on their availability.

39 There are, of course, many very innovative small and medium-sized companies, especially in the biotech field. Their interests are similar to those of the large, internationalized pharmaceutical companies whose cooperation or even guidance they generally need or employ in order to enhance regulatory and marketing opportunities.

Taking especially the interests of the applying companies and the national regulatory authorities into account, it is perfectly understandable that the MRP rarely arrives at the stage of binding European arbitration. A company faced with the deviating opinion of one national authority will hesitate to force this authority into arbitration because this might impinge on an otherwise favorable national regulatory climate between regulator and regulatee. And, as mentioned above, economic rationality will also prefer immediate dealing in some markets rather than waiting until an arbitration procedure has responded to the reservations of a deviating regulatory authority, which might even be the gatekeeper to only a small additional market.

Given the institutional opportunity structure, which does not necessarily lead to binding arbitration, and given the interest structure as described above, it is obvious that the MRP has little chance to succeed as a truly Europeanized procedure and that in case of doubt – as weak as this doubt might be substantially – the autonomy of national regulatory authorities will prevail.

5 Efficacy and Efficiency of European Regulation

This chapter is devoted to the substantive outcomes of the two European procedures. The question is whether or not they contribute to the official goals of European market entry regulation: public health protection, the establishment of an internal market, and the fostering of an innovative and competitive European pharmaceutical industry. In this preliminary evaluation we are interested mainly in the relative impact of the two marketing authorization procedures.

5.1 Improvement of Public Health Protection?

The question whether and how much the European procedures – especially the CP – might have contributed to the protection of public health is practically unanswerable with any degree of precision. Therefore, very limited observations, appraisals and an indirect assessment of the impact of institutional provisions and behavioral orientations must suffice.

There are essentially two perspectives from which this question can be approached. They relate directly to the marketing authorization criteria and the inherent trade-off: on the one hand, the protection given against unsafe medicines, on the other, the provision of access to efficacious medicinal products.

The safety perspective has always been in the forefront of discussions whenever regulations have been intensified in the aftermath of drug disasters. This perspective might be regarded as the politically more pertinent one since it corresponds with the preference of incumbent politicians or administration heads to avoid or to channel blame. The delegation of market entry regulation to functionally specialized administrations can be regarded not only as an attempt to assure "correct" or well-informed regulatory decisions (Gehring 2000) but also to delegate blame in the event of trouble (Hood 2002). This risk-averse attitude of politicians and of the responsible administrators may lead to the dominance of a "precautionary principle" (Majone 2002), which might produce adverse effects by its own logic. This points to the second perspective which maintains that specific regulations and their implementation might hinder the development and / or marketing of potentially beneficial pharmaceuticals either by being too cautious on the safety side or too demanding on the efficacy side.[40]

The observation that no pharmaceutical disasters comparable to the thalidomide affair have surfaced in the meantime has been taken by some observers as an indication that European regulation is at least as protective against safety risks as existing national ones have been.[41] But, in general, systematic information is missing which might help to evaluate the quality of regulatory decisions taken, by systematically observing the utilization and impact of a pharmaceutical product after obtaining marketing permission. Preliminary work at EMEA does not go beyond comparative benchmarking of the decisions in the European Centralized Procedure with those of the US-American FDA, mainly comparing substantive decision outputs and procedural efficiency (EMEA 2000: 21). This does not tell us anything about the quality of regulatory decisions. The Center for Medicines Research International has initiated joint efforts between industry and regulators to develop a concept and indicators for reviewing the quality of regulatory procedures and decisions with the aim of fostering so-called "Good Review Practice" (Hynes / McAulane / Walker 2001; Hynes 2000; Smith 2001a, 2001b.) These efforts seem to concentrate more on internal procedural improvements – such as the appropriateness of the applicant's technical document accompanying an application or the agency's review process – and the reduction of regulatory costs, and less on the improvement of regulatory decisions in a comprehensive public health perspective.

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40 A large amount of research initiated in the USA after the introduction of stricter authorization criteria in the Kefauver-Harris Amendments of the Food, Drug and Cosmetics Act in 1962 is representative of this perspective; overviews of this evaluatory literature are provided for example by Scherer (2000: 1308–1316), Andersson (1992) and Schifrin / Tayan (1977).

41 This would be the conclusion based on David Vogel's analysis (Vogel 1998).

Turning to qualitative evaluations by participating actors, views are split over whether the Europeanization of the procedures has contributed to a leveling-down or leveling-up of safety and efficacy standards. Generally speaking, representatives from industry and also European regulators tend to be convinced that the CPMP assessments are of the highest quality and that the CP is more demanding than the average national procedure (Vos / Hagemeister 2000: 23; Abraham / Lewis 1999: 1657, 1660; DG Enterprise 2000a: 106).[42] Such views mainly have requirements concerning the proof of efficacy in mind. With respect to safety criteria, the views of national regulators in particular seem to be split. Some believe that safety protection might have suffered, partly because of increased competition for clients in the European regulatory context, especially in the MRP (Abraham / Lewis 1999: 1661, 1662). It is feared that safety may be sacrificed for the sake of Europeanization if products are pushed through the Mutual Recognition Procedure with too much speed or pressure to compromise. There is similar skepticism regarding proposals by the pharmaceutical industry to reduce the review time for the application "dossier" from 210 to 150 days (Schweim 2001: 14). All these views are not representative, and they do not adopt a comprehensive view on the impact on public health.

A look at the institutional framework of the European procedures and the administrative orientations might provide some additional – though still inconclusive – hints. The multiple input requirements and mutual checks embodied in the European procedures, most pronounced in the Centralized Procedure, seem to provide filters against extreme deviations from the expected quality of assessments. Mutual checks seem to lead to a stricter application of standards (Abraham / Lewis 1999: 1657–58).[43]

On the other hand, there are criticisms which maintain that the European regulatory authority is oriented and the procedure organized in a way which is supposed to reduce the regulatory costs to industry. Abraham and Lewis argue that such a "neo-liberal" supply-side approach, reinforced through close relationships between regulators and regulatees, informal interactions and a generally high de-

42 In a discussion at EFPIA Info Day in 1998 an industry representative complained that CPMP requirements in the Centralised Procedure seem to have become more severe than they had been in the two years before (EFPIA / EMEA 1998: 40). This was readily acknowledged by the then head of CPMP, Prof. Alexandre, who stated that, with respect to the efficacy or therapeutic benefit criteria, CPMP was stricter than the US-American FDA (ibid. and Alexandre 1998: 11).

43 There is indirect evidence that the quality of assessments was an issue in the CP early on. The standard contract between EMEA and the "rapporteurs" for the scientific assessment of applications has been revised, containing a clause now which allows EMEA to hold back or cancel payments if the CPMP judges a report as not meeting expected quality standards (Griffin 1997: 8).

gree of secrecy in regulatory decision-making, would tend towards a softer, industry-friendly implementation of standards (Lewis / Abraham 2001; Abraham / Lewis 2000: 162–172). This seems to be congruent with the regulatory orientation expressed by the former head of the responsible DG unit of the Commission and subsequent founding director of EMEA, who claimed that "for reasons of public health concerns over safety, the pharmaceutical sector has traditionally been overregulated" (Sauer 1997: 3). This regulatory orientation has its administrative complement in attempts to create a "new public administration" which is supposed to act as a professional and flexible service provider and to abandon the traditional bureaucratic control perspective (Abraham / Lewis 2000; Feick 2000: 244–246).

The possible impact of these *institutional provisions* and *behavioral predispositions* can be interpreted differently. Supporters of a strict control perspective anticipate potential dangers to patients and public health. Those who endorse the facilitating regulatory perspective welcome client-orientation as a prerequisite for speedier regulatory review processes from which both industry and patients should benefit.

Again, these observations cannot contribute anything to a more comprehensive assessment of the public health impact, which would have to take a more long-term and closer view. However, specific patient groups maintain that their health problems are barely accounted for or even ignored in the existing regulatory market entry regimes. There are comparatively small groups of patients with diseases that are so rare that they cannot be an attractive market for developing, producing and marketing the necessary medicines (orphan drugs). There are patients suffering from life-threatening diseases for whom drugs might have been developed in the meantime which are still in the time-consuming testing phases required for marketing authorization. And there are the children below 16 who are particularly undersupplied, partly due to orphan-drug problems and partly due to the fact that it has been legally impossible or too risky, ethically problematic or too costly for industry to test most of the drugs on children before proceeding to marketing authorization (DG Enterprise 2002: 2). While these are certainly public health problems, they are not a unique problem of the European procedures, but rather one of national regimes as well, and their resolution at times goes beyond the regulatory scope of marketing authorization.

5.2 The Single Market Goal

The abolishment of existing technical trade barriers and the prevention of new ones within the EC has been the overarching objective of regulatory harmoniza-

tion, cooperative and coordinative measures concerning national marketing authorizations, and the limited Europeanization of regulatory decision-making. As a result of this development, a convergence of the spectrum of available medicines across EC countries might be expected, although market entry regulation is not the only factor determining the size and composition of medicine supply.[44] Below we will try to find empirical evidence for this expectation and to analyze the potential of the present regulatory situation to enhance such a development.

Converging Volume of Pharmaceutical Products?

Although comparable market data are difficult to obtain,[45] it seems fair to say that the number of authorized medicinal products on the national markets has been sharply reduced in high-volume countries like Germany, Great Britain and France since the introduction of the more stringently harmonized regulations of the 1960s and 1970s, especially since these new legal requirements have been applied to pharmaceutical specialties which were already on the market and had been registered under "softer" legal provisions. Given a wider definition of marketed medicines – say, all specialties (i.e. all trade names counted) – the estimated figures for Germany and Great Britain were as high as 15,000 in the late 1970s, for France around 7,800 (Dukes / Lunde 1979). In 2001 the comparable figures for Britain and France were around 6,700 and 2,100 respectively. For Germany, comparable figures are lacking but, counting active substances only, there was an approximate reduction from 2,550 in 1981 to 1,880 in 2001. As the average number of trade names per active substance should not be lower than for France (approx. 2:1) and probably closer to that of Britain (approx. 6:1), the 2001 figure of available specialties (trade names) for Germany might range somewhere between 4,000 and 11,000.[46] The opposite trend can be observed in traditional low-volume countries like Sweden. Here, the number increased from 750 in 1981 to 1,027 in 2001. In short, there has been a convergence of the number of medicines nationally available since the introduction of stricter control measures, their harmonization and Europeanization, but differences remain high – mainly due to national therapeutic and regulatory traditions (Dukes 1985).

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44 The attractiveness of a specific market depends on many factors, including the size and structure of the population, the prevalence of specific medical indications and prescribing traditions, and also regulatory conditions such as price, reimbursement or prescribing regulations.

45 Quite a lot of data on volumes has been published in the past, but few are comparable due to changing or unclear definitions and categorizations.

46 See G. Dukes (1985) and, also, the EURO-Medicines Database: www.euromedicines.org / index2.html (date of consultation: 23 November 2001); the figure for Germany should drop again considerably once the so-called validation process ("Nachzulassung") for medicines registered before 1978 is terminated.

A More Homogeneous European Pharmaceuticals Market?

The Europeanization of regulation could be expected to contribute to the homogenization of supply across Member States approaching an accessible Single Market for doctors and patients. Longitudinal data are not available, which leaves us with the challenge to project future developments from the status quo. Pair-wise country comparisons of nationally available medicines show that a single market does not yet exist, when measured in terms of equal access to medicines in all European countries. The mutual overlap of available stocks is generally far below 100% (see Table 4). This is hardly surprising, taking differences in national pharmaceutical and medical traditions as well as different regulatory environments beyond marketing authorization into account (McKee / Mossialos / Belcher 1996: 278).

Starting from this situation one can ask whether and how existing European marketing authorization regulations might induce change. Two tendencies are currently leading in opposite directions. The Centralized Procedure clearly contributes to the development of a more uniform supply because centrally authorized medicines have market access in all EU Member States. Yet, this homogenization effect is limited to the most innovative medicinal products for which the CP is obligatory or optional, and the number of CPs is rather small compared to that of the MRPs (see Table 5). The homogenizing impact of the Centralized Procedure would be reinforced if envisaged reform measures are adopted in 2003. They

Table 4 Diversity in the European Medicines Market: Mutual Availability of Active Ingredients (country 1 → country 2, in %)

Country 2 / Country 1	AUT	BEL	DNK	FRA[a]	GER	NED	SWE	GBR
AUT	–	59	49	43	81	57	48	54
BEL	72	–	55	52	79	66	52	60
DNK	81	73	–	60	84	76	73	71
FRA[a]	71	69	58	–	75	68	58	63
GER	68	54	43	42	–	50	42	49
NDL	80	76	65	56	84	–	61	69
SWE	79	71	74	59	83	72	–	70
GBR	68	62	55	60	73	62	53	–

Selected countries; active ingredients categorized according to ATC code (anatomical, therapeutic, chemical).

a EURO-Medicines Database, http://www.euromedicines.org/index2.html (date of consultation: 23 November 2001).

Source: Folino-Gallo et al. (2001).

Table 5 New Applications in the Centralized and Mutual Recognition Procedures (number of applications submitted)

	CP	MRP
1995	36	30
1996	35	141
1997	60	190
1998	45	183
1999	51	275
2000	54	373
2001	58	484
1995–2001	339	1,676

CP: Applications by medicinal product; pharmaceuticals categories A and B.
MRP: Applications are procedures irrespective of number of countries involved.
Sources: EMEA General Reports 1996–2001 (always most recent and revised data).

would open up this procedure to a wider spectrum of pharmaceuticals and would oblige pharmaceutical firms to market authorized products across Europe within a certain period.[47]

The probable future impact of the Mutual Recognition Procedure is not as clear-cut. It is a European procedure leading to similar marketing authorizations in at least more than one Member State, and the more countries are involved and the larger the markets covered by these countries, the more substantial the contribution of this procedure to market homogenization will be. On the other hand, the MRP might even increase cross-national market diversity to the extent that applications may be country-selective. As was discussed earlier, this is already happening. From 1998 to 2001, an average of between 8.69 and 6.53 Member States were involved in the MRPs.[48] Taking into account that in every procedure an application has been withdrawn from at least one Member State (see above, Table 2), then the number of Member States included in MRPs would on average be less than half of the 15 EU countries.

The third procedural alternative, the purely National Procedure, obviously contributes to cross-country diversity. In this respect, it is interesting to note that for

47 See Commission of the European Communities (2001); for a short summary of earlier almost identical Commission proposals, see Koenig / Engelmann / Wunsch (2001), and for evaluatory comments, see Koenig / Müller (2000). Today, companies may still decide not to market an authorized medicine.

48 Own computations on the basis of MRFG Reports; see http: / / heads.medagencies.org.

example in Germany national authorizations by far outweigh European ones.[49] The opposite seems to be true for Portugal and Spain, Member States with considerably smaller markets.[50]

Considering that only a small fraction of applications in the European Union are covered by the CP, that MRPs almost never include all Member States and that national applications in just one Member State also maintain diversity, it seems evident that the diversity between national markets should prevail at least for some time. This projection requires some qualifications and further interpretations. If in the future, due to the ongoing legislative revision, more innovative medicinal products will have to be processed obligatorily in the CP, and if the CP may be chosen for a much wider spectrum of medicines voluntarily – as proposed by the European Commission – then the CP will increasingly contribute to the creation of a homogenized European product market for a much wider array of medicinal products than it does today. But what might become even more important in this respect is a possible change in pharmaceuticals distribution. The key words here are mail-order business and e-commerce – distribution channels which are beginning to take hold for cost-containment reasons even in countries where they are presently prohibited. Thus Internet pharmacies and distribution by mail could become a means which would render other regulatory barriers obsolete.

5.3 Procedural Efficiency: Approval Times

One of the objectives of procedural Europeanization was to increase regulatory efficiency and thus reduce regulatory costs to industry. One important component of these costs is the time regulatory authorities need for the review and approval of applications. In the past, approval times had often been a matter of dispute in those countries in which companies lost months or even years of sales due to slow review processes. It was the aim of the Centralized Procedure in particular to cut approval times and thus contribute to achieving the EU's goals not only in health policy but in industrial policy as well.

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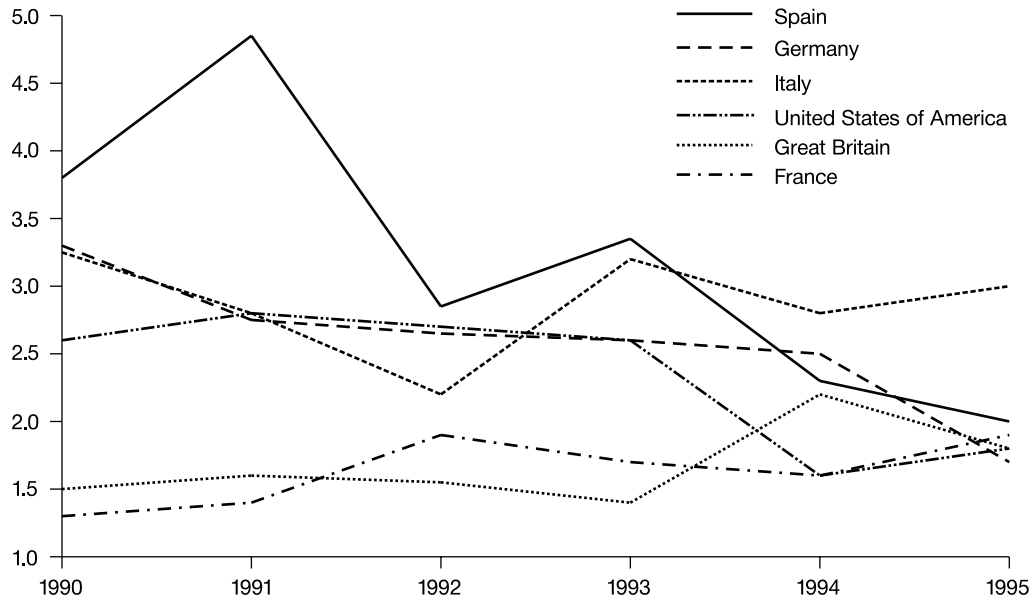
49 German figures for 2001 (data for other years or other agencies not yet being available) show that roughly 71% of all finalized authorizations in 2001 (the total including those stemming from MRPs or CPs and excluding parallel import permits and also the registration of homeopathic and anthroposophical medicines) have been purely national ones (own computations on the basis of BfArM and EMEA data).

50 Interview D–2002–1a.

Figure 3 Mean Regulatory Approval Times (in years)



Responses of 35 pharmaceutical enterprises concerning 377 active substances altogether.
Source: K. E. Thomas et al. (1998: 791).

Convergence Trends before 1995

In the years before the new European procedures became operational, approval times had already tended to converge. From the EU countries reviewed, only Italy deviates from this trend (see Figure 3, which includes data for the USA as a comparative reference). Although national approval times can vary considerably from compound to compound and from country to country for the same compound, the general tendency seems obvious. In 1995 there were still big differences between national authorities, but they were far smaller than those that existed at the beginning of the 1990s.

These findings can be interpreted as the effect of an emerging competition among regulatory agencies.[51] Germany had to catch up in terms of procedural efficiency

51 Analyses show that even the weak procedural attempts at Europeanization before 1995 (multi-state and concertation procedures) must have had some impact. Approval times were shorter when national authorities participated in such a "European" procedure compared to a purely national one. For France and Great Britain these differences were small – both countries already starting from a low time level in the national procedures – while, for Germany, they were considerable, the purely

and, to achieve this, had invested more resources in the Europeanized approaches than in the purely national procedures. The British agency traditionally had comparably short approval times and cultivated this tradition and image through public management reforms and marketing efforts. The situation of the French authority was, again, different. Having had extremely short approval times in the past,[52] the increase in average approval time in France between 1990 and 1995 can be interpreted as an attempt to gain regulatory credibility (Thomas 1996: 116). France prepared itself extremely carefully for the new European "era" when creating a new agency in 1993. It is also the only agency which has set up a small office in London.

The New European Procedures

Comparing the two new European procedures, median approval time for the Centralized Procedure has stabilized around 1.2 years (Figure 4), while corresponding figures for the Mutual Recognition Procedure are four to five months longer for the two years the MRP has been fully operational[53] (CMR international 2001: 1). Not surprisingly, approval times for the MRP, which is still a nationally based procedure, are closer to the figures for the National Procedures in 1995 (see Figure 4).

The differences in efficiency (approval time) between the two procedures – almost five months on average – cannot be fully explained by legal deadlines, which account for roughly one month. What seems to be more important are the modes of monitoring and control established by the different institutional frameworks, on the one hand, and both product and applicant-related factors, on the other. These are mainly the same factors discussed above in relation to the general functioning of the two procedures (see Section 4).

For the Centralized Procedure a rather well-organized and well-equipped coordinating and monitoring organization (EMEA) does exist, which is accountable to a supervisory board composed of members from national authorities and EU institutions and, what is more, whose executive and scientific heads have been

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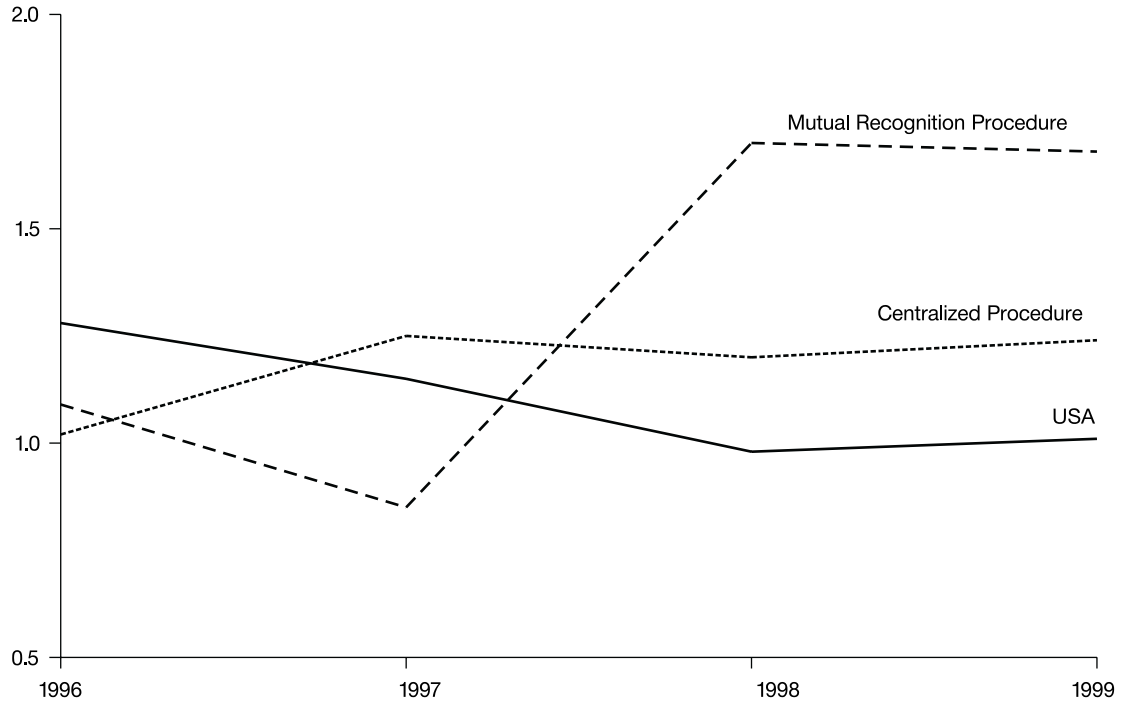
national procedures taking roughly 70% longer than those which required interagency communication and cooperation in the multi-state and concertation procedures (Thomas et al. 1998: 795).

52 Nevertheless, industry did criticize the French regulators: In their view, marketing authorization was speedily granted, but the regulation of prices and reimbursement was much too slow.

53 In this comparison, approval times in the MRP have been counted from the date of application until the end of the 90-day discussion phase between the RMS and the CMSs (Shapiro 2001), after which time the individual CMSs decide whether to grant mutual recognition or not.

Figure 4 Median Approval Times in European Procedures (in years)



Source: CMR international (2001: 1).

highly motivated by their own professional biography to make the new organization and especially the CP work. Such an institutional support does not exist for the Mutual Recognition Procedure. Organizational aid by EMEA has been minimal, and efforts to coordinate and monitor this procedure have to come voluntarily from the national authorities.

Depending on the procedure, *regulatory competition* is *organized differently* among national authorities. In the CP, national agencies are in competition with each other *within* the regulatory procedure by way of collective discussion and decision processes. National authorities' representatives chosen as rapporteurs or co-rapporteurs are under close observation by their peers, including face-to-face discussions. In the MRP, regulatory competition takes place mainly *before* the European procedure. National authorities compete for clients – or, more accurately, fees – to become Reference Member States. After this choice has been made by the applying companies, the Concerned Member States do not have a special incentive to assure procedural efficiency. In an environment of inter-agency regulatory competition they might even try to show that the national authority chosen has worked quickly but not well enough to assure mutual recognition.

Other factors such as the *type of pharmaceutical product* to be processed and the *type of applicant* (firm) seeking marketing authorization are important, too. The CP is reserved for the very advanced or comparatively innovative medicinal products, which tend to be the most important ones, both economically and therapeutically, and are generally linked to the most powerful pharmaceutical companies. Pressures from industry, governments and even concerned professional and patient groups can be expected to be high if the Centralized Procedure – the only one available for Part A pharmaceuticals – does not meet efficiency expectations. Furthermore, companies producing especially innovative medicines and oriented towards international markets are also fairly competent in regulatory affairs. Their applications provide fewer causes for subsequent questions. These favorable conditions for rather smooth and time-efficient regulatory reviews cannot be expected to the same degree in the MRP.

In the USA, median approval time has been substantially reduced since 1995 (Figure 4), putting additional pressure on the EC to streamline its procedures further. Thus, one of the aims of the present legislative review is to cut both the time EMEA needs to produce its opinion upon receiving the CPMP's recommendation, and the time the Commission needs to produce the regulatory decision draft once it has received EMEA's opinion.[54] Yet not only the review and decision-making time in the European institutions and committees are important for companies eager to get their product on the market. Also the so-called stopclock time which companies need to respond to questions regulators feel obliged to pose after an application has been submitted has to be added to the time budget. The average response time to questions of the CPMP in the CP increased from 119 days in 1996 to 179 in 2000. This is an important part of the overall approval time[55] – in 2000 roughly 38% (Humphreys 2001).

The legislative amendment proposals (Commission of the European Communities 2001) try to reduce time consumption at both ends. Shorter deadlines, an increased and more systematic involvement of outside experts, and the new comitology procedure are supposed to further streamline the internal regulatory process. On the other hand, pre-filing interactions between regulators and regulatees are to be encouraged and reinforced, allowing the latter to adapt more easily to regulatory review requirements early on in the pharmaceutical development process and obliging the former not only to provide more guidance for the regulatees but also to introduce some kind of self-binding mechanism for regulators in view

54 Much of this time consumption has been due to the old – by now reformed – comitology procedure and also to the extensive translation requirements.

55 It is difficult to explain this development. Maybe the CPMP became more demanding and the companies less careful, or maybe less experienced companies were using the Centralized Procedure, especially as an optional route for Part B pharmaceuticals.

of the envisaged application. This externally oriented measure has been inspired by FDA practice in the USA and is in line with the new concept of public administration as a client-oriented service organization.

6 Conclusions and Outlook

The Europeanization of regulatory decision-making in the sub-field of pharmaceutical marketing authorization seems to resemble – at least in hindsight – a quasi-logical path of integrationism leading towards a European "domestic regime" (Hooghe / Marks 2001: 39), (Marks 1997: 28). Governing takes place at the European level (Grande 2000: 11), but this "governing in Europe" (Scharpf 1999) is a multi-faceted enterprise. Three different regulatory regimes for the same substantive problem or intervention task are available within the EC. This "patchwork" of policy solutions (Héritier 1996) in a single regulatory subsector is further complicated by the fact that each European procedural regime contains different modes of Europeanization signifying distinctive degrees of invasiveness of European governing vis-à-vis national authorities. Despite "regulatory maximalism" (Scharpf 1996: 239) concerning the harmonization of product standards, only one of the three regulatory procedures represents "procedural maximalism": the Centralized Procedure provides for an integrated, genuinely European regulatory decision-making process which – despite considerable national participation and additional safeguards – represents the most invasive mode of Europeanization, namely hierarchical or central direction. At first sight, such a result seems meager after more than thirty years of policy development, considering that large parts of regulatory assessment and evaluation in this domain are shaped by scientifically and technically oriented deliberations, and also taking into account that the setting and implementing of common product standards are regarded as one of the easier and less conflictive integration exercises (Scharpf 1999: 107). The differentiation into three regulatory procedures obviously responds to the needs and interests not only of a pharmaceutical industry which is heterogeneous with respect to capacity, product range and market coverage but also of national regulatory authorities eager to maintain their regulatory positions and impact, and it responds to the heterogeneity of pharmacological and medical traditions.

We have analyzed the extent to which the different procedures establish effective European governing structures and how these structures affect the balance between European centralization and the autonomy of national authorities. So far, only the Centralized Procedure can be regarded as a regulatory regime which integrates national authorities into a collective procedure, leading to uniform and binding European decisions. This centralized integration, which eliminates exit

options for national authorities, is counterbalanced by ample opportunities for them to raise their voice – be it in the central collective assessment and evaluation phase or in the administrative phase of regulatory decision-making. While the first phase follows the mode of central direction, the second resembles a situation of joint decision-making. Even so, the centralization perspective prevails due to strict legislative stipulations, the functional weight of the central Agency's assessment and the determination of most of the participating actors to make this procedure – reserved for the most innovative and most internationalized medicinal products – succeed. The ongoing legislative review process orchestrated by the European Commission will most probably increase the importance of the CP for the European pharmaceuticals market. Such a development would be in keeping with von Beyme's expectation that whenever consumer protection and industrial policy competences are entrusted to the European level – market entry regulation for pharmaceuticals affecting both – they are bound to become more extensive (Klaus von Beyme 1995 in: Weidenfeld 1995: 110).

The Mutual Recognition Procedure, which was designed to be a European regime, is still a nationally based procedure with national regulatory decisions – not only, or not necessarily, because it applies to a varying subset of Member States to whose authorities applications are addressed but, mainly, because decision-making generally remains national and very rarely arrives at the genuinely European stage. The first phase of this procedure very much resembles a mutual adjustment process in which attempts are made to adjust national assessments, evaluations and decisions to what might be regarded as correct regulatory decisions on the basis of an intensively harmonized legislation. But, in fact, this procedure tends to protect the autonomy of national regulatory decision-making and to work against uniform European solutions because national authorities behave according to national orientations and because the procedure rarely reaches the second phase of binding central arbitration (because firms withdraw applications from dissenting Member States for economic reasons). The ongoing legislative review might bring about changes which will facilitate consensus-building among national authorities involved in an MRP. However, it is unlikely that the really Europeanizing step of obligatory arbitration in the event of deviating national opinions will be taken.

It would be premature to regard the incremental development of different forms of regulatory decision-making as a process which should necessarily lead to a completely centralized system at the European level. Important actors would oppose attempts to marginalize the national authorities in a principal-agent relationship vis-à-vis the European Commission and its agency, EMEA, or even abandon the national structures to a large extent. Industry might be more interested in the efficiency of the existing procedures than their convergence into one

supranational regime which would eliminate the option of procedural choice. Leaving a high degree of regulatory impact or even autonomy to the national authorities and considerable flexibility of procedural choice to industry, the MRP is a complement to the "real" European procedure, the Centralized Procedure, and not – at least not yet – a second genuinely European regulatory path. But there are quite a number of national regulators and other observers who expect there to be a developmental logic of incremental responses to preceding deficiencies, with quantum leaps every once in a while. This might eventually lead to a completely centralized marketing authorization system, which will only function and institutionalize itself if it has substantial financial and administrative resources and if it incorporates the market-oriented flexibility characteristic of the current multiple-procedure set-up.

Our second concern has been the substantive impact the existing regulatory alternatives might have on the attainment of the three official regulatory goals: public health protection assuring safe and efficacious medicines, the creation of a Single Market and the reduction of regulatory costs to industry.

Despite discussions about probable biases towards industry-friendly implementation there are as yet no indications that the European procedures are introducing substantially less safe or efficacious medicinal products than the purely national procedures have done to date. Until now, the concerned countries have been spared another pharmaceutical and medical catastrophe like the thalidomide affair.[56] But from a comprehensive public health perspective, the European procedures face the well-known double criticism that regulations tend to be too applicant-friendly (i.e. industry-friendly) when interpreting allowable safety risks and required efficacy levels, on the one hand, and that there is a bias towards risk aversion, on the other, which might prevent innovative medicines from being developed, from entering the market fast enough or even being marketed at all. Evaluations are lacking which would allow for a more thorough assessment of the quality of regulatory procedures and outcomes in a comprehensive and long-term perspective.

Contributions to the creation of a Single Market for pharmaceuticals are provided unequivocally only by the Centralized Procedure. These contributions are – at least quantitatively – outbalanced by the MRP and the National Procedures. This imbalance might swing in the other direction in the future as a result of institutional reforms which would enlarge the scope of the Centralized Procedure. But,

56 One should, of course, mention the catastrophe of HIV-infected blood for transfusions in the 1980s and early 1990s. But, in most countries, this occurred in regulatory and institutional frameworks different from those in which medicinal products are controlled before market entry.

on the whole, cross-national diversity will probably remain in the EC market. In the interest of protecting their national authorities, their small and medium-sized national pharmaceutical companies relying on regional markets, their national pharmaceutical and medical traditions and, finally, their national health care regulations in a wider sense, Member States might not be inclined to give up their remaining national regulatory autonomy in the foreseeable future.

From an industrial policy perspective, regulatory efficiency and cost reduction measured in terms of approval times has been a permanent issue in the discussion of market entry regulation. One may conclude that procedural efficiency has improved due to Europeanization. Even before the new European regulatory procedures came into force, the envisaged competition between national regulatory authorities was shortening average approval times considerably in a converging move across most national authorities. Comparing the two European procedures, it is the Centralized Procedure which has taken the lead over the Decentralized Procedure. However, prudence is advised: such a limited efficiency indicator risks being highly biased in favor of industry's interests in bringing a product as quickly and cheaply as possible onto the market. More meaningful efficiency indicators would have to evaluate costs and benefits in a more comprehensive way than anyone has yet attempted.

Abbreviations

CMS	Concerned Member State
CP	Centralized Procedure
CPMP	Committee for Proprietary Medicinal Products
EC	European Community
EEC	European Economic Community
EMEA	European Agency for the Evaluation of Medicinal Products
EU	European Union
FDA	Food and Drug Administration
MRFG	Mutual Recognition Facilitation Group
MRP	Mutual Recognition Procedure
NP	National Procedures
RMS	Reference Member State
SPC	Summary of Product Characteristics
TEC	Treaty of the European Communities

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