

Learning and interest accommodation in policy and institutional change: EC risk regulation in the pharmaceuticals sector¹

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1 Introduction

1.2 Subject, questions and paper outline

The main purpose of this paper is to formulate hypotheses about the development of marketing-approval regulations for pharmaceuticals in the European Community since the beginning of the 1960s and the impact these changes have had on the institutional structure in the context of European integration, the institutional accommodation of interests and on the distribution of influence in regulatory implementation. The main focus will be on the institutional results of this development: the astonishing procedural policy-mix which emerged in 1995 after thirty years of substantive policy harmonisation and procedural efforts to foster the mutual recognition of national regulatory decisions, which has undergone further modifications in 2004 after a three-year review of EC pharmaceuticals legislation. The institutional “patchwork” (Héritier 1996: 149) of 1995 provides for three distinctive regulatory procedures within the EC, all of them supposed to tackle essentially the same basic policy problem – to protect public health and patients against qualitatively impure, toxicologically unsafe and medically inefficacious medicines. Two of these procedures are in the tradition of national sovereignty in public health matters (see Art. 30 of the Treaty of the European Communities, TEC), i.e. regulatory decisions are taken by national authorities on the basis of extensively harmonised legislation, and with the potential of European supranational arbitration in one of these two cases. Only one of these three procedures is a really European one, where the regulatory decision is taken at the European level and for the whole EC-market. This procedural alternative signifies a radical institutional change compared to the situation before 1995. The choice of procedures depends on the type of the medicinal product (e.g. bio-/high-tech basis; innovativeness) and/or the number of EC countries targeted for marketing.

This regulatory situation is surprising for three reasons. First, the espoused substantive policy goals of these regulations are practically similar, namely those of patient and public health protection in keeping unsafe and ineffective medicines off the market, and also the genuine EC goal of creating a Single Market for pharmaceuticals. Second, the scientific and technical characteristics of this specific policy domain (Feick 2000b) nurture the expectation of converging policies and policy implementation. In this policy field which is based on established disciplines such as pharmacology, toxicology and medical science one might expect convergence of the guiding policy ideas, policies and institutional design (Hall 1993: 291). However, such expectations can be misleading if they do not take into account scientific heterogeneity as well as prevailing discretion in technical and regulatory decision-making as an opening for the influence of social and economic as well as political and administrative interests (Hall 1993: 289). A third cause for puzzlement might be the high degree of legal harmonisation which had already been achieved within the EC. In trying to make sense of the development and its results in this field of regulation different approaches will be pursued.

One perspective will concentrate on the dynamics of European integration with respect to substantive policies and institutional organisation. An attempt will be made to distinguish historical stages and modes of Europeanisation (see (Scharpf, F.W. 1999), (Scharpf 2001c), (Scharpf 1996)) and to analyse types of institutional change more generally (see for example (Thelen 2003) (Thelen/Steinmo 1992)) and European integration particularly (see for example (Armstrong/Bulmer 1998: 50-63), (Bulmer/Burch 2001: 81-82), (Aspinwall/Schneider 2001)).

Encountered fundamental structural changes can be interpreted as evolutionary results of incremental processes, where “l’accumulation d’une série de transformations apparemment mineurs peut déclencher une transformation d’ensemble de l’architecture institutionnelle” (Boyer 2003: 197), the results of voluntary decisions after experiencing the limits of a given approach or policy paradigm (Hall 1997).

The exogenous and endogenous factors accounting for or facilitating such changes can be manifold (Thelen 1999). The institutionally complex European multi-level and multi-actor system of legislative and implemental decision-making (see (Falkner 1999), (Héritier 2003: 186) (Scharpf 2001b)) is adding to the complexities of change. In this paper the goals and interests of influential actors together with policy-related learning during thirty years of policy-making and implementation experiences will be regarded as the main factors of institutional change. In addition, attention will be paid to the impact of these changes on the distribution of influence in this regulatory domaine.

The focus of this paper will be on actors, mostly corporate ones or groups, who – depending on their cognitive capabilities, normative preferences and the availability of direct or indirect resources of influence – have been and are trying to influence policies and policy-implementation. The search for influence within facilitating or constraining institutional contexts and situational constellations² targets not only substantive policy-making outputs or implementation outcomes but also the institutional design of decision-procedures on which future chances for policy-related actions depend – or, to use Albert Hirschman’s terms, the chances for voice-raising or exit-taking (Hirschman 1981). Of course, substantive policy contents such as product standards and criteria for regulatory decision-making are important parts of politics. But, as Mark Thatcher has observed in another policy field, namely telecommunications, conflicts over substantive policy contents are often much less pronounced compared to matters of “the institutional allocation of powers” (Thatcher 2001: 573) despite the embeddedness of the regulatory task in scientific or technical discourse.

The main argument in this paper is that policy inertia and the impact of diverse interests have prevented consequential institutional Europeanisation in this regulatory policy field for several decades, but that policy-related and interaction-learning have accompanied incremental changes, allowing finally for more radical – though still partial – institutional transformations in the context of the existing interest and power structure. Thirty years after the first harmonisation Directive on medicines approval in the EC, a European marketing authorisation procedure has been institutionalised which has shifted regulatory decision-making competencies from the national to the European level, depriving national governmental and regulatory authorities of a significant amount of cherished autonomy, which most of them had defended for decades. In the overall procedural policy mix (see below) this truly European procedure represents only one alternative, limited to the most innovative part of the medicinal products market. The present procedural policy mix itself and the implementation requirements for these procedures have to be interpreted as a reflection of the heterogeneous interest

² See the analytical framework of actor-centred institutionalism in Mayntz, Renate/Fritz W. Scharpf, 1995: *Der Ansatz des akteurzentrierten Institutionalismus*. In: Renate Mayntz/Fritz W. Scharpf (eds.), *Gesellschaftliche Selbstregulierung und politische Steuerung*. Frankfurt/New York: Campus Verlag, 39-72.

structure and power balance which governs this policy field. Thus, the accommodation of diverse interests has been an important, maybe the most important, precondition for radical institutional change besides the facilitating convergence of “policy ideas”, the driving force of specific policy goals and the learning of operational cooperation especially in the implementation process.

In the following subchapter I will briefly describe the problem situation and regulatory rationale in this policy field, before outlining and structuring the development of regulation and trying to categorize the type of institutional change encountered and the modes of European integration applied. In a further step, attempts are made to interpret this development as the result of policy-related learning processes and as the direct or indirect impact of diverse interests. Thus, social learning, on the one hand, and the influence and accommodation of interests, on the other, will be central for “explaining” the existence and viability of the present structure of regulatory diversity within the European Community. Finally, the consequences of this regulatory constellation itself for the distribution of influence and the consideration of interests, on the one hand, and for the balance between Europeanisation and the national autonomy and diversity, on the other, will be analysed.

The interpretations proposed in this paper are based on extensive studies of primary material such as legislative documents, actor-related position papers and institutional process-produced data and evaluations. More than 50 participating actors and interested parties have been interviewed over several years at the national (mainly D, F, UK) and European levels: legislative and governmental bodies as well as regulatory authorities, pharmaceutical industry associations, a few single firms of different size, consumer associations and some outside expert-observers. An extensive amount of secondary literature of academic origin and also professional publications, leaning more or less towards one or the other interested actor, have been consulted. The interpretations of the observations and data are hardly to control in the sense of rigid, intersubjectively assessable measurements and deductions. They are prudently advanced inductive interpretations with an attempt at a phenomenological understanding of developments and their driving forces, and should not be misread as scientific explanations (Wright 1971).

1.2 The rational for market-entry regulation

The policy problem

Medicines are among the most extensively and intensively regulated products on the market (Hart et al. 1988; Feick 2000: 228-229). Historically, they have always been under some form of social control. Professional differentiation and the systematic experience with medicines, subsequently knowledge creation through scientific and technological advances, originally led to forms of professional self-regulation which became more and more legalised through procedural regulation (see (Schmitz/Kuhlen 1998); (Ridder 1990: 22)). This form of legalised self-control by medical doctors and/or pharmacists remained the preferred way of medicines regulation until the 20th century.

It was the impact of the scientific and industrial revolution which paved the way for substantial increases in legal codification and direct governmental intervention in the development, production and distribution of medicinal products (Feick 2000b). Scientific and technological advances increased the knowledge base not only for developing and producing pharmaceuticals but also for the capacity to control medicinal substances both for their desired therapeutic effects and for their adverse reactions. Furthermore, the development of the industrial mass production of prefabricated pharmaceutical specialties increasingly replaced individual pharmacy preparations, spreading the risks of medicine consumption dramatically and posing a public health problem. The impact of these two developments became obvious around the turn of the nineteenth century. All this happened practically without or little governmental control. While the individual pharmacies and pharmacists were regulated to a certain degree, industrial production of medicines and the distribution of these products, although much more dangerous in public health terms, were not. This opened the door for adultery, fraud and neglect. The situation was especially difficult in a country like the US, which had practically no established system and tradition of intra-professional control in comparison to European countries, even though their control systems were weak and insufficient, as future drug accidents would show. Therefore, it is not surprising that the US was the first large country to introduce approval procedures on the basis of systematic pharmacological quality and toxicological safety tests in the 1930s³ – and also the first one to react to the biggest drug catastrophe to date, in the 1960s ((Silverman/Lee 1974); (Abraham 1995)).⁴

The regulatory advances in drug approval and pharmacovigilance by the 1960s and 70s were reactions to dramatic accidents in pharmaceuticals consumption, the most important being the so-called thalidomide catastrophe of the late 1950s/early 1960s (Kirk 1999). The thalidomide affair, though not the only one during these decades, has since been classified as “the single most important event to influence our attitudes to the unwanted effects of medicines” (McEwen 1999: 269). These revelations had an immediate impact on policy discussions. For practically all the countries in Europe it had become evident that effective pharmaceuticals regulation,

³ In the 1930s the US had institutionalised quality and safety-oriented marketing authorisation 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 in reaction to the thalidomide scandal. In Scandinavia, some rather strict licensing regulations, though largely unrecognised elsewhere, had already been in force in Norway since 1928 and in Sweden since 1934 (Abraham/Lewis 2000: 55; Dukes 1985).

⁴ There are many accounts of this catastrophe; see for example Silverman, Milton/Philip R. Lee, 1974: *Pills, Profits, and Politics*. Berkeley, Los Angeles: University of California Press., Abraham, John, 1995: *Science, Politics and the Pharmaceutical Industry. Controversy and bias in drug regulation*. London: UCL Press., Kirk, Beate, 1999: *Der Contergan-Fall: Eine unvermeidbare Katastrophe? Zur Geschichte des Arzneistoffs Thalidomid*, Greifswalder Schriften zur Geschichte der Pharmazie und Sozialpharmazie. Vol. 1. Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH Stuttgart. and Luhmann, Hans-Jochen, 2000: Die Contergan-Katastrophe revisited - Ein Lehrstück vom Beitrag der Wissenschaft zur gesellschaftlichen Blindheit. In: *Umweltmed Forsch Prax* 5, 295-300.. For short overviews of the spread and the harmonisation of pharmaceuticals approval regulation in different European countries, as well as at EU-level and beyond, see Mann, R. D., 1989: The historical development of medicines regulation. In: Stuart R. Walker/John P. Griffin (eds.), *International Medicines Regulations. A Forward Look to 1992*. Dordrecht / Boston / London: Kluwer Academic Publishers., Vogel, David, 1998: The Globalization of Pharmaceutical Regulation. In: *Governance: An International Journal of Policy and Administration* 11, 1-22., Feick, Jürgen, 2000a: Marktzugangsregulierung: Nationale Regulierung, internationale Harmonisierung und europäische Integration. In: Roland Czada/Susanne Lütz (eds.), *Die politische Konstitution von Märkten*. Opladen: Westdeutscher Verlag, 228-249..

capable of protecting the public from health hazards, was on the whole lacking. The policy problem was visible, public pressure was high, and a viable policy option was obviously available as the US-American example had shown. The handling of this situation by way of non-decisions or purely symbolic politics⁵ was forestalled and 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 or delegate blame if accidents should occur despite regulatory precautions.⁶

Regulatory rationale and the normative component of regulatory decision-making

In welfare-economic thinking, product-oriented risk regulation in the pharmaceuticals sector, meant to protect patients against qualitatively inferior, unsafe or ineffective medications, can be understood as a reaction to market failure or to deficiencies in market coordination (see for example (Bator 1958); (Müller/Vogelsang 1979: 31-44, 181-184)). This can be conceptualised as a problem of information asymmetries, where the direct consumer or patient and even his professional intermediaries, doctors and pharmacists, are generally less well informed about the product than the producer himself. And there is also a negative-externalities problem beyond the potential welfare losses of single patients, insofar as adverse medical reactions may lead to subsequent medical costs which represent a welfare burden for members of collective health care systems and/or taxpayers. Medicines regulation, assuring either necessary market transparency or guaranteeing the overall quality of the product through approval procedures and pharmacovigilance, delivers a public good. In more abstract terms this means that uncertainty can be reduced and confidence established through regulatory intervention. Daniel Carpenter goes a step further, maintaining that an information problem exists not only for patients and doctors but also for industry itself, “the inherent uncertainty that firms themselves have about the quality and safety of their products “ concluding that “FDA regulations reduce the uncertainty over product quality and hazards (...), and thereby contribute to both firm’s profitability and consumer’s welfare” (Carpenter 2003: 254).

The political perspective is a different one. Against allegations, made primarily by economists, that governmental regulatory policies generally produce sub-optimal outcomes, James Q. Wilson once responded that this may be so, but that, firstly, it might be impossible to devise optimality criteria for policies so that “in the nature of things no such policy can exist”⁷ and that, secondly, regulatory policies are legislated and implemented just because policy-makers have preferred the imperfections of regulation against the imperfections of markets – for example in fields like consumer and environmental protection (Wilson 1974: 135-136,145-146). Applying Lowi’s and Olsen’s perspectives, he distinguishes different types of cost/benefit constellations for concerned parties and the consequences of these constellations for politics. Risk regulation, as found in in the control of medicines,, contains diffused benefits for consumers, while concentrating at least the visible and immediate costs on industry. In traditional interest politics, an industry as strong as the chemical or pharmaceutical industry should have been

5 It took some years, though, until effective control systems were installed in the different countries. For a comparison of policy-making “speed”, see Mayntz/Feick (1982) and Feick (2000).

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

7 See also Daniel P. Moynihan’s assertion that problems entering the political arena are not of a character conducive to solutions but that they can only be coped with. Moynihan, Daniel Patrick, 1995: *The Professionalization of Reform II*. In: *The Public Interest*, 23-41.

able to veto such policies – which it was able to do for most of the first half of the 20th century in the US and until the 1960s in Europe. Wilson maintains that a change in politics occurred through shifts in “national mood”,⁸ the public becoming receptive to consumerist and ecological issues, emotionalised by “crusaders” and “watchdogs” and popularised by the “skilful use of the media”, which itself displayed an increasingly critical role, forcing politicians to respond to these popular demands and to institutionalise what in the US has been called “new social regulation” or to strengthen already existing legislation and implementation. In the case of pharmaceuticals control, dramatic events have been of the utmost symbolic importance in shifting “national mood” (Wilson 1974: 146, 165-1966). Such a policy–politics constellation fits the political rationales of public good production and of blame avoidance or blame shifting through risk regulation regimes (Hood 2002). And it is not only politicians who are motivated by the risk of blame-taking, but industry as well. The at times almost panicky reactions of companies in pharmacovigilance matters – see, for example, Bayer with Lipobay/Baycol in 2001 – shows how much they have to fear public reaction, not just litigation, which can be devastating economically. In the face of high public sensitivity, industry too has to display a precautionary attitude – in both pharmacovigilance and marketing approval serving the aim of confidence creation.⁹

There is a politics dimension which is linked especially to regulatory decision-making in the implementation process. Disputes over the institutionalisation of approval procedures and the allocation of participation rights in them are so important because case-by-case regulatory decision-making provides substantial opportunities for partial interests and preferences to become influential. This is the case also in policy fields such as pharmaceuticals control, where scientific and technological information is of the utmost importance for regulatory decision-making. Although the boundaries are blurred, the implementation of risk regulation can be broken down into two phases (Breyer 1993): the scientific and technical measurement of risks (“risk assessment”) and the political or administrative evaluation of assessment results and their transformation into regulatory decisions and actions (“risk management”). In both phases, decisions in the proper sense of the word have to be taken,¹⁰ even though these are subject to different internal logics, and even though it might be difficult to recognise the normative content of scientific/technical assessments.¹¹ The refusal of national authorities to recognize one another’s assessments and evaluations, even though they are based on extensively harmonised legislation, is just such a consequence of the discretionary space in regulatory decision-making. As this discretionary power exists (Feick 2000b), the choice of institutional structures, of decision-making procedures and of rules for the selection of participants in decision-making are such an important political issue in this regulatory arena.

⁸ Wilson is characterising American politics although the basic argument can be transferred to the European political context.

⁹ It is interesting to note that the German pharmaceutical industry, though it successfully fended off direct market-entry regulations in the 1920s, at the same time – unsuccessfully - tried to obtain quality certificates from government without state control, with the aim of raising the image of the exporting companies and the confidence of customers abroad Murswiek, Axel, 1983: *Die staatliche Kontrolle der Arzneimittelsicherheit in der Bundesrepublik und den USA*, Beiträge zur sozialwissenschaftlichen Forschung, Bd. 46. Opladen: Westdeutscher Verlag..

¹⁰ Decisions are normative jumps in the face of uncertainty when no further rationalisation is possible.

¹¹ See Nelkin (1979: 11) on concealing political choices behind scientific rationalisations; Abraham (1994) on the interest content of scientific assessments in the approval procedures for marketing authorisation; also Abraham/Reed (2001).

1.3 The wider regulatory context

The regulation of market entry for pharmaceuticals is one of the many governmental interventions in the pharmaceuticals sector, thus influencing this industry which is of great importance in most industrialised countries, especially those with a considerable pharmaceutical industry. Economically it is an important branch, not only through its contributions to GDP but also because it contributes positively to the trade balance and supplies over-proportionately high-skilled jobs in many countries. Parts of it also belong to the scientifically and technically innovative branches that are expected to be part of the future growth-sector: health care. This part of pharmaceuticals regulation is also relevant for the health care system at large. The supply of medicines for all the therapeutical schools practising in a country is determined by the entry gate of approval regulations. It has also relevance for health care costs or savings. Some of the reasons why national regulatory authorities have not been prepared to mutually recognize one another's regulatory evaluations and decisions has to do with repercussions of market-entry decisions on the national provision and financing/reimbursement of health care goods (Feick 2002: 24-25, 40). We should also mention the social and political orientational context in which the pharmaceutical industry and its regulation operate. This context contains contradictory orientations. In many societies there is quite some distrust in the pharmaceutical industry with respect to its ethical credibility, at the same time great hopes are placed in its contribution to overall economic performance and much-needed therapeutic innovation.

This highly complex regulatory environment meets complex governance structures and tasks at the European Union level, thus making the introduction of European regulations and their implementation especially difficult. The complexities are partly mirrored in the multiple goals which are pursued by European market entry regulation: not merely the protection of public health, by controlling the quality, safety and efficacy of medicinal products prior to obtaining marketing approval, but also the design and implementation of regulatory policies in a way which improves the innovativeness and the international competitive position of the European pharmaceutical industry – partly through more efficient, i.e. less costly, regulatory procedures and partly through the establishment of a Single Market with its economies of scale. The increasing importance of the goals of fostering innovativeness and competitiveness have to do with the decline of the internationally oriented and research-intensive European pharmaindustry vis-à-vis US and also Japanese pharmaceutical companies especially as far as the invention and launch of new chemical, molecular or biotechnical entities or economic success on the world market are concerned – with, maybe the exception of the UK and Switzerland. Although the data are not completely conclusive¹², it was and is at least the perception that especially the US pharmaceutical has gained a clear competitive advantage.

¹² See for example: Economics, Europe, 1998: *Benchmarking the competitiveness of the EU pharmaceutical industry*. Europe Economics (December 1998)., van den Haak, Marieke, 2001: Fewer launches in 2000. In: *CMR International News* 19, 10-14.; there is also the argument of a general "innovation deficit" which the pharmaceutical industry is facing Drews, Jürgen Ryser Stefan, 1996: Innovation Deficit in the Pharmaceutical Industry. In: *Drug Information Journal* 30, 97-108..

2. Development of EC medicines' approval policy, institutional change and modes of European integration

2.1 Policy goals and developmental stages in the EC

When the Thalidomide catastrophe (Kirk 1999) struck societies in Europe and abroad medicines control was not a complete tabula rasa. Different regimes existed at national levels. Most tended towards industrial self-regulation as in the UK and Germany; few consisted of already institutionalised state controls, e.g. via agency-based approval systems as in the US and some Scandinavian countries, or had formal approval requirements, even if they were not effectively implemented as in France. The Thalidomide scandal gave rise to either fundamental legislative reforms in European and other industrialised countries or to a tightening of already existing regulation.¹³ Politically it was obvious that purely symbolic or feet-dragging policy responses would not be an option in face of public pressure, which remained high for years due to lawsuits and their media coverage. The Thalidomide scandal 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 or rigorously implemented legislation 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 design a regulatory framework for the control of the pharmaceutical industry, to prescribe the regulatory action to be taken by implementing administrations with the effect of influencing the availability of pharmaceuticals for medical therapies. In fact, the EC Commission was well aware from the outset that national differences could always jeopardize the desired effects of legal harmonisation.¹⁴

The general goals of European pharmaceuticals regulation have been straightforward. In the words of the Pharmaceuticals Unit of the Enterprise Directorate-General, regulatory measures are supposed to ensure a high level of public health protection, to establish a Single Market, for medicinal products 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 Council Directive 65/65/EEC of 1965 “on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products.” This Directive states that “the primary purpose ... must be to safeguard public health,” adding that this objective has to be

¹³ See also Silverman/Lee (1974), Murswieck (1983), Abraham (1995). France had drug approval legislation (“visa”) since 1941. It was motivated by the wartime economy and not implemented very stringently in the years following World War II, but rather served protectionist goals (Baumheier 1994). Sweden and Norway had national regulations even before World War II, but they were not well known abroad (Dukes 1985). The US regulatory procedures, which had been in existence since 1938 - albeit limited to quality and safety control and only extended to clinical efficacy controls with the Kefauver-Harris amendments of 1962 – were regarded as a model for other countries. When the adverse effects of Thalidomide surfaced, the US regulatory agency FDA had not yet approved the drug for safety reasons – not as a result of official policy but because of the insistence and courage of a single employee, despite political pressure and very little support from agency superiors (see Silverman/Lee (1974).

¹⁴ The European Commission expressed its scepticism about a purely legal harmonisation strategy only one year after the Council had adopted the General Programme on legal harmonisation with the goal of automatic mutual recognition (28 May 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).

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 the goals of patient safety and public health protection along with industrial growth and competitiveness have been common concerns of European and national pharmaceuticals regulation 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 efficiencies of scale of larger markets (Cecchini et al. 1988: 5, 27) as well as contributing to the rationalisation of regulatory practice and the reduction of regulatory costs to industry (Deboyser 1995: 33) through substantive harmonisation, procedural coordination and, finally, even regulatory centralisation were meant to maintain or strengthen the EU region as a competitive research, development and production site.¹⁵ These goals are partly conflicting. With respect to patient protection and public health, trade-offs have to be made in regulatory decision-making between the safety and efficacy aspects of medicinal products. The industrial policy aim to promote pharmaceutical and medical innovativeness and to foster the competitiveness of the European pharmaceutical industry via the reduction of direct and indirect regulatory costs can conflict with regulatory strictness and jeopardize patient safety.

The quasi-constitutional goal of establishing a Common Market and of removing hindrances to it has its limits in Art. 30 (formerly Art. 36) of the Treaty of the European Communities (TEC), which still largely protects national sovereignty in matters of public health. This prerogative is effective in the respective regulatory domain for as long as legal Europeanisation has not yet been established and as long as equivalent implementation cannot be assured Europe-wide (Collatz 1996: 30). The European Court of Justice has endorsed this view in several of its judgements, while at the same time making it clear that deviations by national authorities/governments – for example, with respect to mutual recognition of national decisions based on harmonised law – have to be justified on reasonable, scientific grounds. The scientific complexity and the discretionary openness of the assessments and evaluations in pharmaceuticals approval provides national authorities with an opportunity to deviate from the regulatory decisions of other authorities.¹⁶ Even twenty-five years after the first Council Directive of 1965 had established the basic regulation, this “sacred founding act” (Brunet 1999: 13), and after many more Council Directives, Commission Guidelines and Communications had followed (see Annex, Table 1), “there was still no actual free movement of medicinal products”. These products or the sector to which they belong seemed especially “Treaty-resistant” (Brunet 1999: 16).

¹⁵ See EU Commissioner for Enterprise and the Information Society Eric Liikanen (Liikanen 2002).

¹⁶ For a short time, the European Commission had tried to apply the European Court of Justice’s *Cassis de Dijon* decision on mutual recognition to the field of marketing authorisation for pharmaceuticals, based on the idea of minimum harmonisation and functionally equivalent national regulatory implementation, a strategy that did not work in this sector due to the complexities of the product (see Hancher 1990: 104, 112-117).

Table 1**Chronology of major regulatory steps in the EC concerning pharmaceuticals marketing approval**

1965	Directive 65/65/EEC requiring national approval before marketing pharmaceutical specialities controlling for pharmacological quality, toxicological safety and therapeutical efficacy (only national authorisations available)
1975	<p>Directive 75/319/EEC</p> <ul style="list-style-type: none"> - Detailed requirements for application dossier (technical contents, e.g. analytical and test results); - Details concerning controls to be performed by national implementing authorities; - <i>Community-Procedure</i> for parallel applications in at least 5 Member States as an option; establishment of the <i>Scientific Committee (CPMP)</i>, members are national authority representatives) for providing a non-binding opinion on request of a Member State (still only national marketing authorisations available); - Establishment of the <i>Pharmaceutical Committee</i> for participation in the preparing of legislative measures
1983	Directive 83/570/EEG, slight procedural modifications of the <i>Community Procedure</i> , becoming the <i>Multi-State Procedure</i> (now optional with parallel applications in at least 2 Member States; still national marketing authorisations)
1987	Directive 87/22/EEG, <i>Concertation Procedure</i> for the most or more innovative pharmaceutical products; obligatory pre-decision involvement of <i>CPMP</i> , but without binding opinion (still national marketing authorisations)
1993	<p>Regulation 2309/93/EEC, Directive 93/39/EEC</p> <ul style="list-style-type: none"> - Introduction of the <i>Centralized Procedure</i>: emanating from the <i>Concertation Procedure</i> but with regulatory decision taken at the European level and for the whole Community (EC-wide marketing authorisations); - Introduction of the <i>Decentralised Procedure</i> emanating from <i>Multi-State Procedure</i>, still nationally based but with option of centralised, binding arbitration in case of diverging national assessments and/or evaluations (national marketing authorisations)
1998	Complete replacement of parallel national applications by <i>Decentralised Procedure</i>
2001	Directive 2001/20/EC: Standardisation of clinical test requirements
2004	Regulation 726/2004/EC: Amendment of the <i>Centralised Procedure</i> : increase of scope, some efficiency measures (deadlines) and organisational changes (EMA, CHMP)
2004	Directive 2004/27/EC: Amendment of <i>Decentralised Procedure</i> : obligation of binding arbitration in case of dissent among national authorities (still national authorisations)

The first Directive of 1965 had made approval procedures obligatory in the Member states, controlling for the quality, safety and efficacy of pharmaceutical specialities, but leaving the transformation and implementation of this generalized regulatory obligation to national governments. It took until 1975 for the next directives to materialise, which detailed the requirements for the pharmaceutical entrepreneur's applications and the subsequent national regulatory assessments, evaluations and decisions. From 1975 onwards, obligations of national authorities to communicate or to cooperate were stipulated alongside the institutionalisation of respective procedures and institutions which were meant to support national cooperation, foster the harmonisation of national regulatory behaviour and to facilitate mutual recognition. All these measures left the authority of regulatory implementation at the

national level. The most important institutional changes occurred in 1993, effective from 1995/1998, introducing the a completely European procedure, the *Centralised Procedure (CP)* succeeding the *Concertation Procedure* of 1987, and reinforcing the *Multi-State Procedure* of 1983 to become the *Mutual Recognition or Decentralised Procedure (MRP/DP)*. The latest development has been the legislative review of 2004, which will be dealt with only marginally in *this paper*.¹⁷

2.2 The strategies of European regulatory integration

The goal market integration, of creating a Common Market for pharmaceuticals, has been pursued by basically two different strategies over time (see Figure 1):

- a) increasingly detailed harmonisation of national legislation and implementation with subsequent mutual recognition of national regulatory decisions;
- b) the institutionalisation of regulatory decision-making at the European level, which would prevent national disparities by definition.

Legal harmonisation and mutual recognition versus institutional centralisation

There have been discussions about these two conflicting institutional alternatives since the early 1960s.¹⁸ But the Member States (at that time the six founding states) and their regulatory authorities were not willing to surrender their autonomy. The pharmaceutical industry itself was still preoccupied with preventing or weakening regulatory intervention and was principally opposed to anything that would look like the build-up of a European super-bureaucracy. The Commission vacillated for a short time, but then it opted to pursue a strategy of harmonisation and mutual recognition because it anticipated insurmountable national resistance while being mindful of its own limited administrative capacities and experience.

The first Directive of 1965 (European Council 1965) prescribed a formal regulatory procedure for all its Member States, a "minimal" harmonisation demand, which left substantial discretion in the transformation and implementation of these European requirements to the national legislators and governments (Blasius/Cranz 1998: 66-67). The Commission suggested that the Member States be required to mutually recognise the others' decisions, but this suggestion failed due to Member State opposition for reasons of regulatory autonomy, the securing of national regulatory traditions and, partly also, the protection of national industries. The next big steps taken were the Directives of 1975 towards more detailed harmonisation of application and approval requirements (Council of the European Communities, 1975a). The Directives also introduced some provisions for communication and cooperation between the national regulatory authorities in an optional *Community Procedure*. The aim was to foster mutual understanding in assessments and evaluations (Council of the European Communities, 1975b). However, the differences between national implementation practices prevailed due to vague legal concepts and general clauses that were open to interpretation. The goal of establishing a Single Market for pharmaceuticals remained out of reach (Collatz 1996: 48-50).

¹⁷ This review is the topic of another project (see URL http://www.mpi-fg-koeln.mpg.de/review/index_en.html).

¹⁸ See Hancher (1990: 103-117) and Hart/Reich (1990: 14-36).

Attempts at procedural coordination

Two procedures were introduced between 1975 and 1987: the so-called *Community Procedure* in 1975, transformed into the *Multi-State Procedure* in 1983, and the *Concertation Procedure*, the latter being limited to the most (obligatory) or more (optional) innovative medicinal products,¹⁹ which came into effect in 1987 (Council of the European Communities, 1987a). This was the institutional result after the Commission's futile proposal in 1980, to introduce automatic mutual recognition at least for pharmaceuticals with new active substances, had been revived in the mid-1980s. Although the latter procedure obliged national authorities to wait for the opinion of the Scientific Committee before deciding on an application,²⁰ neither of these procedures fulfilled the expectations of mutual recognition. Measured against this goal, the *Community Procedure* and, later on, the *Multi-State Procedure* failed completely.²¹ The *Concertation Procedure* was comparatively successful insofar as it actually resulted in national evaluations being quite close to the CPMP's position. But the Scientific Committee's recommendations were not automatically adopted at the national level, as the innovative industry and the EC Commission had hoped. Nor was the procedure more efficient for industry than the national procedures, because national authorities very often conducted time-consuming assessments and evaluations on top of the CPMP's work (Scrip 1993: 25-28). Nevertheless, the Commission rightly considered this procedure as a first step towards centralising evaluations, which it planned to pursue at a further stage when the evaluation of the Multi-State Procedure would be due in 1990.

The "new" harmonisation approach: short-lived hope in the pharmaceuticals sector

In its White Paper of June 1985 (Commission of the European Communities 1985, June 14) the Commission proposed its new approach or strategy for the completion of the Common or Single Market in the European Community, an approach which became part of the Single European Act of 1986. This new strategy had been developed on the basis of the Cassis-Dijon ruling by the European Court of Justice (ECJ), which suggested that minimal harmonisation of product norms and standards can be sufficient for obliging national governments to mutually recognise national regulatory decisions and, in such an instance, desist from stopping the free movement of goods across their borders. For the Commission the practically unmanageable task of maximum harmonisation seemed avoidable and mutual recognition finally attainable as a reliably mechanism of integration based on minimal framework harmonisations that left regulatory transformation and implementation to the national level. This general principle should only be "subject to certain important constraints" (ibid.) and "a clear distinction needs to be drawn in future internal market initiatives between what it is essential to harmonize, and what may be left to mutual recognition of national regulations and standards; ..." (Commission of the European Communities 1985, June 14: no 65). In the Annex to this White Paper, the

¹⁹ Appendix with list of "technologically high-quality" pharmaceuticals (Council of the European Communities, 1987b); the procedure is obligatory for category A pharmaceuticals that are derived from certain biotechnological research and production methods and optional for category B pharmaceuticals ("other technologically high-quality pharmaceuticals").

²⁰ The Committee for Proprietary Medicinal Products (CPMP) is made up of representatives from the implementing national regulatory authorities. The Pharmaceutical Committee, which was established in the same year, is made up primarily of representatives from national ministries and is concerned with more general policy questions dealing with medicinal products. Both committees were institutionalised alongside the EC Commission.

²¹ See Vos (1999: 206-211), Scrip (1993: 13-14, 20-28). The types of innovative products covered remained practically the same in the Centralised Procedure of 1993, in force since 1995 (see note 1).

Commission established task lists and timetables, including one for “pharmaceuticals and high-technology medicines” with the task of the “completion of work eliminating obstacles to free circulation of pharmaceutical products.” (Commission of the European Communities 1985, June 14: Annex, 2.4.) Critics pointed to other rulings of the ECJ which, so the argument, had all made it clear that the mere congruence of legislative and regulatory goals, without assuring the equivalence of the means and methods of transformation and implementation, would not legitimise the obligation of mutual recognition of national protection arrangements. Their conclusion: the former strategy of maximum harmonisation (old approach) could not be abandoned in these policy fields and that the Commission had overstretched the applicability of the new approach beyond fields such as rather simple product quality controls or technical norm-setting and thus not only neglected court rulings but also neglected legitimate concerns for health, environment and consumer protection. In fact, the new approach would even entail the danger of abandoning much-needed further harmonisation and have the counterproductive effect of becoming a hindrance for the completion of the internal market (Sedemund 1987: 44-49).

The pharmaceuticals sector – and there marketing approval as the main policy field in the EC – was one in which the new approach was never consistently pursued. What happened after 1985 was, first, the still incremental extension of substantive harmonisation in terms of increasingly encompassing and comprehensive legal harmonisation, on the one hand, and the procedural evolution with the so-called *Concertation Procedure* in 1987, on the other. This was another incremental evolutionary step – but with two seemingly minor innovations: the regulatorily consequential separation of medicinal products into groups treated differently in the regulatory framework, and the increase in importance of the CPMP.

In 1987, there was no publicly observable indication that the Commission of the EC might be heading for the centralisation of marketing authorisation procedures at the European level, to say nothing of a European regulatory agency. Publications in 1988 still expressed the conviction that regulatory Europeanisation in the form of binding European decisions was not on the timetable due to opposing national interests, which would prevent unanimity in the Council required for such a major institutional step. Nevertheless, some observers regarded “centralisation” as “an optimal solution” for achieving “harmonisation of decision-making” and establishing “the Common Market”, but this “desirable” strategy did not “seem to be enforceable”. Since 1967 the EC Commission had tried to convince the national governments of the automatic mutual recognition of one another’s marketing approval decisions, but the Council had always refuted this automatism, leaving the last decision to the national regulatory authorities. This was still the case in the 1980s. The Commission regarded patient protection as being sufficiently developed through European legal harmonisation but did not see much progress being made towards the free circulation of pharmaceutical products in a Common Market (Deboyser 1991: 103-105, 127). The European Court of Justice, too, had not presented the solution because “although the Court is prepared to narrow the scope for residual national measures under Article 36 ..., it is unlikely to require automatic mutual recognition of product licenses given the present stage of harmonization of national licensing requirements” (Hancher 1991: 831). With automatic mutual recognition being regarded as “une utopie dans ce secteur” (Deboyser 1991: 127), further development was expected to be of an incremental nature improving “coordination procedures” as the more “realistic perspective” (Glaeske/Hart/Merkel

1988: 40-41). But the crux of the mutual recognition mechanism was – and still is – that “mutual recognition is very much an *additional* tool of integration ... in its complementarity to harmonisation through rule-making ... [and – J.F.] contingent on the existence of institutional structures through which technical equivalences can be recognised, and also on different national rules actually pursuing equivalent strategies” (Armstrong/Bulmer 1998: 250). The national institutional and cognitive bases for this recognition did not exist. In face of this situation Majone’s conclusion applies: “Until regulators can trust each other to avoid ... selfish strategies, centralisation of regulatory authority is the only practical way of correcting trans-boundary externalities, or preventing the local regulation of a local market failure from becoming a trade barrier” (Majone 1998: 32).

Unexpected by most observers, in 1988, the EC Commission called upon concerned parties, and especially professional actors, to develop proposals for a European approval system for pharmaceuticals, publishing its own ideas and conclusions in a Memorandum in April 1989. A discussion process was set in motion in which, above all, the Commission, the national authorities, the pharmaceutical industry or its associations and, to a lesser extent, the European consumer association BEUC took part. It finally resulted in the legislation of 1993, which left market entry regulation for pharmaceuticals with a veritable institutional “patchwork” of regulatory procedures.

2.3 The “European” procedures: distribution of decision-making power, opportunity structures and implementation behaviour²²

The reform legislation adopted by the European Council in 1993 resulted in two “European” regulatory procedures which, together with the national procedures still available, provide a wide range of institutional alternatives. The procedural landscape in 1995/1998²³ consisted of:

1. the still existing ***national procedures***, which are based on harmonised legislation and are available if the medicinal product is to be marketed in one Member State only and is not considered a category A pharmaceutical (see 3. below);
2. the ***Mutual Recognition (MRP)*** or ***Decentralised Procedure (DP)***²⁴ for all pharmaceuticals that are to be marketed in more than one Member State (except medicines for which alternative 3. is obligatory) and
3. the ***Centralised Procedure (CP)***, which is obligatory for the most innovative pharmaceuticals (category A) and optional for category B pharmaceuticals, also defined as innovative (see note 18).

National procedures were not covered by the reform legislation of 1993 and were also not completely replaced by it. They are subject to all the legal harmonisation since 1965, the

²² The analyses in this paper mainly reflect the institutional and regulatory situation until the legislative reforms of 2001-2004. Only in rare cases is it necessary to allude to the impact of these legal changes.

²³ 1995-1998 was a transition period for the second procedural category. Until 1998 pharmaceutical companies had the choice between the MRP/DC and multiple national procedures.

²⁴ The *Mutual Recognition Procedure* is applied when a product has already been approved in one or more Member States and approval is sought in one or more additional Member States. In the *Decentralised Procedure* the product has not yet received authorisation in any Member State. Both sub-

original goal of which was to guarantee functionally equivalent marketing authorisations by all national authorities. Although restricted to less innovative medicines and to single-country applications, they still represent a large part of the applications.²⁵

Concerning the **Decentralised Procedure** or **Mutual Recognition Procedure** the authorities of those Member States in which pharmaceutical entrepreneurs have made applications continue to be the competent institutions for authorisations which are valid nationally. The procedure is based on national regulatory decision-making processes, with additional communication and cooperation obligations incumbent on the national authorities affected. But there does not exist a formally institutionalised coordination infrastructure at the European level.²⁶ In this respect, it is rather similar to the previous Multi-State Procedure (see above), the important difference being that the *MRP/ DP* includes an original Europeanisation phase allowing for binding arbitration at the European level in cases of disagreement among national authorities. But there is no obligation to take this path in any event (see below).²⁷

The fundamental innovation has been the **Centralised Procedure**, which for the obligatory products deprives pharmaceutical companies of the chance to strategically select their target countries and reduces the regulatory autonomy of the national regulatory authorities considerably in that regulatory decisions are taken by European institutions and are valid for the entire EU. However, it is “only” one procedure in this policy mix, though it covers the more important part of the medicines market, therapeutically as well as industrially – and its scope is extended by the 2004 reform.

Institutional description of the CP

The **Centralised Procedure** (see Figure 1) transfers all the final assessment, evaluation and regulatory decision-making to the European level, but complements this transfer of regulatory power from the national to the European arena with an extensive participation of national regulatory agencies in the scientific assessment and evaluation (agency level) and of national governments in the administrative/regulatory comitology phase (ministerial level). In practice, the tendency towards centralisation is further strengthened by the fact that the assessments and evaluations conducted by the Scientific Committee (CPMP) at the European Medicines Evaluation Agency (EMA), almost without exception, anticipate the final regulatory decisions at Commission level. These decisions are taken with the involvement of the Standing Committee, which is made up of representatives from the national ministries. Altogether, this is a “multi-level and multi-actor” decision-making process, the institutional procedures of which are governed by a supranationally integrating framework despite its polycentric participation structure.²⁸ Institutionally joint decision-making²⁹ does take place, but in practice with clear overall features of central direction.

procedures belong to the same category because the decision-making processes are fundamentally identical.

²⁵ The number of national applications in Germany in 2001, for example, by far exceeded the total for both European procedures. This seems to be the case at least in the larger countries (markets).

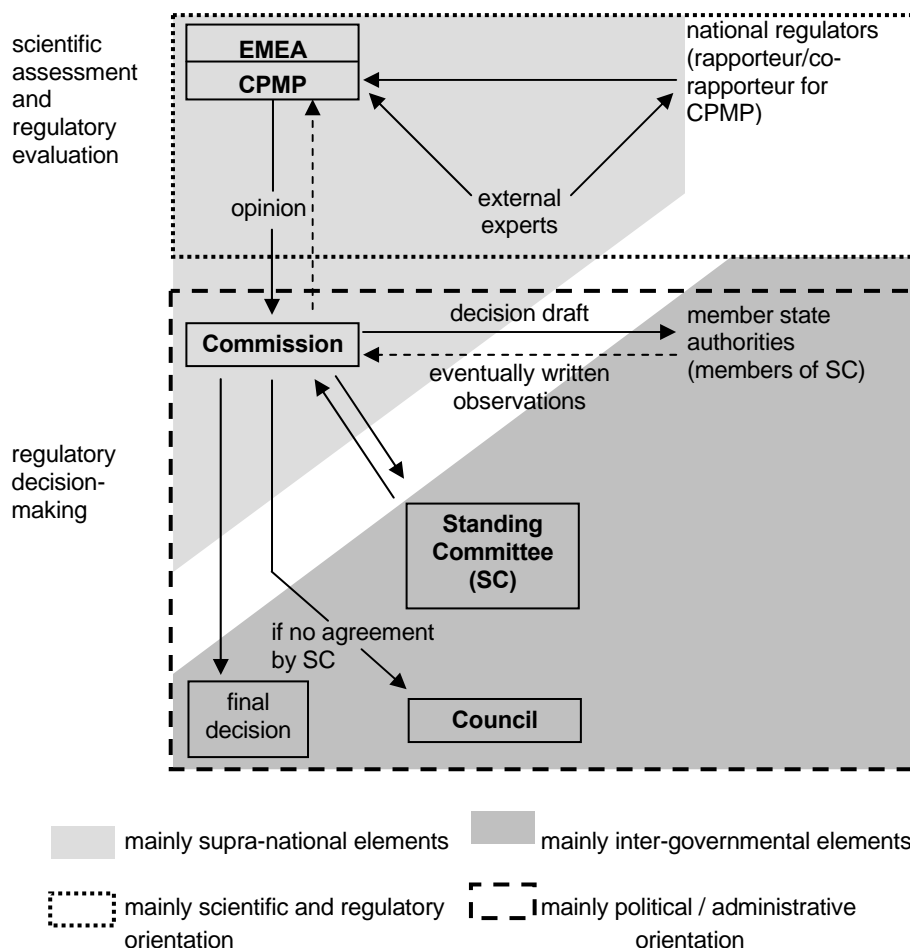
²⁶ This has been changed to a certain degree through the legislative review of 2001-2004.

²⁷ This has also been changed in 2004, although there remains some interpretive dispute over the automaticity of the arbitration path.

²⁸ To describe this institutional configuration E. Chiti uses the term “decentralised integration” (Chiti 2002).

Figure 1**Centralised Procedure (simplified)**

supra-national and inter-governmental elements
 scientific and political/administrative orientations



EMA: European Agency for the Evaluation of Medicinal Products (since May 2004)
 EMA: European Medicines Agency

CPMP: Committee for Proprietary Medicinal Products (representatives of national regulatory agencies); (since May 2004 CHMP: Committee of Medicinal Products for Human Use)

SC: Standing Committee (representatives of national authorities/ministries)

Source: Council regulation (EEC) No 2309/93;
 Commission regulation (EC) No 1662/95;
 Notice to Applicants, Volume 2A, chapter 6, August 2002

The Scientific Committee (CPMP)³⁰ assesses and evaluates the incoming applications for the EMA, the latter then formulating an opinion for the Commission's decision draft, which itself is

²⁹ F. Scharpf distinguishes different "modes of integration" ranging from "mutual adjustment" and "open modes of coordination" to "central direction". He ascribes the European regulation of product standards to that of "joint decision-making" which characterises the cooperation between centralised European and decentralised national institutions in the decision-making process (Scharpf 2001a).

³⁰ Until 2004 the CPMP was composed of two representatives from each national regulatory authority. The legislative review changed this to one per national authority in order to accommodate enlargement. The CPMP (now named CHMP), additionally, may co-opt 5 further members on the basis of their scientific specialisation and credits.

introduced into the comitology procedure at Commission level. The CPMP's recommendations are based on assessments and evaluations by two of its members from different national authorities (rapporteur and co-rapporteur) who produce or coordinate the scientific assessments at their home institution internally and/or with the help of external experts selected from a EU-wide list of more than 3200 accredited experts. Both the administrative and scientific support of the national regulatory authorities is vital for the functioning of this procedure. An absolute majority is necessary, consensus or near consensus generally achieved for the decisions of the CPMP. The European Commission then initiates the regulatory decision-making process (comitology procedure) based on the recommendation of the EMEA/CPMP. The Standing Committee decides by qualified majority vote – mostly in writing, with face-to-face meetings occurring only exceptionally – whether or not to accept the Commission's decision draft. The Commission issues a regulatory approval decision if the Committee has given its consent (which is usually the case) or asks the EMEA/CPMP for further clarifying discussions on specific scientific/technical issues (which happened only twice between 1995 and 2001 and was resolved in the sense of the initial evaluation)³¹. The Council of Ministers intervenes only if the Standing Committee does not approve the draft or fails to deliver an opinion. To date, this has not yet happened, but it still remains in the background as a last institutional option for nationally motivated intervention. Despite the formal centralisation of decision-making competences in European bodies, the assessment and decision-making process depends on the participation and cooperation of national authorities at all stages of regulatory implementation. The national levels can introduce their views and interests, but no simple veto is possible; "coalition-partners" are needed.

At this point it is important to note that the *Centralised Procedure* is reserved for especially innovative medicinal products. These medicines are not "encumbered" by the impact of preliminary national decisions, and both their novelty and their scientifically demanding background raise the chances that the assessments and evaluations of national regulatory authorities will converge. This probability, together with the extensive participatory rights for national authorities, made it easier for the national governments to accept this centralised decision-making procedure unanimously in 1993. For the concerned internationally oriented companies, the interest in a functioning *Centralised Procedure* is evident. They are the ones who are looking for a more efficient access to a larger market. Thus, this procedure complies with the European objectives of an unhindered Single Market for pharmaceuticals and the fostering of pharmaceutical innovations – objectives of both the EU Commission and the national governments. Up until now, the *Centralised Procedure* has by and large lived up to expectations (see (European Commission 2000); (Feick 2002: 22-25, 38-42)). In the legislative review just ended, the Commission and the European Parliament proposed enlarging the scope of this procedure, making it obligatory for all new active substances. Most Member States had resisted this attempt in the Council and even the innovative industry had been sceptical, preferring optionality – and thus "flexibility" – between the *Centralised* and the *Decentralised Procedures*. But industry finally supported the Commission and Parliament in the hope of being able to exchange this support for favourable decisions in other areas, such as direct information for patients concerning prescription medicines, and harmonised, longer protection of application data, measure against generic competitors. The result has been a

³¹ This information has been elicited through personal communication with EMEA in 2001 (EU 2001 – 10).

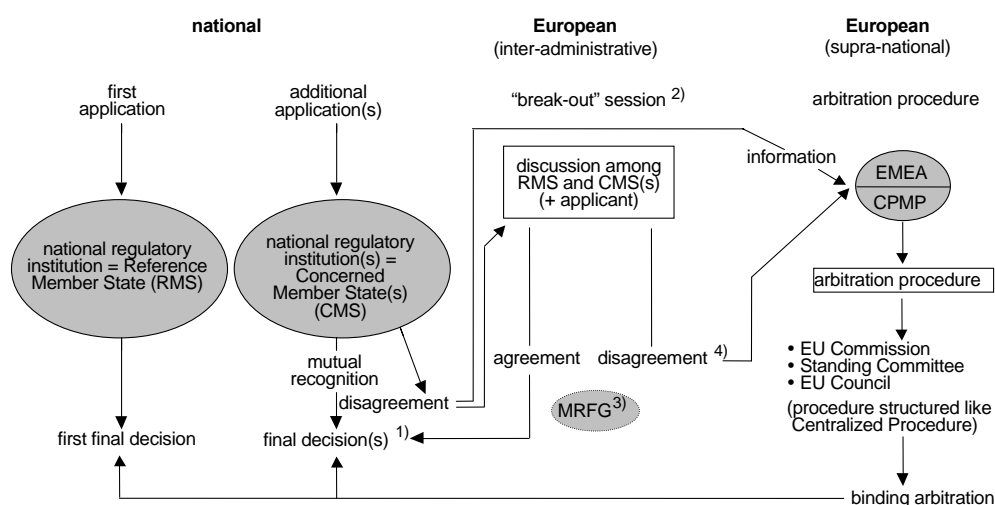
compromise with the scope of the obligatory *Centralised Procedure* being extended to all new active substances in three indications and the legal obligation to reconsider the Commission's initial position after four years.

Institutional description of the *MRP/DP*

The *Mutual Recognition* or *Decentralised Procedure* (see Figure 2) contains a component of European centralisation which is almost never applied. The national authorities have been able to maintain their autonomy at the core of this procedure. It offers the companies strategic

Figure 2: The Decentralised Procedure

National, inter-administrative, and supra-national



* In the sub-case of the MRP the medicinal product has already been authorised in one or more Member States, one of which is then chosen by the applicant as RMS.

Note: pharmaceutical products for human use

CPMP: Committee for Proprietary Medicinal Products (representatives regulatory of national agencies/authorities);(since May 2004 CHMP: Committee for Medicinal Products for Human Use)

EMEA: European Agency for the Evaluation of Medicinal Products; (since May 2004 EMA: European Medicines Agency)

MRFG: Mutual Recognition Facilitation Group

- 1) All final decisions in MRP are national decisions.
- 2) "Break-out" sessions are organized by the RMS to discuss and resolve conflicting positions (scientific assessment and evaluation) with CMS(s).
- 3) The MRFG is an informal group of representatives of the national authorities to discuss general issues of the procedure and to provide overall monitoring (attendance by Commission); meetings of the MRFG also with industry associations.
- 4) An applicant may withdraw his application from dissenting countries to avoid binding arbitration.

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

flexibility in selecting the countries where they would like to market their products. But they pay for this flexibility with a procedure that they feel is not as efficient as it could be and with the much-criticised exploitation of national autonomy by the individual authorities (European Commission 2000: 122, 148-151).

In this procedure, Member States that are chosen for applications have to be differentiated into a Reference Member State (RMS) – where the respective medicinal product has already been authorised or, in case of the *Decentralised Procedure*, a Member State, chosen by the

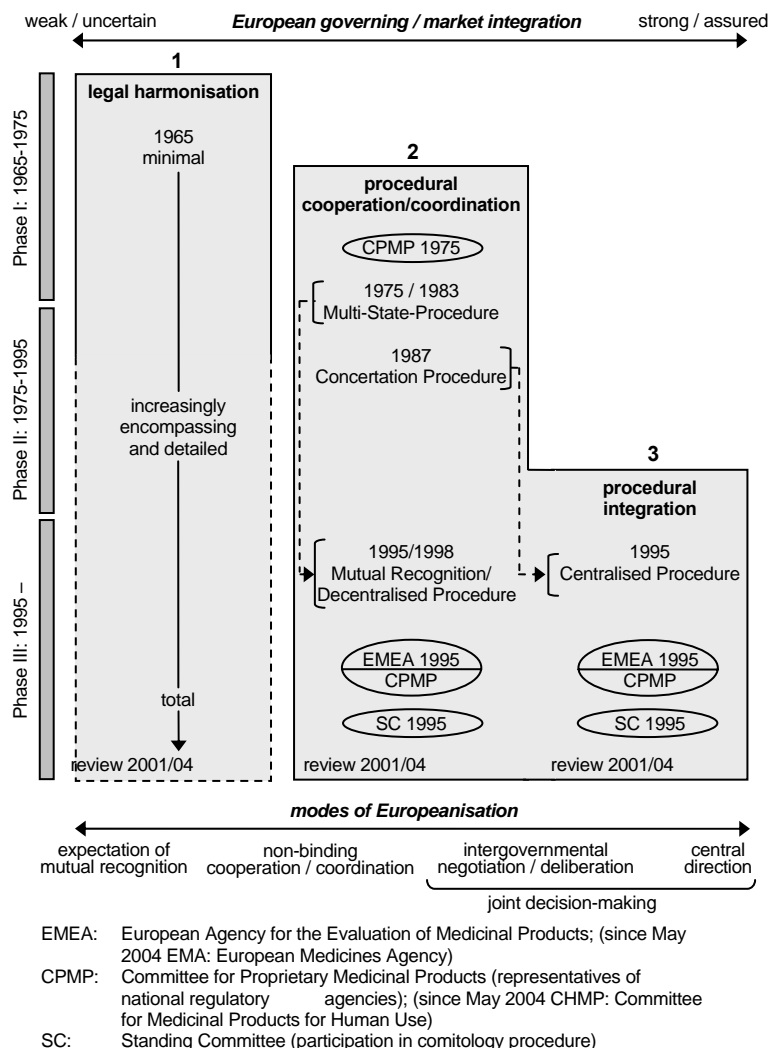
applicant to provide the model decision for the other national regulatory authorities of one or more Concerned Member States (CMS). The procedure itself is broken down into three phases: a) a national phase, in which the Concerned Member States strive to adapt their decision to the regulatory decision of the Reference Member State (mutual recognition); b) an inter-administrative phase in which the Reference Member State and the Concerned Member States are supposed to resolve eventual differences of opinion in so-called “breakout sessions”, and c) a binding supra-national arbitration procedure activating the EMEA/CPMP and the Commission roughly in the same way as in the *Centralised Procedure*. Formally the final regulatory decisions would still be national ones but would be bound by the output of European arbitration.

As in the *Multi-State Procedures* after 1983 (see above), the mechanism of mutual recognition has not been functioning satisfactorily here either. “Serious concerns” are often expressed by Concerned Member States vis-à-vis the position of the RMS. And attempts to overcome these differences of evaluations between the national authorities in “break-out sessions” often fail despite the efforts of an informal group of representatives from the national regulatory authorities (the Mutual Recognition Facilitation Group, MRFG), which is active in the background without European institutional support. The MRFG works as a multi-national network (Perkmann 1999) that supports and tries to develop the trans- or supra-national European regulatory structures in this procedural arena in which national institutions still dominate. Moreover, remaining disagreements in the second phase rarely result in binding arbitration, which occurs in less than four per cent of the cases where national evaluations differ (Feick 2002: 23-25). Instead, the applying pharmaceutical entrepreneurs tend to withdraw their application for approval from the countries that are not willing to engage in mutual recognition. In other words, the *Decentralised Procedure* often only undergoes the national and inter-administrative phases of an open, less formalised attempt at coordination, the outcome of which depends on the voluntary consent of the national authorities concerned and, in practice, stops short of assured European integration. This was the situation until the legislative reform of 2004, which has introduced – at least this is the interpretation of the Commission and the European Parliament – an obligation to proceed to binding arbitration if no agreement is reached in the second phase, disregarding eventual application withdrawals by the applicant (Directive 2004/27/EC).

2.4 Institutional change, political Europeanisation and market integration

The four decades between 1960 and 2004 have witnessed different types and mechanisms of institutional change ranging from incremental steps to structural transformations. Different modes of Europeanisation or European governance have been experienced, and different degrees of market integration have been accomplished (Figure 3). The procedural mix or institutional diversity to which this policy development has led and which we have described above combines different logics or modes of integration and achieves different degrees of economic market integration.

Figure 3
EC pharmaceuticals authorisation - Integration strategies and stages



Two or even three “critical junctures” can be observed in this regulatory policy field.³² The Directive of 1965 obliging Member States to introduce formal marketing authorisation procedures was the first fundamental structural step in the European Community. Although one might argue that, due to the exogenous shock of the Thalidomide scandal, the introduction or extension of marketing approval had been on the agenda of all European governments, for the European level this Directive marked the European take-off in this policy field. In pursuing the EC Treaty goal of abolishing obstacles to trade and establishing a Common Market, this first step also applied a specific mode of integration: legal harmonisation of national regulatory policies was introduced with the expectation of voluntary mutual recognition by national authorities. This can be regarded as a weak mode of political Europeanisation and an equally weak and uncertain form of market integration.

³² For an explication of the concept of “critical juncture”, see Collier/Collier’s study of the regime dynamics in whole countries and societies Collier, Ruth B./David Collier, 1991: *Shaping the Political Arena*. Princeton: Princeton University Press..

The second and institutionally most important “critical juncture” so far was the introduction of the *Centralised Procedure* in 1995. It fundamentally altered the regulatory decision-making frame and integration approach – of course, only for those medicinal products for which the procedure was designed. Regulatory decision-making changed from national to European. The integration mode of this procedure became joint decision-making with final responsibility residing at the European level. Because of the practically decisive impact of the CPMP’s assessment and evaluation, this procedure is even leaning towards central direction. The decisions taken are valid in all EC Member States, institutionally guaranteeing a Single Market for these products. The national level is extensively integrated in this *Centralised Procedure*, but the Member States and their regulatory authorities have lost their singular decision-making autonomy.

A third structural change occurred with the legislative review of 2001-2004. As a result, the amended Directive dealing with the *Mutual Recognition or Decentralised Procedure* (see Figure 2) now contains the obligation to start binding arbitration at the central European level, should mutual recognition fail in the preceding phase of this procedure. If this interpretation of the amended Directive by the legal service of the Commission is correct,³³ then the *MRP/DP* would be deprived of the exit option for applicants and become truly European in the third phase. Thus, beginning as a nationally based procedure, the national level would lose its autonomy if the Member States affected by a multi-state application failed to arrive at mutual recognition or a consensus position. This is an interesting configuration where the same procedure can remain within the general frame of national regulation and belong to the integration mode and instruments of legal harmonisation and mutual recognition, combined with cooperative procedural requirements, but turn into a European joint decision-making procedure if mutual recognition fails. In the phase of binding arbitration, the regulatory decision-making process would resemble that of the *Centralised Procedure*, i.e. switch to the Europeanisation mode of joint decision-making. Economically this would mean only partial market integration because, on average, applications in the *MRP/DP* are targeted at less than half of the Member States (Feick 2002: 40-42).

In between the more or less profound structural changes, different modifications and extensions were introduced within the harmonisation and mutual recognition framework, which can be interpreted as incremental steps as regards substantive content and procedural measures. From 1965 to 1995 the standards to be observed by applicants when establishing and submitting the application data, on the one hand, and by national authorities when assessing and evaluating them, on the other, became increasingly detailed. Through these substantive and further procedural measures, EC pharmaceuticals regulation approached total harmonisation – albeit still on the basis of national autonomy.³⁴ Other incremental steps were

³³ See Interviews EU- 2004-03-24-2, EU- 2004-04-05, EU- 2004-04-14-1 and EU- 2004-06-24; once in force and applied this interpretation might be challenged by applicants in the ECJ.

³⁴ It should be added that, additionally, harmonisation measures beyond the EC contributed after 1990 to the incremental evolution of substantive standards in the context of the International Conference on Harmonisation (ICH) up to the point of the so-called Common Technical Document in 2000. This defines the standards that application data and application documents have to satisfy (see D’Arcy, P.F./D.W.G. Harron (eds.), 1992: *Proceedings of The First International Conference on Harmonization. Brussels 1991*. Belfast: The Queen’s University of Belfast.; Sickmüller, Barbara/Siegfried Throm, 2001: 10 Jahre ICH: Rückblick, aktueller Stand und Ausblick. In: *Pharmazeutische Industrie* 63, 546-555.; Franken, Andreas/Elmar Kroth, 2004: ICH 6-Konferenz. In: *Pharmazeutische Industrie* 66, 43-49.). These are

the institutionalisation of partly voluntary, partly obligatory procedures (1975/77, 1983, 1987), which did not oblige national regulatory authorities in their decision-making but were meant to foster communication and cooperation among these, thereby allowing for institutional learning. The institutions which were created in 1975 to facilitate the attainment of common positions in scientific assessments and evaluations were instrumental in this respect – the Scientific Committee (CPMP) as well as the Pharmaceutical Committee.

After the structural transformations in 1995/98 with the introduction of the *Centralised Procedure* and the *MRP/DP*, incremental changes occurred mainly with respect to additional harmonisation measures valid for regulatory decision-making at the national and the European levels, such as the guidelines for clinical testing. There have also been incremental changes since concerning the two European procedures alone, especially those of 2004, with changes in the regulatory scope of the *CP* and, in consequence, the *MRP/DP*, institutional changes with respect to the composition of the Scientific Committee of the European Agency (EMA) and of its supervisory administrative Management Board, an a more formal position of the *Mutual Recognition Facilitation Group (MRFG)* in the *MRP/DP*. These incremental steps contribute to further Europeanisation via the harmonisation of national legislation or the further development of European procedures.

What we can observe here is a sequential interactive process of incremental developments and structural transformations within a developmental and institutional framework that is characterised by the tension between a goal-oriented dynamic of Europeanisation and the institutional and orientational resistance of national regulatory systems. Incremental policy and institutional development has prepared the ground for structural or “transformational” changes (Bulmer/Burch 2001: 81) by demonstrating the limits of an existing institutional structure in the face of exogenous and endogenous challenges and, at the same time, has helped to form the orientational and organisational preconditions so that the structural institutional innovations could be envisaged as workable alternatives by policy-makers and affected parties alike. The phases of incremental change can be perceived as opportunities for institutional learning that provide incentives and also functional preconditions for the intentional structural transformations (see Chapter 3).

These institutional choices have been made on the basis of sector-specific preconditions and policy legacies, subsequently creating not only policy and institutional legacies but also dynamics of their own, and have allowed qualitatively new institutional structures to evolve. The European development in this policy field exhibits different strategies or modes of European integration, from legal harmonisation with the mechanism of mutual recognition to increasingly centralised regulatory decision-making within a joint decision-making framework ((Scharpf 2001b); (Scharpf 2001a)). What is especially characteristic and interesting in this policy field is that both different modes of integration and different levels of institutional development now exist simultaneously for practically the same task, the main differentiator being the type of medicine to be processed in approval procedures. This institutional variety is incorporated in the three different regulatory procedures. Their installation can be understood

voluntary agreements between the regulatory agencies and industry associations of the EU, USA and Japan and are integrated into regulatory implementation by the respective national and European agencies.

as a process of “institutional layering”, a specific mode of institutional change, whereby new institutional structures are added to existing ones, leaving the latter by and large intact but changing the character of the overall institutional configuration. Historically, these changes did “not push developments further along the same track, ...” but opened up the possibility of new structural paths – at the horizon or as alternatives in concrete decision-making situations. And, to a certain degree, “institutional conversion” took place insofar as, in the 1980s, relative priorities in the hierarchy of goals had changed (Thelen 2003: 226-228). Patient and public health protection was, of course, not abandoned, but lost in relative importance to the policy goals of industrial competitiveness, through reorientations that stressed regulatory efficiency and the regulatory costs to industry. We will take up this perspective again when discussing the accommodation of interests in this institutional mix in Chapter 4.

3 Policy-related learning in European pharmaceuticals approval

3.1 Conceptual remarks

“An entity” is supposed to learn “if, through its processing of information, the range of its potential behaviors is changed” (Huber 1991: 89). The result of information processing for learning can also be the confirmation of an already assumed action space. But even then, learning would have taken place insofar as such a confirmation reduces uncertainty.

The object of policy-related learning can be the development and implementation of policies as responses to given problematic situations. It can include substantive and institutional-organisational elements of such policies, as well as interactional orientations relevant for behaviour in policy-making or implementation. Learning for policy can occur in very different ways. It can include “lesson-drawing” (Rose 1991) through “learning from abroad” (Dolowitz/Marsh 2000) or through being based on internal comparisons perceiving “failings of a previous policy” (Hecl, 1974, 303). Learning can occur in a more intuitive, unplanned and even partly unconscious fashion, but the learning process itself can also be rationalised in a way that corresponds to what D. P. Moynihan termed the “professionalization of reform” (Moynihan 1965),³⁵ in which ex ante or ex post assessments and evaluations are systematically undertaken up to the point of sophisticated experimental designs. An important part of policy-related learning can be interaction learning, be it in the context of mutual collective search processes or in a competitive environment (March 1991). This kind of learning enables participants to behave in ways that possibly improve the overall results of interaction processes, i.e. policies or their implementation.

Peter Hall distinguishes three types of changes as results of “social learning” (Hall 1993: 278-279):

Third order change: This highest level of learning leads to changes in basic policy goals and “paradigmatic” policy approaches. In our case, the policy goals whose significance might

³⁵ See also Moynihan, Daniel Patrick, 1995: The Professionalization of Reform II. In: *The Public Interest*, 23-41. for an account not of the deprofessionalisation of reform but of the way professionally designed social reforms became anathema in the US or, at any rate, were crushed by the arguments of costs and deregulatory requirements, arguments brought forward mainly by economists: again, the same expert group that had advocated economic and social engineering in the sixties Moynihan, Daniel Patrick, 1965: The Professionalization of Reform. In: *The Public Interest* 1..

change are the protection of public health, the supply and accessibility of effective and safe medicines, the furthering of medicinal innovation and industrial competitiveness, or the “constitutional“ goal of creating a Single Market. With respect to EU governance, fundamental institutional questions such as the constitutional framing of the regulatory procedures, i.e. the distribution of institutional responsibility to the European or national levels, belong to changes of this order.

Second order change: This relates to the choice of policy programmes as derived from the more fundamental policy approach and goals – e.g. the decision in favour of formal marketing approvals, of post-marketing controls (pharmacovigilance), etc. – and the main instruments employed in these programmes, such as the types of tests to be performed, the application data to be provided, etc.

First order change: These changes relate to the operational level of implementation requirements such as directly applicable standards: e.g. norms and standards for testing, assessing and evaluating the quality, risks and efficacy of a medicinal product, which are meant to guide single-case regulatory decisions. To this category one might like to add the decision behaviour of regulatory authorities and the way in which regulatory authorities and regulatory interact in decision-making processes.

These policy-related categories can be collapsed into what is known in cybernetically originating system-theoretical learning models as simple or complex forms of learning, whereby the first defines feedback mechanisms of programmed technical responses on the basis of given goals, while the latter is conceptualised as a “goal-changing feedback” (Deutsch 1966: 92) characterised by the capacity of a system “to reprogram itself through the action of internal sources of new behavioral ideas, transformation motives and transformation behavior” (Dunn 1971: 21). In organisational theory a similar distinction is made with the concepts of single and double-loop learning. ((Argyris/Schön 1974) (Argyris/Schön 1978: # #)), and “between learning within a frame of reference and learning a new frame of reference”. But, as Huber notes, it might be difficult to find the two analytically separable types “to be distinct in practice” (Huber 1991: 93).

Policy decisions are not only, and probably most often to a lesser degree, the result of learning processes; other factors might play a more important role in political decision-making, where actors with their specific interests and power resources try to influence decision outputs in the face of constraints. But learning can play an important part in constituting preferences and influencing the concrete decision behaviour of actors. Proponents of learning concepts do not negate the validity of interest and resource-related action theories or choice models, but try to complement them in providing a longer term perspective (Jachtenfuchs/Huber 1993) on the evolution of new policy ideas and paradigmatic frames (Hall 1993), of preference structures at a more operational level or in providing interaction experiences which facilitate joint policy-making or implementation.

3.2 Policy-learning in European pharmaceuticals approval

Fundamental policy changes in the 20th century

The 20th century witnessed fundamental changes in the control of pharmaceuticals, the single most important factors or motives leading to these initial basic changes being dramatic drug accidents. But cost considerations for patients and health care systems played a role also, as

did rationing attempts in wartime economies ((Dukes 1986); (Dukes 1985); (Silverman/Lee 1974); (Feick 2000a)). There was a fundamental switch of policy concepts from industrial self-regulation to the establishment of state-based approval systems with increasingly comprehensive criteria, detailed standards and control procedures. These changes in policy concepts were accompanied by a market-economical justification of governmental intervention: market deficiencies – information asymmetries and lack of market transparency for patients (consumers) and even physicians – and, consequently, the failure of markets to function properly was taken as a justification for corrective governmental intervention. Regulation was seen as providing the public good of medicinal quality, safety and efficacy.³⁶

All regulations in the pharmaceuticals sector after the Second World War, national or European, were based on these fundamental changes to regulatory ideas, which were meant to react to perceived failures in medicine development, production, distribution and consumption. Learning in European countries in the early sixties meant searching for new regulatory design knowledge, mainly as "learning from abroad" (Dolowitz/Marsh 2000). The 1960s and 70s witnessed a form of 'policy tourism' by a number of European policy-makers, especially to the US, but also to countries like Sweden, in order to learn from the more advanced regulatory experiences of these countries.³⁷

EC policy experience: discrepancies between goals and reality

The discrepancy between espoused policy goals of the EC and the relative meagre achievements might have contributed to what has been termed in psychology "cognitive dissonance" (Festinger 1957). By the 1980s it had become quite evident that the goal of creating a Common Market and of abolishing obstacles to trade in the pharmaceuticals sector had not been achieved. Moreover, the EC pharmaceutical industry on the Continent was losing ground vis-à-vis its US-American and also the commercially still less important Japanese competitors, especially as far as pharmaceutical innovations were concerned (see above 1.3). Europe was becoming less attractive as a favourable site for the research, development and production of pharmaceuticals. The reasons which can be cited for this unsatisfactory situation

³⁶ That the concept of market failure and the activity of governmental regulation became fiercely debated under the heading of governmental or regulatory failure and that, starting in the seventies in the US, regulatory reform, deregulation and privatisation became the big issues should perhaps be mentioned (see for example Weidenbaum, Murray L., 1981: *Buseiness, Government, and the Public*. 2. Auflage. Englewood Cliffs, N.J.: Prentice-Hall., Argyris, Chris, et al., 1978: *Regulating Business: The Search for an Optimum*. San Francisco: Institute for Contemporary Studies., Schultze, Charles L., 1977: *The Public Use of Private Interest*. Washington, D.C.: Brookings., Weidenbaum, Murray, 1997: *Regulatory Process Reform. From Ford to Clinton*. In: *Regulation* 20., Feick, Jürgen, 1980: Zur Kritik regulativer Politik in den Vereinigten Staaten. In: *Politische Vierteljahresschrift* 21, 42-61.. These discussions focus on state–society (market) relations and presuppose rather clear borderlines between the public and the private spheres, an assumption which Kenneth Shepsle characterised as a fiction Shepsle, Kenneth A., 1979: *The Private Use of Public Interest (With Apologies to Charles L. Schultze)* Working Paper Number 46. St. Louis, Missouri: Center for the Study of American Business, Washington University..

³⁷ For Germany, see Hasskarl, H., 1978: Die internationale Interdependenz des neuen deutschen Arzneimittelrechts. In: H. Helmchen/B Müller-Oerlinghausen (eds.), *Psychiatrische Therapie-Forschung. Ethische und juristische Probleme*. Berlin / u.a.: Springer Verlag, 61 - 77.; this has been confirmed by participating policy-makers (see D 2000 - 1); from a comparative perspective, see Mayntz, Renate/Jürgen Feick, et al., 1982: *Regulative Politik und politisch-administrative Kultur. Ein Vergleich von fünf Ländern und vier Interventionsprogrammen*. Projektbericht. Köln: Institut für angewandte Sozialforschung. and Gephart, Werner, 1990: Kulturelle Aspekte des Rechts - Vom Klassen- zum Kulturparadigma? In: *Zeitschrift für Rechtssoziologie* 11, 177-187..

are manifold, but the failure to establish a large and appealing single pharmaceuticals market in the EC and the efficiency losses due to the non-Europeanisation of approval procedures were seen as one of the main causes for missing out on these and other policy goals.³⁸ Such a situation of “cognitive dissonance” can be remedied by adapting the goals and expectations to the deficiencies of a perceived reality or by adapting the means (policies, policy instruments and institutional arrangements) to the espoused goals. Both reactions can be observed.

Substantive policy changes in the context of learning

Since the “paradigmatic” third order changes in the policy concept at both EC and national levels in the 1960s, EC legislation on substantive policy content has been one of continuous reform. Over the years, the product and process standards to be observed, the tests to be performed and the controls to be undertaken have become more and more comprehensive and detailed. The breadth and intensity of harmonising regulation at the EC level have increased, as has the transforming Member State legislation, though with some national variation (see (Mayntz/Feick 1982: 120-179)). These incremental policy reforms – second order changes in Hall’s terms – can be interpreted partly as a dynamic evolving from the regulatory policy programme itself, whose missing parts have become progressively visible and have had to be inserted, and partly as a reaction to the non-attainment of the policy goals. The substantive policy development towards total harmonisation can be understood as a learning process. Policy actors, especially the EC Commission as the main driving force, but also Member States, have had to acknowledge that minimal harmonisation has been insufficient to achieve equivalent regulatory implementation conditions and results at the national level, and they have had to learn that even the quasi-total harmonisation of substantive rules have not led to market integration and a regulatory situation that would improve the innovativeness and competitiveness of the European pharmaceutical industry.

Institutional organisation in the context of learning

What has been said about changes in substantive policy content applies also in part to changes to the institutional organisation of approval procedures. There have been continuous, incremental attempts over two decades to strengthen the Europeanisation of drug approval by introducing institutional supports such as the introduction of two European bodies – the Pharmaceutical Committee and, especially important for implementation, the Scientific Committee (CPMP), both in 1975 – and the establishment of procedures intended to improve communication and cooperation among national regulatory authorities – the *Community Procedure* in 1975, the *Multi-State Procedure* in 1983, and the *Concertation Procedure* in 1987. All these incremental changes stopped short of establishing regulatory implementation competences at the European level, but tried instead to provide support for the practical harmonisation of implementation output at the national level. They were reactions to the failure to achieve mutual recognition, which was the aim of legislative harmonisation and favoured by Member States as the mechanism for market integration. When it had become evident that these incrementally improved supports for mutual recognition would remain insufficient, a third order learning step occurred which led to the introduction of a truly European procedure, the *Centralised Procedure*, albeit only for the innovative segment of the pharmaceuticals market. The logic behind this fundamental institutional change is the recognition that European

³⁸ Not only approval regulation influences these economic efficiencies, but other regulations also, such as price regulation and reimbursement regulation, which vary among EC Member States.

“centralisation of regulatory authority is the only way of ... preventing the local regulation ... from becoming a trade barrier” (Majone 1996:279-280). What makes the European situation so unique is that three different approval procedures have been used within the EU since 1995 which are applied according to the types of drugs to be processed and the number of national markets in the EU targeted for marketing. But this procedural mix cannot be understood solely as the result of a learning process.

Changes in the goal structure

The reversal of the integration approach has only been partial, restricted to the more innovative parts of the pharmaceuticals market. Both Europeanisation and integration modes – that of mutual recognition on the basis of national autonomy as well as that of joint decision-making at the European level – exist side by side. This means that the policy goal of establishing a Single Market has lost in priority relative to other goals such as industrial innovativeness and competitiveness. Neither the *Mutual Recognition Procedure*, nor the still existing national procedures contribute to the integration of the pharmaceuticals market. It is only the *Centralised Procedure* which contributes fully to this goal, while the other two procedures do not. This regulatory situation can be interpreted, utilising the concept of cognitive dissonance, as the adaptation of goals to a reality which cannot be changed in the short run. The constraints prohibiting a complete reversal of the institutional constellation direct our attention to the successful influence of interested actors (see chapter 4).

Interaction learning and the acquisition of trust

Besides learning from failures at the policy level, there has been administrative learning at the implementation level. Although the early policies and attempts at regulatory integration largely failed, they nevertheless provided a learning environment for regulatory policy-makers and administrators from the different EC Member States. These political and, above all, administrative interactions required in the purely nationally based procedures, which had been established in the seventies and eighties, contributed to the mutual understanding of national regulatory practices and the aptitude for joint discussions and consensus-building despite national differences in regulatory traditions and behaviour. This experience brought forth regulatory personnel in the national agencies who were actively disposed to European cooperation in regulatory matters.³⁹ It would be imprudent to understate the importance of this kind of interaction learning via interaction experiences as a prerequisite for the kind of joint decision-making foreseen in procedural centralisation. In these interactions and exchanges, participants mutually learn to understand each other’s regulatory systems, their functioning and embeddedness in the wider constitutional and political setting constraining the choices of national policy-makers and implementers. In interviews with national and European regulators, practically everybody involved in or closely observing the European regulatory system confirms that the development of European regulatory policies and institutions towards an increasingly

³⁹ It is quite impressive to learn in interviews from retired and active regulators alike just how much orientations and behaviour changed over time. Germany might serve as an example: while in the sixties and early seventies regulatory documents for internal ministerial circulation written in English might have been sent back unread with the written remark that this was not the official working language (interview D 2000 - 1), thirty years later increasingly large groups of regulators can be found in the national regulatory agencies who are not only able and willing to communicate easily and naturally in English as the most practical working language and to interact cooperatively with their counterparts in other national or European agencies, but who also take a personal interest in making European regulatory procedures work (interview D 2002 –1a, D 2002 – 1b).

close procedural Europeanisation of regulatory decision-making would not have been possible without this kind of learning experiences over several decades.

Interactions over the years have allowed for cognitive as well as affective learning. This has reduced uncertainty about the professional approaches and capacities of other actors, their positions with respect to specific substantive policy or implementation matters, and also such character traits as honesty and trustworthiness. These have been the ingredients in the evolution of mutual trust, a learning process enhanced by the fact that membership of the respective EC bodies (Pharmaceutical Committee in legislative policy-making, CPMP in regulatory implementation, now also the Standing Committee) have remained rather stable over longer periods of time. In the more technical implementation context, national participants experienced the difficulties of joint assessments and evaluations in the first European procedural attempts of 1975/1983, but they also experienced improvements in joint evaluations, especially in the *Concertation Procedure* of 1987. Although this positive experience was restricted to especially innovative medicinal products implementers and policy makers learnt that even joint regulatory decision-making might become a viable alternative. One might argue that the lack of mutual understanding and trust among national regulatory authorities made centralisation indispensable if the goals of market integration were to be achieved at all (Majone 1998: 32), but it is also true that joint decision-making in centralised European evaluation and decision-making procedures requires a certain degree of mutual understanding and trust in order to avoid malfunctioning or blockage. What had been expected by observers of European regulation especially after 1987 when the *Concertation Procedure* was established for “high-tech” medicinal products – that “la concertation qui s’en suit devant développer la confiance réciproque entre partenaires” (Duneau 1996: 36) – really happened and established an orientational basis for further institutional integration.

Learning: intentional and unplanned, by failures and successes

There has been “learning from search” (Huber 1991:96-100), especially during the first phase of EC pharmaceuticals’ regulatory policy in the 1960s, when national governments as well as the EC Commission were searching for policy models which could be adopted as a response to the Thalidomide catastrophe. There has been “intentional learning” from own experiences (Huber 1991: 88-89), especially on the basis of legislated evaluations of the newly established procedures in 1975/83 and 1987 or the *Centralised Procedure* and the *Decentralised or Mutual Recognition Procedures* of 1995 and 1995/98 respectively. These intentional learning processes through legislated evaluations have led to both the incremental and the structural changes described above. But much of what has been declared by participants ex post as learning took place rather unintentionally and unsystematically as a consequence of repetitive interaction experiences over longer periods of time in the environment of rather stable, partly overlapping memberships in political, administrative or scientific bodies.

There has been learning from negative experiences, on the one hand, as well as learning induced by positive feedback, on the other. A major negative learning experience has been the failure to attain espoused policy goals such as the creation of a Single Market for pharmaceuticals – and this has always occurred after each incremental stepping-up of legislative harmonisation or procedural attempts at fostering communication and cooperation among national regulatory agencies. These experiences have led to incremental procedural

improvements that stop short of abandoning national autonomy, on the one hand, but, ultimately, also to the structural institutional changes of 1995/98, on the other. The positive learning effect had been primarily established with the *Concertation Procedure* of 1987, showing that consensus in assessment and evaluation could be attained jointly in the CPMP and that the recommendations on innovative medicines had a good chance of predetermining the regulatory decisions of national authorities.

4. Actor interests and interest accommodation in regulatory institutionalisation and implementation

The development of consecutive policies, including their procedural-institutional implementation requirements, has not just been the result of policy-related learning processes. The regulatory patchwork of marketing approval policies for medicinal products in the European Community can also be interpreted, very generally, as an “isomorphic association” (DiMaggio/Powell 1991) of interest and regulatory constellations or as a relative equilibrium reflecting the interest and influence (power) structure in the pharmaceuticals sector as it has evolved over time. The main argument in this chapter is that the present procedural mix is able to take account of and largely integrate a requisite variety of influential interests in this policy field. Different regulatory implementation arenas are offered allowing actors to exploit the discretionary space of technological and scientific assessments (Abraham/Lewis 2000: 25-31) and administrative problem handling (Luhmann 1976). Despite maximally harmonised and comparatively dense substantive legislation there is still sufficient latitude for influential actors to have their specific orientations taken into account in the implementation process.

Although this kind of regulation depends on an especially high input of scientific and technical knowledge, it would nevertheless be misleading to ignore this discretionary space as a potential gate for the influence of interests.⁴⁰ There are multiple points where normative decisions have to be taken – from the definition of the problem(s), the formulation of policy programmes, the setting-up of institutional-procedural structures to the operationalisation of criteria via standards and their application on a case-by-case basis in the implementation process. There are many occasions where the question has to be asked: “How good is good enough?” (Cranor 1993: 28) – not only with respect to the political and administrative evaluations at the end of the regulatory decision-making process, but also when the scientific assessments of health risks and therapeutic benefits have to be made. In a practical regulatory sense a “cautionary note” is advised “that there are substantial limitations to the extent to which risk assessments can measure up to present standards of good scientific evidence and continue to serve the aims of regulatory institutions in which they are used”... because strict “fidelity to scientific tradition [would] produce regulatory paralysis” (Cranor 1993: 28). Scientific measurement itself requires normative decisions which cannot be rationalised completely through scientific discourse. Answers to questions such as “How long should toxicological tests with animals or clinical trials with patients take in order to assess risks and benefits – six, nine,

⁴⁰ For a general discussion on this issue, see Nelkin, Dorothy (ed.) 1979: *Controversy. Politics of technical decisions*. Beverly Hills: Sage. Jasanoff, Sheila, 1986: *Neutral Expertise*. In: Sheila Jasanoff (ed.) *Risk Management and Political Culture. A Comparative Study of Science in the Policy Context*. New York: Russell Sage Foundation, 69-77..

twelve months or longer?” or “Which safety tests are most appropriate and which safety thresholds should be examined?” establish the “scientific and technical” norms for the setting of regulatory standards. All these decisions within a scientific assessment framework, on the one hand, and a political management framework, on the other,⁴¹ are of the utmost importance for the distribution of regulatory costs and benefits among pharmaceutical companies, patients and health care providers, and – further down the impact chain – for the financing of medicinal supply through health care institutions. Therefore, it is evident that regulatory institutional frameworks which distribute access to and influence in regulatory decision-making processes with respect to policy development and policy implementation are of specific importance to political, economic and other actors. Our investigation will focus especially on these institutional questions when analysing the three separate procedural alternatives.

4.1 Relevant actors, their interests and political resources

Interests are an important component of actors’ preferences. They constitute a relatively stable motivational background for action, and should not be confused with the more flexible behavioural intentions, which can be adapted to specific decision-making situations. They can be conceptualised as self-interest including self-preservation, and the securing of autonomy and of growth oriented towards the actor’s specific goals.⁴² We can roughly distinguish four major groups of actors as being obviously or potentially affected by marketing approval regulations for pharmaceuticals⁴³:

- the *pharmaceutical industry* as the main target of this regulatory policy and the *interest associations* that represent it;
- European and national *regulatory authorities*, comprising policy-making as well as operational levels;
- affected “*user groups*” such as patients and health care professionals and their *associations*;
- *expert observers*” of different background, with different motives and liaisons.

The pharmaceutical industry

Because regulations can “represent important sources of competitive advantage and disadvantage for firms” (Vogel 1995: 12) *pharmaceutical companies* – and the *interest associations* representing them – have a vital interest in influencing marketing approval policies and their implementation in order to keep market entry as cost-effective as possible for their specific product ranges.

The situation is complicated by the fact that enormous differences of interest exist within the pharmaceutical industry, mainly based on the type of medicinal product developed, produced and distributed, as well as by the likelihood that the same pharmaceutical company might be active in different product markets. Therefore, expectations and demands on policy-making and implementation – e.g. approval criteria, standards of control and implementation procedures – can vary substantially among groups of pharmaceutical enterprises and even within the same company. The more traditional, less innovative, less research-intensive and less internationalised medicines tend to be produced by smaller or medium-sized companies

⁴¹ For the distinction between “risk assessment” and “risk management”, see Breyer, Stephen, 1993: *Breaking the vicious circle. Toward effective risk regulation*. Cambridge: Harvard University Press..

⁴² For a detailed discussion of the concepts, see Scharpf (2000: 116-122).

with comparatively low investment in research, smaller organisational and financial capacities, and the practice of targeting just a few or even single national markets. Their capacities for complying with demanding substantive standards and their regulatory competences for facing internationalised procedural environments are comparatively low. On the other side of the spectrum are companies whose strength are predominantly innovative medicinal products and which are generally the bigger players in the industry.⁴⁴ High research and development costs, an international orientation and high regulatory competence characterise these companies. Such a dichotomous differentiation between companies simplifies the real situation, but is justified in the light of our main question because it suggests different interests at work with respect to regulation. The first group prefers approval criteria, standards and implementation procedures which are anchored in national or regional policies and regulatory environments that make allowances for national pharmaceutical and therapeutic traditions. A regulatory policy that is internationalised by opening up larger markets with as few approval procedures as possible, applying regulatory criteria uniformly and even more strictly, suits more the interests of the second group of companies, which may even derive competitive advantages from a more resource-demanding regulatory environment.⁴⁵ A third group, the generics industry, needs to be mentioned. This group waits for the patents of innovative medicines to expire so that it can then produce generic versions (copies) of original products at lower costs and supply them at lower prices. Its interests can differ widely from those of the innovative industry as far as specific areas of regulation are concerned (e.g. patent and application-data protection, price and reimbursement regulation), but as regards marketing approval in the EC their position is quite close to that of the innovative, research-based companies.

There are, nevertheless, generalised interests across the pharmaceutical industry. These interests entail, first, the reduction of regulatory costs whatever the concrete institutional regulatory situation might be and, second, the preference of flexibility within the European regulatory framework, meaning freedom of choice among the different procedural alternatives. This general preference of flexibility in procedural choice has to do also with the above mentioned fact that even large multinational pharmaceutical conglomerates whose strength are innovations produce a variety of product lines. Direct or indirect activities in the generics and OTC (self medication) markets can be substantial.⁴⁶ But even here large companies invest in OTC-products with an international market potential while self-medication products targeted at

⁴³ The simplified characterisations of the interests of different corporate actors or actor groups are based on primary documents, secondary literature and interviews.

⁴⁴ This category also includes innovative small or medium-sized companies which occupy highly specialised niches and are nowadays especially active in the area of biotechnology and genetically engineered medicines. However, they are often associated with larger, internationalised companies in one way or the other.

⁴⁵ This is the experience gained from interviews with large and smaller pharmaceutical companies evaluating the regulatory reforms of 1976 in Germany (see Mayntz, Renate/Jürgen Feick, et al., 1982: *Regulative Politik und politisch-administrative Kultur. Ein Vergleich von fünf Ländern und vier Interventionsprogrammen*. Projektbericht. Köln: Institut für angewandte Sozialforschung.). Lindblom cites an example in the US's food sector, where the large meat packers had favoured stricter inspections that disadvantaged the smaller meat packers, who could scarcely bear the additional costs of stricter governmental controls Lindblom, Charles E., 1977: *Politics and Markets. The World's Political-Economic Systems*. New York: Basic Books..

⁴⁶ It is rare that a large multinational actually concentrates on less innovative medicines, an exception being Bayer, Germany, which is just planning to buy the OTC-sector from Roche with the aim of becoming a world leader in the self-medication market. Wassener, Bettina, 2004: Bayer in € 2.4bn deal for Roche's OTC arm. In: *Financial Times*, July 20, 2004, S. 15.

national or regional markets are the domain of smaller companies which often even depend economically on this type of medicines.

The diversity of interest constellations in the pharmaceutical industry is mirrored in the variety of interest associations at both the national and the European levels. There are associations representing the innovative, research-based, internationally oriented industry (at EC level, the EFPIA), the generics industry (at EC level, the EGA) and the companies producing more traditional medicines for the non-prescription, partly even non-pharmacy, market, also referred to as OTC (over-the-counter) medicines (the association at EC-level is the AESGP).

In general, the pharmaceutical industry and its associations, together with certain single large companies, are the most potent private actors in this policy field, the EFPIA being certainly the most resourceful and powerful of the European associations (see (Greenwood/Ronit 1992); (Greenwood 1995)). But as the recent regulatory review (2001-2004) has shown, the other two European associations have had quite some impact on this legislative process, too.⁴⁷ Industry and its associations have developed great organisational action capacity, entertain the most densely knit network of contacts and have the easiest access to and the most frequent contacts with practically all political institutions and competent administrative bodies. Their capacity to marshal information and expertise relevant for regulatory policies and to cooperate with or to mobilise other private actors (e.g. certain patient groups, large parts of the scientific community and doctors) and to lobby forcefully with politicians and administrative heads is unrivalled by other actors. Although one can scarcely overestimate the influence potential of the pharmaceutical industry, this does not mean that it always gets what it wants. This has to do with conflicting interests within industry, on the one hand, and with the existence of important adversaries and a professional, public and political environment, on the other, which is partly characterised by suspicion of an industry whose profits and economic stakes are high and which has not always proven trustworthy.

National and European regulatory authorities

The *political regulatory institutions* at the national level comprise the competent *ministries* and *implementation authorities*. At EC level it is the *European Commission* as the most community-oriented political actor and, since 1995, its evaluative agency, the *EMEA* with the *CPMP* (since 2004 the *CHMP*), as the scientific expert committee. The *European Council* together with the corresponding bodies of *Coreper* and the *Working Party* links the national governments to the European decision-making processes. Thus it has a transmission function for national governmental positions as well as the function of constructing a joint European position starting from different national positions. On the operational implementation level, the *CPMP* has a similar dual function, being composed of representatives of the national regulatory agencies and commissioned to effect European assessments and evaluations. The *European Parliament*, like the Commission a primarily community-oriented institution, has played an important role in the legislative review of 2001-2004 due to the application of legislative co-determination (Art 252 TEC). Before that, it had only a consultation role. Nevertheless, it can be shown that the *EP* has been the most reliable policy-coalition partner of the *Commission* when it comes to strengthening the European level in regulatory decision-making in this sector

⁴⁷ See the ongoing, and soon to be completed, research project on the political process of the legislative review of 2001-2004 (<http://www.mpi-fg-koeln.mpg.de/review/>).

(Deboyser 1991: 171). Even in the late 1980s it would have preferred a more courageous step being taken towards regulatory centralisation than that which was realised with the Regulation and Directives of 1993.

Although substantive topics of regulatory Europeanisation have been important in the face of national regulatory traditions, the focus of this paper is mainly directed at the institutional questions of access to and participation in the procedures of regulatory decision-making at the policy-making and, even more so, at the implementation level. Regulatory internationalisation or even supranationalisation runs counter to the interest of *national institutions* in regulatory autonomy, at least that of *Member States* with a substantial regulatory infrastructure and capacity. Even the very organisational existence of implementing agencies could be at stake due to the Europeanisation of implementation responsibility. Only in countries with a lower regulatory capacity is there greater willingness to cooperate with other regulatory agencies in approval matters, to adopt their decisions or, ultimately, to agree to regulatory centralisation at the European level. Otherwise, self-interest in regulatory autonomy and organisational survival prevails. And whenever other goals and interests suggest the acceptance of supranational implementation structures and procedures, then there is at least a strong demand for participatory structures which fully integrate national authorities into the European implementation procedures giving them a “voice” and making their requisite regulatory capacities indispensable.

The *European Commission* and its *Pharmaceutical Unit* have always been driving forces and the principal advocates of both substantive and procedural harmonisation and – after the failure of the mutual recognition strategy – of the Europeanisation of regulatory decision-making, their main European motives being the establishment of the Single Market and the attainment of industrial policy goals such as the competitiveness and innovativeness of the EU-based pharmaceutical industry.⁴⁸ In this framework, the *Commission* has shown an interest in establishing or expanding regulatory competences. With the introduction of the *Centralised Procedure* in 1995, in 2004 the enlargement of its scope, the further Europeanisation of the *Mutual Recognition/ Decentralised Procedure* and the strengthening of the European authorities' impact on EMEA and its bodies, the *Commission* has succeeded in realising these organisationally self-interested goals for parts of the pharmaceuticals market. And, together with the *EMEA* and the CPMP, it has been eager to demonstrate its abilities as an effective and efficient regulator.

“Users” and experts: consumers, patients and doctors – internal and external experts

The “users” are a very heterogeneous group and normally not directly or predominantly involved in the policy-making or implementation process. Their importance and potential impact rests is predicated on two aspects: they can be useful as advocates in policy coalitions (Sabatier 1975)) and their heterogeneous interests have to be taken into account somehow by policy-makers because they represent a large voter reservoir and because some of them possess strong qualities as multipliers.

⁴⁸ Of course, governments of Member States with a concerned industry also share these industrial policy goals.

There are *consumer protection organisations*, on the European level in particular BEUC, which has been in favour of institutional Europeanisation for many years and, as such, is a supporter of Commission proposals which lean in this direction (Sermeus/Adriaenssens 1984). As an advocate of strict safety controls and transparency with respect to data and procedures, BEUC was a natural ally of all those groups and individual actors with a rather critical view of the pharmaceutical industry and implementing authorities. As far as specific *patient groups* are concerned, there have been initiatives lately concerning rare or especially severe diseases such as Aids, Alzheimer's, Parkinson's etc., for which no or insufficient medicinal treatments exist. These groups have been in favour of pharmaceutical and therapeutic innovations and rapid access to treatments, sometimes even at the cost of lower safety levels. Some of these groups have been supported by industry and have played the role of policy-coalition partners (see, for example, (EFPIA 1999)). Taking the *prescribing medical practitioners* and their *patients* as a whole, a wide range of therapeutic preferences, varying between and within countries according to therapeutic traditions, has to be serviced in order to satisfy these "user" groups. These specific interests are taken care of mainly at the national level and are transported into European decision-making primarily via national governments, national regulatory authorities and Members of the European Parliament.

Scientific experts play a vital role in this regulatory field, especially those *inside the regulatory process* as experts for industry as well as those for regulatory authorities. This is a rather small world considering the differentiation into highly specialised pharmacological, toxicological and medical fields and the fact that the number of very good specialists is rather limited. These persons are well known and, if not tied to an institution, in high demand by the industry and regulatory authorities as external experts, often providing their expertise to both sides (see interview EU / F 2001-07-13). This situation is criticised by other *outside experts* who are not directly or indirectly involved in regulatory matters but who understand their role as critical watchdogs of the industry and regulatory authorities, generally presupposing that industry's influence on regulators is too strong, that the regulatory process is not open and transparent enough, and that the safety and health of patients is at risk of being ranked behind commercial and industrial policy goals. Often these critical experts can be linked to or cooperate with consumer protection organisations. Some of them are editors of or contributors to professional journals or drug bulletins. Their power base is rather limited compared to experts working directly with pharmaceutical companies, associations or regulatory institutions. If they have an impact, it is more through their potential as credible informants of a professional or even larger public.

4.2 The widening of policy options in the late 1980s⁴⁹

For roughly 25 years the idea of regulatory centralisation at EC level was refuted and abandoned whenever it emerged as a solution to the Common Market problem. Given the heterogeneity of interests and the fear of European super-bureaucratisation, industry was, to say the least, ambivalent in its position on centralisation of regulatory authority. There was advocacy of such a solution by the European consumer organisation BEUC (Bureau Européen des Unions de Consommateurs), which expected stricter safety controls and less industry protection from the Europeanisation of regulatory implementation. Member States with their veto power were for the most part still against such an institutional change. At least the larger national regulatory agencies were not fond of surrendering regulatory autonomy, preferring the nationally based mutual recognition framework and, even then, avoiding the structural change towards automatic mutual recognition but defending instead a voluntaristic implementation regime (Vos 1999: 210). Therefore, two questions arise: Why was the strategic change at the beginning of the 1990s, with the introduction of a European-based approval procedure, possible at all? And, if such a strategic change was envisaged, why was it only a partial one and not a complete substitution of the nationally based procedures, given the practically total legal harmonisation in this field, the highly scientific nature of this regulation, the largely disappointing experiences with mutual recognition, and the development of cooperative working relationships among national regulators at the European level over the years?

The hypothesis is that the basic interest constellation had not, or not substantially, changed, but that the regulatory strategy pursued by the Commission in particular had been adapted to the prevailing interest structure, on the one hand, and to a modified hierarchy of goals, on the other – all this on the basis of 25 years of policy-related learning. For obvious reasons the safety issue dominated public discourse in the 1960s and 1970s, while the issues of industrial competitiveness, pharmaceutical innovativeness, and regulatory efficiency gained in prominence in the 1980s. In the light of tough international competition and the decreasing attractiveness of Europe as a research and production site for the pharmaceutical industry (Bangemann 1994), the regulatory costs and inefficiencies, along with the lack of a common market for pharmaceuticals, became major concerns, at least with respect to the more innovative part of the medicinal market.⁵⁰ The disparities in innovativeness and

⁴⁹ For this paragraph, see especially Abraham, John/Graham Lewis, 2000: *Regulating Medicines in Europe. Competition, expertise and public health*. London and New York: Routledge.; Bel, Nicolaas, 1975: L'oeuvre Communautaire en Matière d'Harmonisation des Législations des Produits Pharmaceutiques. In: *REVUE DU MARCHÉ COMMUN*, 505-514.; Bel, Nicolaas, 1980: Die Entwicklung der pharmazeutischen Gesetzgebung in der EWG. In: *Pharmazeutische Industrie* 42, 38.; Brunet, Philippe, 1999: *Dictionary of the Main Reference Terms. Pharmaceutical Law in the European Union*. Paris: Editions de Santé.; Deboyser, Patrick, 1991: Le marché unique des produits pharmaceutiques. In: *Revue du Marché Unique Européen* 3, 101-176.; Hancher, Leigh, 1990: *Regulating for Competition: Government, Law, and the Pharmaceutical Industry in the United Kingdom and France*. Oxford: Clarendon Press.; Hart, Dieter/Norbert Reich, 1990: *Integration und Recht des Arzneimittelmarktes in der EG. Eine Untersuchung zum Produkt- und Marktrecht der Gemeinschaft und ausgewählter Mitgliedstaaten*. Baden-Baden: Nomos Verlagsgesellschaft.. It is also based on primary documents and interviews with participating actors at the national and European levels.

⁵⁰ See, for example, Kaufer, Erich, 1990: The Regulation of New Product Development in the Drug Industry. In: Giandomenico Majone (ed.) *Deregulation or Re-regulation? Regulatory Reform in Europe and the United States*. London: Pinter Publishers, 153-175.; Ager, Brian (General Director of EFPIA), 1996: European construction and research: industry expectations. In: ABPI SNIP (ed.) *Le médicament: une ambition pour l'Europe? Colloque organisé le 15 septembre 1995, Palais du Luxembourg, Paris*. Paris: John Libbey Eurotext, 113-119.; Sauer, Fernand, 1997: A New and Fast Drug Approval System in

competitiveness, especially between Europe and the United States, and the industrial advantages of a large single market for pharmaceuticals were emphasised.⁵¹ This changing perception of the policy problems in the late 1980s and early 1990s also increased the prospects of more fundamental regulatory changes, especially in the innovative pharmaceutical sector. And, of course, the establishment of a Common Market was still the 'constitutional' goal of the EC – emphasised again in the White Paper of 1985 and the Single European Act of 1986, and envisaged for 1992 in the pharmaceutical sector too. Beside existing national disparities in the regulation of national health care systems and prices for pharmaceuticals – about which the EC could do virtually nothing (Burstall 1996: 108-109) – the diverse, cumbersome, time-consuming and costly system of nationally based marketing approval could be blamed for preventing a Single Market, missing efficiency gains and, thus, for forfeiting industrial competitiveness and innovativeness.

The partial change in the Commission's official approach to European pharmaceuticals regulation in the late 1980s was also the result of the aforementioned learning process, corresponded to its specific task as EC Commission as to the espoused European policy goals and was in line with its institutional interest of extending its implementation competences. There was also rising discontent in parts of the pharmaceutical industry, whose negative experiences with the mechanism of mutual recognition nourished the ideas of an EC-wide approval system (Vos/Hagemeister 2000: 22). It was the more innovative and internationally oriented segment of the pharmaceutical industry which combined its emerging preference for centralisation with its interest in more efficient regulatory procedures and lower concomitant regulatory costs. Moreover, the relation between this internationally inclined and research-oriented part of the industry and both the Commission and the Committee for Proprietary Medicinal Products had become rather cooperative and close over the years. So, this part of the industry could be regarded as a policy-coalition partner of the Commission (Ager 1996: 116). However, given the heterogeneous policy preferences within industry as a whole, there was no plea for a complete reversal of the regulatory regime. The following citations from a memorandum of February 1992 by Rhône-Poulenc Rorer (RPR) – a then French multinational which later merged with Hoechst to become Aventis – are symptomatic of the position of the pharmaceutical industry: "RPR has used the existing Community level procedures to obtain marketing authorisations ... However, the existing multi-state procedure (...) has been beset by disagreements between the authorities of the Member States and RPR is keen to see the

Europe. In: *Drug Information Journal* 31, 1-6.; Majone, Giandomenico, 2002: What Price Safety? The Precautionary Principle and its Policy Implications. In: *Journal of Common Market Studies (JCMS)* 40, 89-109.. It is revealing that the safety issue was ranked last in a recent speech by the competent Commissioner on the legislative review – behind industrial competitiveness, the challenge of enlargement, development of the European science base, therapeutic innovation and quick access to medicinal products. Liikanen, Eric, Member of the European Commission, responsible for Enterprise and the Information Society, 2002: Pharmaceuticals in Europe. Getting the Future Legal Framework Right. Paper presented at onference on 8th Annual Pharmaceuticals Conference, London, 14 February 2002. <<http://europa.eu.int>>

⁵¹ See Burstall, E. G-Kommission: M.L., 1985: The Community's Pharmaceutical Industry. In: *Luxembourg: Office for Official Publications of the European Communities, 1985.*; Economists/Advisory Group, 1988: *The "Cost of Non-Europe" in the Pharmaceutical Industry*, Research on the "Cost of Non-Europe". Vol. 15. Luxembourg: Office for Official Publications of the European Communities.; Cecchini, Paolo, et al., 1988: *The European Challenge 1992. The Benefits of a Single Market*. Hants: Wildwood House.; REMIT, 1997: *Pharmaceutical products*, The Single Market Review. Subseries I. Vol. 2. Luxembourg: Office for Official Publications of the European Communities.; Gambardella, Alfonso/Luigi Orsenigo/Pammolli Fabio, 2000: *Global Competitiveness in Pharmaceuticals - A European Perspective*.

current procedures develop into a system for drug approval which is effective, authoritative and speedy. ... RPR supports the concept of twin procedures (decentralised and centralised) in the Commission's proposal. It does however wish to see equality between these two different routes with a free choice of routes for applicants and mechanisms to achieve clear binding decisions. ... it [RPR] has some misgivings regarding the Agency proposed since it perceives there is a danger that this could become a large bureaucratic and non-responsive organisation. RPR has also concern in that the Commission's proposal envisages quite a rapid shift from the national to the new European procedures. It is vitally important ... that a step-by-step approach is taken, ..." (Rorer 1992, February: 56). Industry wanted efficient procedures, not full-blown centralisation, nor any large-scale European regulatory bureaucracy, but flexibility of procedural choice, and a step-by-step approach towards Europeanisation.

An orientational change had also emerged with the governments, especially Member States that had a significant research-based and internationalised pharmaceutical industry. Governments were well aware of the international competition in which, above all, US-American companies had taken the lead with respect to medicinal innovations and economic success. But national governments, generally, had to represent a wide spectrum of interests besides pursuing their more selfish goal of regulatory autonomy.

That, in the end, the necessary consensus for the radical structural transformation could be achieved in the European Council⁵² was not merely due to the changing perception of the policy problems, the effectiveness of policy-related learning and the situational adaptation of actor preferences; it was also due to the nuanced, multi-faceted regulatory proposal presented by the EC Commission that was discussed in the late 1980s and early 1990s. It represented an institutional accommodation of a wide variety of interests⁵³, which facilitated unanimous adoption of the Regulation and Directives in the Council in 1993.

4.3 Interest accommodation in the institutional structure of the three procedures

This availability of three different procedures serving basically the same regulatory purpose of marketing authorisation provides not only the directly involved but also either the directly or indirectly affected institutions, organisations and groups with a range of opportunities and regulatory results, allowing them to find their specific interests more or less sufficiently represented in this procedural policy mix. The maintenance of such an interest-based variety of

⁵² Even though the Single European Act of 1986 had introduced qualified majority decisions in the Council in many areas of harmonisation, Art. 100a of the Treaty of the European Communities (TEC) could not be applied in the case of regulatory centralisation because of the transfer of the operative regulatory sovereignty of EC Member States and the establishment of a new European institution, the EMEA (Thompson 1994: 4-5); the Commission had first thought that qualified majority would suffice and was surprised by the "bombshell" of its legal service in 1992 when this advised that, not Art. 100a, but Art. 235 would be the correct legal basis House of Commons: Health Committee, Third Report, 1992, March: *The European Community and Health Policy. Report together with an appendix, the proceedings of the Committee, minutes and evidence and appendices*. London: HMSO..

Table 2
Authorisation procedures in the EU and actor interests/preferences*
 - before regulatory changes of legislative review 2001-2003/04

actors	procedures		
	national procedures	Mutual Recognition/ Decentralised Procedure	Centralised Procedure
EC-Commission	---	- potential of regulatory Europeanisation	- extension of competence - regulatory Europeanisation - Single Market - industrial policy goals
	- no Europeanisation - no Single Market	- Europeanisation uncertain - Single Market unlikely	- influence of national authorities
national governments (ministries)	- national autonomy - protection of less innovative industry and employment	- national autonomy - protection of industry and employment	- participation in comitology - industrial policy goals
	---	- potential loss of autonomy	- loss of autonomy
national regulatory authorities (mainly agencies)	- organisational survival - organisational autonomy	- organisational survival - organisational autonomy	- organisational survival - organisational involvement
	---	-	- loss of control
		regulatory competition among national implementing authorities	
Industry	flexibility of procedural choice adapted to product range of enterprises		
product 1 - research-intensive - innovative medicines - internationally oriented	---	---	- rationalisation and efficiency - market size - regulatory orientation: international, innovative
	---	---	---
product 2 - less research-intensive - less innovative (generics; partly new but less innovative products) - internationally or multi-nationally oriented	---	- selective choice of markets	- rationalisation and efficiency - market size - regulatory orientation: international, innovative
	---	- complexity and length of procedures - lack of mutual recognition	- demanding application requirements (documentation, fees)
product 3 - not research-intensive - traditional medicines - more nationally oriented	- accustomed regulatory environment - market protection - economic survival	- accustomed regulatory environment - market protection - economic survival	--- (no access)
	- length of procedures	- complexity and length of procedures - lack of mutual recognition	---
medical profession/ patient groups 1	variety of medicinal products		
	medicines adapted to national/regional medical traditions/ demands		- fast EU-wide availability of innovative medicines
	---	---	- too strict for specific indications
medical profession/ consumer groups 2 ("pharmaceutical and medical critics")	---	---	- improved transparency - comparatively strict
	- less transparent national procedures - country-specific regulatory strictness		- still not transparent and strict enough
	too much influence or consideration of industry interests		

positive for actor

negative for actor

*The assessments in this table are based on primary documents, secondary sources, including surveys, and on interviews. Nevertheless they are simplifying taxonomies.

⁵³ This corresponds to Héritier's observation of an "accommodation of diversity" in European environmental policy within a "policy patchwork" (Héritier 1996).

procedures might be interpreted as an isomorphic constellation (DiMaggio/W. 1983), which relates the given interest configuration to the resulting institutional policy output.

The national procedures

They accommodate the interests of those mainly *smaller or medium-sized companies* which primarily produce so-called "traditional", often scientifically and therapeutically less demanding medications for a smaller clientele that is defined by national medical-cultural traditions. These companies would rarely have the resources to stand more demanding and more costly regulatory processes. The national approval alternative can be vital for their economic survival. Depending on the industrial structure of a *Member State*, the contribution of those less innovative companies to GDP and

employment can be important for *national governments*. Furthermore, their product range corresponds to the national medicinal demands of certain groups of *doctors and patients*. Even when prevailing pharmacological and therapeutic schools of thought are critical with respect to these 'traditional' or 'alternative' medicines, there are enough *health care professionals and patients* whose cognitive and evaluative orientations support therapies which employ them. And *politicians*, members of national governments and parliaments, cannot afford to ignore these groups for their own political self-interest; in fact, the degree to which influential politicians and symbolic public figures actively share these preferences has been a surprising experience for some policy-making participants.⁵⁴ At the same time, national approval procedures guarantee the organisational existence and regulatory autonomy of *national regulatory authorities*, whose regulatory output provides a range of nationally demanded medications that could be put at risk by the uniformity of a European Centralised Procedure.

The Mutual Recognition and the Decentralised Procedure (MRP, DP)

A partly similar consideration of interests can be established with respect to the *MRP/DP*. This procedure allows the *applicant (the pharmaceutical entrepreneur)* to strategically choose to serve multiple national markets according to the type of products demanded and offered and the regulatory as well as marketing capacities of the applicant. But it is not just *small and medium-sized companies* that appreciate this procedural alternative. As long as part of the new medicinal products (those with new active ingredients or chemical entities), may, but are not obliged, to utilise the *Centralised Procedure*, the *MRP* applies to many categories of medicines and is therefore of interest to *large companies* as well, most of which offer a wide variety of medicines and do not want to miss the provided flexibility of procedural choice. The processing of the applications and the final decision remains under the control of *national regulatory administrations* and is only transferred to the European level of centralised binding evaluation

⁵⁴ In the debates surrounding the German Pharmaceutical Law (Arzneimittelgesetz) of 1976 influential members of the German parliament and the executive branch strongly supported the protection of so-called alternative therapies and medicines such as natural, anthroposophical or homeopathic medical treatments, making sure that especially the requirements for proof of efficacy did not represent insurmountable hurdles (Murswiek 1983). From the UK it is known that there are prominent supporters of these 'soft' medical therapies – for example in the Royal Family. Depending on the medical tradition and culture of the different Member States, these specific therapies have been protected from too stringent regulation.

in very rare cases. Thus the *MRP/DP* protects the interest of *national authorities* in regulatory autonomy and organisational continuity. They are therefore in favour of it, actually even more so than the concerned *pharmaceutical companies*, which criticise its inefficiencies in the evaluation of 2000 (European Commission 2000). The satisfaction of many *national regulatory authorities* actually stems from the relative failure of this quasi-European procedure to arrive at binding arbitration in the event of dissenting national regulatory agencies. As applying companies have an economic incentive to withdraw their application from dissenting Member States – they are not allowed to market in any Member State before the phase of binding arbitration has been completed – the European decision-making level (the third phase, see Figure 2) is only rarely reached.⁵⁵ This interest-driven behaviour on the part of applying companies, in turn, allows national authorities to adhere to their dissenting opinion without the risk of being subjected to and overturned in arbitration proceedings.

Table 3

New applications in the Centralised and Mutual Recognition Procedures
Number of applications submitted

	CP	MRP/DP
1995	36	30
1996	35	141
1997	60	190
1998	45	183
1999	51	275
2000	54	373
2001	58	484
2002	31	587
2003	39	620
∑ 1995-2003	409	2.883

CP: Applications by medicinal product; pharmaceuticals categories A and B.

MRP: Applications = procedures irrespective of number of countries involved.

Sources: EMEA Annual Reports 1996-2003 (always most recent and revised data)

From the point of view of the *EU Commission*, which is striving for the Europeanisation of regulatory policy – not least because this will also contribute to the establishment of a Single Market –, neither of the aforementioned, still nationally based procedures is satisfactory. On the contrary, they actually lead to or even reinforce differences in the availability of medicinal products between countries, because applications in the *MRP/DP*-framework by far outweigh those in the *Centralised Procedure* (see Table 3) – not even counting the purely national applications and, so far, have not brought about equal access (Feick 2002: 38-42; see also Table 4). In the legislative review of 2001-2004, therefore, the Commission tried, first, to enlarge the scope of applicability of the *Centralised Procedure* by obliging all new medicines (NCE = new chemical entities) to follow this regulatory procedure and, second, to introduce

⁵⁵ The review of 2001-2004 has changed this. Binding arbitration is now obligatory, and companies no longer have to wait for the result of European arbitration before marketing in consenting Member States.

obligatory binding arbitration in the *Mutual Recognition/Decentralised Procedure*. The *European Parliament* supported this position: With respect to the first aim, there was strong opposition from many *Member States* and, partly, *industry* too before a compromise was reached. As to the second aim, the *Member States* gave in even though the respective articles of the Directive might still be a matter of judicial interpretation.

Table 4

Diversity in the European medicines market

Mutual availability of active ingredients: country 1 → country 2 (%)

Country 1 \ Country 2	AUT	B	DK	F *	GER	NL	S	UK
AUT	-	59	49	43	81	57	48	54
B	72	-	55	52	79	66	52	60
DK	81	73	-	60	84	76	73	71
F *	74	69	58	-	75	68	58	63
GER	68	54	43	42	-	50	42	49
NL	80	76	65	56	84	-	61	69
S	79	71	74	59	83	72	-	70
UK	68	62	55	60	73	62	53	-

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

Sources: EURO-Medicines Database; Folino-Gallo, P. et al. 2001, Availability of medicines in the European Union, in *European Journal of Pharmacology*, 57: 443

* EURO-Medicines Database, <http://www.euromedicines.org/index2.html>,
date of consultation: 23.11.2001

The Centralised Procedure

Out of all the procedures this one alone meets the stipulated goal of regulatory Europeanisation, guaranteeing access to the whole European market via one application and establishing a Single Market. It also fulfils efficiency demands by reducing regulatory approval time and overall regulatory costs. A larger product market with its economies of scale is supposed to stimulate pharmaceutical innovation and to foster the international competitiveness of Europe as a site for pharmaceutical research, development and production. For these reasons it is welcomed not only by industry but also by most other concerned or interested actors. In addition, the *Commission* looks favourably on it to extend its regulatory competences. It has the support of the *Member States*, too, because of their basic agreement with the aforementioned goals, at least insofar as it deals with the most advanced pharmaceutical products. The *pharmaceutical companies* for whose product range this procedure was introduced in 1995 are those which invest heavily in research and development, are internationally oriented and so are able to handle internationalised and more demanding regulations. They not only had no reason to fear regulatory Europeanisation but, on the contrary, could even hope to profit from regulatory efficiency gains. On the part of the 'user groups' (doctors, patients), there is an interest in faster marketing authorisation and Europe-wide access to therapeutic innovations. Among the most critical observers of the pharmaceutical industry and regulatory authorities there are those who acknowledge that the European Centralised Procedure comes closer, though not close enough, to their expectation

of a more transparent regulatory framework and practice.⁵⁶ Among these professional critics there are also those who would argue that regulatory competition among regulatory agencies within the EC and the race for efficiency could jeopardise the safety criterion.⁵⁷

The variety of procedures accommodating a variety of interests

National regulatory authorities have had to give up regulatory autonomy – but only for part of the pharmaceuticals sector, albeit the most important one in economic and medical terms. *National governments* have only been willing to sacrifice national decision-making autonomy in the *Centralised Procedure* under the condition that the nationally based structures remain intact. This is guaranteed by the existence of the two nationally based procedural alternatives and by the fact that even the *Centralised Procedure* requires intensive regulatory participation on the part of *national authorities* in the implementation of this procedure. They are not only represented in the evaluating Scientific Committee (CPMP, now CHMP), but the preceding scientific assessments are actually coordinated by or carried out in the *national agencies* of those CPMP members who have been chosen rapporteurs on a case-by-case basis. And in the administrative decision-making process there are additional safeguards for national involvement via the comitology procedure (*Standing Committee*, eventually *Council*). For the *pharmaceutical industry* the “flexibility” of procedural choice has been crucial. Given the heterogeneity of interests, it would have been difficult or impossible for *the pharmaceutical industry associations* – especially the EFPIA as the most important European one, but even more so the national associations – to balance the logic of influence with the logic of membership (Schmitter/Streeck 1999) without lobbying for the maintenance of procedural variety and, at the same time, to advocate the introduction of the *Centralised Procedure*. The same perspective can be applied with respect to the ‘users’. The variety of procedures allows the supply of a variety of medicinal products adapted to heterogeneous medical demands.

5. Asymmetries of interest accommodation and influence

The fact that a plurality of interests are embedded in the established regulatory policies, providing direct participatory access to the implementation procedures or assuring their indirect consideration in the deliberation, negotiation and decision-making processes at EC and national level, does not mean that asymmetries in the influence and consideration of interests does not exist. In fact, the opposite seems to be true for different reasons. These have to do with structural features of the regulatory field as well as with specific policy goals and intentional implementation strategies. Both the structural features and the behavioural

⁵⁶ See, for example, Abbasi, Kamran/Andrew Herxheimer, 1998: The European Medicines Evaluation Agency: open to criticism. In: *British Medical Journal* 317, 898 - 900. and the reply from the then director of the European agency Sauer, Ferdinand, 1998: European Medicines Evaluation Agency is ahead of national licensing authorities. In: *British Medical Journal* 317, 1078..

⁵⁷ This is a highly contentious issue; for voices anticipating the risk of reduced safety, see Abraham, John/Tim Reed, 2001: Trading risks for markets: the international harmonisation of pharmaceuticals regulation. In: *Health, Risk & Society* 3, 113-128. and Abraham, John /Graham Lewis, 1999: Harmonising and competing for medicines regulation: how healthy are the European Union's systems of drug approval? In: *Social Science & Medicine* 48, 1655-1667., for opposite views, see Vogel, David, 1998: The Globalization of Pharmaceutical Regulation. In: *Governance: An International Journal of Policy and Administration* 11, 1-22. and Vos, Ellen/Marcus Hagemester, 2000: Views of the

evidence suggests that, in general, industry seems to be in an especially privileged position compared to the ‘users’ of medicines (prescribing medical professionals and consumers/patients) or even vis-à-vis the implementing regulators.

There are specific factors and conditions in implementation which put industry in such a privileged position. These relate to

- informational supremacy
- institutionalised and de facto “secrecy” of regulatory procedures and data
- cooperative needs for implementation success
- changes in organisational arrangements and administrative orientation.

5.1 Asymmetric influence through informational supremacy and procedural secrecy

The information on which regulatory authorities depend for their complex assessment and evaluation tasks – the analytical, toxicological and clinical data accompanying marketing applications – are provided by the applicant (pharmaceutical entrepreneur). Regulatory agencies generally do not have the resources to conduct tests on their own or to initiate and supervise especially toxicological and clinical trials. Internal and external experts working for regulatory authorities have many ways of checking the plausibility of the data provided, and existing regulations are relatively precise with respect to substantive criteria and standards. But industry might have an interest in designing tests in a way which promises favourable results, to present only series of tests with convincing results or to communicate them in a way which furthers their regulatory and economic goals. There are subtle ways of doing this, and many of the accusations in this respect concentrate on the often too intimate relationships between industry and certifying outside experts or on publication strategies in professional journals.⁵⁸ As the investment in drug development up to the point of marketing approval can be tremendously high,⁵⁹ there are, of course, strong economic incentives to present only those application data which increase the chances of marketing approval and to hide others which shed a less favourable light on a medicinal product. Certainly, industry does have an interest in avoiding the distribution of unjustifiably unsafe drugs, because such a strategy threatens to backfire sooner or later and can put the economic future of companies at risk. But there are margins of discretionary interpretation.

pharmaceutical companies on the new EU licensing procedures. Survey conducted Mid 1998. In: *ESRA Rapporteur*, 22-27..

⁵⁸ For a critical discussion of these issues, see for example Davidoff, Frank, et al., 2001: Sponsorship, authorship, and accountability. In: *The Lancet* 358, 854-856., Quick, Jonathan, 2002: Maintaining the integrity of the clinical evidence base. In: *Essential Drugs Monitor (WHO Publication)*, 3., WHO, 2002: Editors act on clinical trial reporting. In: *Essential Drugs Monitor (WHO Publication)*, 2., Abraham, John, 1994: Distributing the Benefit of the Doubt: Scientists, Regulators, and Drug Safety. In: *Science, Technology, & Human Values* 19, 493-522., Medawar, Charles, 1997: The Antidepressant Web. Marketing depression and making medicines work. In: *International Journal of Risk & Safety in Medicine* 101, 75-126..

⁵⁹ Estimates of drug development costs in the innovative pharmaceuticals sector show that they have increased roughly tenfold within about twenty years Sykes, Sir Richard, 1997: *The Pharmaceutical Industry in the New Millennium: Capturing the Scientific Promise*, CMR International Annual Lecture. Carlshalton, Surrey: Centre for Medicines Research International. and the average costs per new drug application (NDA) are estimated to have reached approx. 800 million US dollars by 2000, including the expenditure for failed projects and opportunity costs Cockburn, Iain M., 2004: The Changing Structure of The Pharmaceutical Industry. In: *Health Affairs* 23, 10-22..

Medicine approval systems are known for the secrecy that dominates proceedings (Dukes 1996), which is officially justified as a measure to protect commercial confidentiality, on the one hand, and to avoid the politicisation of a complex science-driven regulatory process, on the other. The lack of transparency criticised by many outside observers concerns the data, the supporting dossier on the basis of which regulatory decisions are taken, the regulatory decision-making process and the detailed justifications of the final decisions. While the European Agency, the EMEA, has tried to be more transparent than most national regulatory authorities in Europe, the EMEA's efforts, though acknowledged by those critics, are still judged to be far from sufficient.⁶⁰ Secrecy restricts public control – which is de facto extremely limited anyway due to the complexity of the subject matter – even by those outside actors that can be regarded as professionally competent. The legislative reforms of 2004 contain further transparency requirements at the European level, on the insistence of the European Parliament.

5.2 Opportunities of influence through changes in administrative orientation and organisation

In complex regulatory policy fields, successful implementation seems to depend on cooperation between regulators and regulated. The cooperative state, a cooperative or negotiating implementing administration (Schuppert 2000: 113-119, 427-430), is regarded to be more effective even in regulatory fields where one might expect administrative behaviour to be modelled on the traditional bureaucratic control scheme. From a political guidance and control perspective (Kaufmann 1986), one has to acknowledge that “the capacity of states to design and implement effective regulation of risks is constrained” by such a “need to work with regulated entities” (Hutter/Power 2000: 1). The necessity of cooperation can open windows of opportunity for the influence of those regulated who not only might possess critical regulatory information, but might also be in a privileged position due to their bargaining power on the basis of economic strength and political influence.

Since the 1980s, orientational changes in public administrations have been initiated as intentional administrative policies within a new public-management framework. The aim has been to replace “traditional public governance” by “modern public governance” (Lane 2000: 37), which includes a completely different perspective on the relationship between the public and the private sphere, between the regulators and the regulated. Inspired by US developments in public management, it was taken up by the UK Government of Prime Minister Thatcher in the 1980s and spread from there to the Continent. The aim was to replace the behavioural model of bureaucratic control with a managerial and professionalised approach modelled on the private sector. Service and client orientation towards regulatees was propagated under the heading of delivering “value for money” – which in pharmaceuticals approval regulation with its fee-based procedures has to be understood literally. Approval procedures are supposed to deliver a service which, within the legal limits of quality, safety, and efficacy requirements, guides applicants as efficiently as possible through the procedures and over regulatory hurdles. (Feick 2000: 244-246). Different mechanisms translate this client-

⁶⁰ For an exchange between external critics and the EMEA, see Abbasi, Kamran/Andrew Herxheimer, 1998: The European Medicines Evaluation Agency: open to criticism. In: *British Medical Journal* 317, 898 - 900. and Sauer, Ferdinand, 1998: European Medicines Evaluation Agency is ahead of national licensing authorities. In: *British Medical Journal* 317, 1078..

friendly approach into practice. There are regular meetings between regulatory bodies, companies and industry associations in the context of congresses, information days and workshops, where information in regulatory matters is exchanged, implementation problems are discussed and future practices and expectations are formulated. It is a rather small world in which the main actors on every side get to know one another quite well. Furthermore, regulatory agencies have become increasingly open to the inquiries of applying companies, even during the assessment phase – an approach which was almost unthinkable two decades ago. And it is intentional policy today, at the EU level and in national contexts also, to provide active pre-application guidance for future applicants, partly in order help not so resourceful companies master the complicated and burdensome procedures, and partly to assure smooth implementation later on.

All this has been organisationally reinforced by the tendency, evident since around 1990, to remove regulatory implementation from the ministries in countries where it had been previously integrated by establishing independent agencies – as in the United Kingdom and France – or to strengthen their relative independence where separate administrative structures had already existed – as in Germany. At the European level, it is the EMEA (since June 2004 the EMA) which has been handed the coordination of the assessment and evaluation task and whose influence on final approval decisions and therefore its regulatory independence is greater than its institutional embeddedness in the multi-level EC-comitology system would suggest (see above).

These features add up to a separation of regulatory decision-making from closer political scrutiny. They make regulatory agencies relatively independent, an independence which is meant to prevent the politicisation of decision-making processes that are supposed to be governed by scientific and technological reasoning. On the other hand, it does make these authorities and the day-to-day procedures vulnerable to those influences which have institutionalised access, are able to communicate on a professional peer-group level and might even be equipped with superior informational resources and other advantages.

5.3 Professionalised regulatory implementation or capture by industry?

There are those who argue that these institutional arrangements and behavioural orientations facilitate problem-oriented deliberations (see (Joerges 1999); (Gehring 2002)) and prevent conflictive politicisation. Assessments and evaluations in a non-majoritarian context by scientific or professional committees such as the EMEA's CPMP are expected to deliver the more problem-oriented regulatory decisions ((Majone 1997); (Krapohl 2002); (Thatcher/Stone Sweet 2002)). There is evidence that CPMP assessments and evaluations are most often the result of a consensual decision-making, majority decisions being the exception. And the opinions delivered to the Commission via the EMEA, which are the basis for the final approval decision, have never been changed significantly in the succeeding comitology procedure ((Krapohl 2004); (Feick 2002)). Nor has the comitology procedure ever necessitated the intervention of the Council in the *Centralised Procedure*, as the intergovernmental European body of last resort. But regulatory smoothness in the implementation process does not necessarily signify that the discussions and decisions in the CPMP are not biased towards one or the other scientific and professional orientation or in line with the interests of relevant stakeholders – in the *Centralised Procedure*, for example, the innovative pharmaceutical

industry and those Member States in which it is located. In the nationally based *Mutual Recognition/Decentralised Procedure*, deviations in national regulatory decisions, actually preventing mutual recognition, are a common experience. Whichever factors are responsible for this variance among national regulatory authorities – differing scientific orientations, regulatory traditions, former regulatory decisions, perceived impact on economic development, the health care system, etc. – the regulatory outcome will have an impact on the distribution of direct and indirect costs and benefits among the interested parties.

Relatively independent regulatory authorities whose day-to-day implementation activities are hidden from direct political control or public scrutiny, which depend on information and cooperation from the regulated for reasons of effective implementation, whose budgets are largely financed by service fees, and which are guided by a partly conflicting goal structure containing strong industrial policy elements might be especially vulnerable to the influences of the regulated – a situation favouring what M. Bernstein tried to explicate as agency capture in his capture theory (Bernstein 1955). Even though Bernstein's life cycle theory of independent regulatory agencies is based on observations made in the American political arena and was criticised, modified and expanded subsequently,⁶¹ his hypothesis deserves special attention considering that the *pharmaceutical industry* and its *associations* include powerful actors whose organisational motives and capacities are high according to "collective action" criteria.⁶² In contrast, the interests of *pharmaceutical 'users'* are much more difficult to organise and can be mobilised only under extreme attention-grabbing conditions (see the Thalidomide scandal).⁶³ In the regulatory process, consumer protection is placed in the hands of the regulatory authorities. According to Bernstein's life cycle expectation, regulatory authorities eventually risk losing motivational strength and the ability to strictly control their regulatory targets for exogenous political, economic and social reasons, as well as endogenous organisational, psychological and self-centred reasons.⁶⁴ Under such circumstances, regulatory policy and its implementation might take on features of "private government" Bernstein (1955): 263, 268, 270, 277-278.

The question of whether "big pharma is too close to the regulators" has even been posed by the former Head of the Medicines Division of the British Department of Health, who afterwards became Director General of the Association of the British Pharmaceutical Industry (ABPI) and thereafter a consultant and author of professional books and articles: "There is no doubt ... that pharma companies shop around the various regulatory agencies and EMEA and test the water before deciding where and how to file new drug applications ... – thus generating competition between agencies to get regulatory business." (Griffin, Nov. 2002: 18) This competition for

⁶¹ For overviews, see (Baldwin/Cave 1999: 24-25); (Hood 1994: 20-26); (Feick 1980: 49-50).

⁶² (Olson 1968), (Wilson 1980); for an estimate of the political strength of the pharmaceutical industry, especially the European association, the EFPIA, see (Greenwood 1995).

⁶³ It has to be mentioned that, since the 1960s, increasing public sensitivity, media attention, professional scrutiny by outside 'watchdogs' (critical pharmaceutical journals and other publications) and the readiness of patients to claim compensation for drug damages has made pharmaceutical companies more prudent when it comes to avoiding economic damage due to bad publicity and liability payments.

⁶⁴ Parts of these intra-administrative mechanisms have been called "institutional attenuation" whereby, for institutional reasons and due to characteristics of especially complex regulation regimes, administrators' perception of risks, on the one hand, and of the applicability of policy provisions to problematic situations, on the other, are impaired, resulting in ineffective implementation (Rothstein 2002).

regulatory work is motivated not the least by the fact that agencies are more or less dependant on fees, and that the differences in fee structure between the agencies and the allocation of fees between the European and the national rapporteur agencies in the *Centralised Procedure* encourages national agencies to acquire more volume in order to finance their budgets. What was intended as a measure to make regulatory agencies more independent of normal budgetary constraints and the hierarchical environment of ministries and governments, to allow for more flexibility in budgetary spending, and to make agencies work more efficiently has also been criticised for its presumed tendency to make them more dependent on the regulated and increase the latter's influence potential. Griffin cites US-American data and examples, showing that the FDA's post-marketing withdrawal rate on safety grounds has gone up since 1992, the year when user fees were introduced at the US-american regulatory agency FDA. This can be interpreted as indicating that user fees might have led to less rigorous approval procedures. There are critics of FDA regulatory behaviour towards industry who maintain that some of its safety management might make economic sense but less so when it comes to public health.⁶⁵ Whether it was industry itself, or patient groups or an alliance of both which led to the approval and re-approval decisions in the case referred to, a tentative conclusion of the cited article is that, instead of helping regulatory agencies to fulfil their regulatory task within the legally stipulated timeframe, the introduction of user fees might have "hampered it [the FDA] by allowing pharma undue influence over marketing approval." A former employee of the FDA is quoted who even suggests that the "FDA has become a servant of industry" and that internal debate and discussion was repressed (Griffin 2002: 19).

"Agency capture" is difficult to prove empirically in any systematic way beyond citing known single cases. In the European context, with its multitude of regulatory agencies at the national and European levels and its three procedural alternatives, the term "agency capture" might not be adequate for the complex situation. The industry's privileged position in the European context stems from a rather complex constellation of institutional and orientational factors whose interplay allows industrial forces – not reflecting homogeneous interests, it should be noted – to play a dominant role in the whole regulatory arena of marketing authorisation of medicinal products. As we have said before, exogenous factors and events can produce situational pressures contrary to industrial economic interests, but under normal political and economic conditions a reasonable working hypothesis would be that the pharmaceutical industry is in a privileged position in the implementation process, facilitating "capture" or other forms of influence.

5.4 Impact: More efficiency, less safety?

It is one task to analyse how interests are embedded in existing policies and how existing institutional structures and procedures favour some interests over others, providing influence positions and channels of influence. It is a completely different task to analyse the probable impact of these influences on policy outcomes. There are those, both outside observers and regulatory participants, who fear that the internationalisation of market entry regulation in general, and its Europeanisation in particular, has undermined safety standards to the

⁶⁵ The pharmacovigilance example cited is that of the Lotronex (alosetron), which had been approved in 2000, withdrawn in the same year, reassessed and finally authorised again in 2002 (Griffin 2002, 19).

disadvantage of public health and in favour of industrial policy goals.⁶⁶ And there are historical case studies which suggest that such an asymmetry in influence distribution and such a bias in interest consideration has a long tradition in market entry regulation and its development in the last century (Abraham 1995; Murswieck 1983). Indeed, unless there are dramatic events that stir public attention, reveal corresponding regulatory deficiencies and require visible political action, the goals of consumer, patient and public health protection tend to be less prominent in politicians' minds than the goals of a viable and competitive industry and economic success. As regards administrative regulatory decision-making, in periods without any publicised dramatic adverse effects of medication, the consideration of safety aspects might become less pronounced to the advantage of faster and smoother approval processes, with or without explicit signalling from the political level.

This would conform to Lindblom's conclusion generalizing across industrial sectors that industry and business officials are privileged in polyarchic market economies "not only with respect to the care with which governments satisfy business needs in general but also in privileged roles as participants in policy deliberations in government." And this for the reason that "business simply needs inducements, hence a privileged position in government and politics, if it is to do its job." By this situation, so Lindblom, "the authority of government is ... curbed and shaped by concern for possible adverse effects on business." (Lindblom 1977: 175, 178) No politician, considering the impact of industrial success and economic well-being on his or her chances of being (re-)elected, can ignore the perceived needs of such an industry. Therefore, the "business predicament" is an important preoccupation whenever government interferes with economic decisions in the marketplace, say, for reasons of "social responsibility" (Wilson 1974).

There are observers of the pharmaceutical industry and regulatory participants who would maintain that not only has the internationalisation and Europeanisation of market entry regulation failed to lead to a negligence of safety aspects (Vogel 1998) but that even the opposite is the case – that the safety aspect has been overemphasised and the whole sector is over-regulated.⁶⁷ This position is in line with the literature claiming that the "precautionary principle" (Majone 2002) on which much of the so-called "new social regulation" is based has produced adverse regulatory effects by its own logic. The argument is that overly risk-averse, safety-biased regulation and implementation might impede pharmaceutical innovations whose therapeutic benefits would outweigh the safety risks.⁶⁸

Such views imply that *industry* might have been less influential than suggested by other observers and as a conclusion of the analysis presented above. As we have argued, industry is neither a monolithic block nor the only influential actor in this regulatory arena. This

⁶⁶ See for example (Abraham/Lewis 1999; Abraham, John/Graham Lewis, 2000: *Regulating Medicines in Europe. Competition, expertise and public health*. London and New York: Routledge. Abraham/Reed 2002: 162-172); Garattini, Silvio/Vittorio Bertele, 2001: Adjusting Europe's drug regulation to public health needs. In: *The Lancet* 358, 64-67.

⁶⁷ Such is the position of the former head of the EMEA, Fernand Sauer; see Sauer, Fernand, 1997: A New and Fast Drug Approval System in Europe. In: *Drug Information Journal* 31, 1-6.

⁶⁸ A large amount of research initiated in the USA after the introduction of stricter authorisation criteria in the Kefauver-Harris Amendments of the Food, Drug and Cosmetics Act in 1962 is representative of this perspective; overviews of this evaluative literature are provided, for example, by Scherer (2000: 1308–1316), Andersson (1992) and Schiffrin/Tayan (1977).

heterogeneous interest constellation has actually led to a policy output and outcome that correspond to this diverse interest structure, in which *national governments* and *regulatory authorities* play an important role as guardians of this diversity. This diversity in turn is translated into a differentiated regulatory landscape – including the variety of procedural options extensively discussed in this paper. In these complex procedures it depends on a number of exogenous and endogenous conditions and factors as to which interests receive privileged access and/or stronger consideration at a particular point in time.

Yet, the somewhat ‘byzantine’ institutional structure of marketing approval regulation for pharmaceuticals, which serves a large variety of interests, should not be misread. The most powerful section of the pharmaceutical industry, the internationally oriented and research intensive companies, and its associations have been able – in harmony with the internationally oriented industrial policy goals of national governments and the Commission alike – to arrive at a regulatory situation which guarantees a larger market for their products, an overall less costly regulatory procedure and linkages to a regulatory arena which even transcends the EU. This further internationalisation has opened up additional rationalisation potential through harmonisation – and has done so through close cooperation between the research-based, internationalised pharmaceutical industry and its main association, the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) together with national regulatory agencies of the USA and Japan as well as the European EMEA. One of the major figures in the industry, the Chairman of Glaxo Wellcome, Sir Richard Sykes, commented on the relationship of the pharmaceutical industry and regulatory agencies: “We should not forget that great progress has been made in harmonising requirements through the ICH (International Conference on Harmonisation) process. This is a tremendous example of co-operation between agencies and the industry, ... In addition, regulatory agencies around the world have contributed by cutting assessment times and industry applauds their efforts.” (Sykes 1997: 6)

6. A conclusion: learning and the accommodation of interests in an institutional and situational context

Learning processes and interest politics do not occur in a vacuum. The focus of this paper is not meant to deny the influence of other facilitating or constraining factors and conditions. The importance of single exogenous events has been mentioned, such as the dramatic or even catastrophic adverse effects of pharmaceuticals consumption, which are able to provoke public demand for public controls of the pharmaceuticals market. The institutional conditions of EC policy-making have been of crucial importance in defining the goals of European market entry regulation for pharmaceuticals and in determining the rules under which the Commission and the national governments have been able to pursue their interests and policy strategies. The quasi-constitutional imperative of European market integration has provided the Commission with a policy lever for integration strategies which have had to meet and consider the resistance of Member States based on national interests and armoured with the unanimity rule in the Council – up to and including the structural changes of 1993 – and the legal opportunities to pursue nationally based, not community-oriented, regulatory policies in implementing harmonised legislation at the national level.

An astonishing policy mix of three distinct approval procedures characterises the regulatory situation in the EC since 1995 and obey different logics of European integration. This policy

“patchwork” has been analysed as the result of a policy-related learning process over three decades, on the hand, and the pursuit of interests within an institutional decision-making framework and influence structure, on the other, which has allowed a variety of actors to have their partly overlapping, partly contradictory basic interests and situational preferences accommodated in this procedural policy-mix.

The development of policies over three decades has been described as sequences of incremental and structural transformative changes in which actors, trying to influence and shape overall policies, have learned by institutional trial and error. Failures to achieve certain goals and to satisfy certain interests through incremental changes have produced pressure to overcome the threshold of structural or transformative change. Of great importance, too, has been learning in the interaction context of implementation, which has led to the learning of cross-national interactions in European procedural settings. Thus, policy-related learning has included both: the recognition of the limits of harmonisation and mutual recognition as strategies of market integration, on the one hand, and the evolving conviction – based on interaction learning – that European joint decision-making in regulatory implementation is a viable option, on the other.

The fundamental changes of 1993 with respect to the *European Centralised Procedure* – in force in 1995 –, partly and only insufficiently in the *Mutual Recognition or Decentralised Procedure* – in force 1995//98 – mark the difference between institutional conditions of a voluntaristic nature, leaving exit options to pharmaceutical companies and/or national authorities and institutional determinism forestalling such an exit opportunity and leaving national authorities with the option of voice or loyalty as the only behavioural choice in the implementation process.⁶⁹ As long as the Europeanised procedures – those of 1975, 1983, 1987 and the *MRP/DP* of 1995/98 – were still based on national regulatory decision-making, national authorities pursued their regulatory interests, thus making actual European market integration dependent on voluntaristic decisions. It was the fundamental policy change in the *Centralised Procedure* of 1995 – with the legislative reforms of 2004 finally extended to the Europeanised phase of the *MRP/DP* – which transferred decision-making responsibility from the national to the European level. This changed the institutional context for the regulatory behaviour of national authorities. From then on, they had to participate and raise their voice if they wanted to influence regulatory outcomes in a joint decision-making situation. The regulatory decision-making behaviour of national authorities is, at least partly, driven by national interests, and the extent and manner in which these interests can be pursued depends on the institutional conditions of regulatory decision-making.

The main conclusions of this paper are that the evolution of marketing authorisation in the EC and the resulting procedural patchwork is a product of learning processes at both policy-making and implementation level in this European multi-level/multi-actor system and that this evolution is the outcome of a variety of interests in the EC’s pharmaceutical policy field which have had to be accommodated institutionally. Without such a relative isomorphism of interest and institutional structures, the hurdles, especially in the European Council of Ministers, could

⁶⁹ For the concepts of voice, loyalty and exit, see Hirschman, Albert O., 1981: *Exit, Voice, and Loyalty: further reflections and a survey of recent contributions*. In: Albert O. Hirschman (ed.) *Essays in Trespassing. Economics to politics and beyond*. Cambridge, London, et al.: Cambridge University Press, 213-235..

not have been cleared. But the accommodation of a wide variety of interests does not mean that they are symmetrically represented in this complex institutional setting. We have argued above that there are strong indications that in marketing approval regulation it is the regulated industry itself – different parts in different procedures according to the respective medicinal product range – which occupies the most influential positions on the basis of the resources it commands, the importance it has for other influential actors and the policy coalitions it is able to join. According to some critics, its direct and indirect influences can go as far as jeopardizing the regulatory goals of public health protection, namely the safety and efficacy of marketed medicines. Conversely, there are other observers who would maintain that an already overly precautionary control of medicinal products threatens to hamper pharmaceutical and medical innovation as well as industrial competitiveness.

To analyse systematically the distribution of influence and of interest consideration and accommodation among different concerned/affected actors and groups is a difficult task if it goes beyond rather eclectic and impressionistic evidence. This has partly to do with the traditional secrecy and continued lack of transparency that governs large parts of this regulatory domain. Greater transparency might not only facilitate policy and politics research but, possibly, also “counteract the risk of particularistic capture” (Papadopoulos 2003: 494). But with this outlook we enter a completely different debate – that of the democratic legitimation of regulatory decision-making in policy sectors of high substantive complexity, a complexity which is institutionally intensified by the European system of regulatory policy-making and implementation that transcends hierarchical patterns of authority and lends itself to or even requires cooperative forms of governance with all its problems of transparency, accountability, and democratic control (see (Papadopoulos 2003); (Scharpf, Fritz W. 1999))

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