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

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

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1. Introduction

1.1 Questions and paper outline

The purpose of this paper is to formulate hypotheses about the emergence of marketing-approval regulation for human-use pharmaceuticals in the European Community since the beginning of the 1960s. Focusing on the developmental and institutional logic of the regulatory structures at different points in time, it highlights the way in which policy learning and actor interests have shaped the resulting regulatory policies and the way in which a variety of interests have been accommodated in the institutionalised procedures. At the same time, this analysis sheds light on the asymmetric distribution of influence especially in the implementation process.

The institutional result of this development has been a procedural policy-mix which emerged in 1993 (in force in 1995) after thirty years of substantive policy harmonisation and procedural efforts to foster the mutual recognition of national regulatory decisions. This "policy patchwork" (Héritier 1996: 149) – which has undergone further modifications in 2004 after a three-year review of EC pharmaceuticals legislation – 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 follow the tradition of national sovereignty in public health matters (Art. 30 of the Treaty of the European Communities, TEC, former Art. 36), ie, regulatory decisions are taken by national authorities for national markets. 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. It signifies a radical institutional change compared to the situation before 1995.

This procedural variety is surprising at first sight for three reasons: first, the espoused substantive policy goals of these regulations are similar for the three procedures, and also the genuine EC goal of creating a Single Market for pharmaceuticals. A second cause for puzzlement is the high degree of legal harmonisation which had already been achieved within the EC since the first directive of 1965. Third, the scientific and technical characteristics of this specific policy domain (Feick 2000) nurture the

* Parts of this paper were presented in a seminar at CARR on 20 May 2003 while staying there as a visiting researcher. I am grateful for this inspiring opportunity and the helpful discussions with my colleagues. This paper has profited, also, from discussions in a workshop at the University of Bamberg on "Good Governance in Supranational Market Regulation: How do Regulatory Institutions Matter?" in January 2004. I would like to thank anonymous referees for their useful comments. Fabian Pfeffer was, as usual, of invaluable help as research assistant. And I owe many thanks to Sabrina Fernandez for her thorough proof-reading and copy-editing.

expectation of converging policies and policy implementation on the basis of scientifically and technically inspired policy ideas (Hall 1993: 291).

In analysing this development and its results 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 2001b), the types of institutional change more generally (see for example Thelen 2003) and within the EU-setting particularly (see eg, Armstrong/Bulmer 1998: 50-63, Bulmer/Burch 2001: 81-82, Aspinwall/Schneider 2001).

The exogenous and endogenous factors accounting for or facilitating such changes can be manifold (Thelen 1999). 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 important or even the main factors of institutional change. Therefore, the main 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 introduce their interests into policy-making and -implementation. The search for influence within facilitating or constraining institutional contexts and situational constellations[1] 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). Conflicts over substantive policy contents such as product standards and decision criteria are important parts of politics. But, as Mark Thatcher has observed in another highly technical policy field, namely telecommunications, these kind of conflicts are often less pronounced compared to matters of "the institutional allocation of powers" (Thatcher 2001: 573).The other actor-related perspective concerns policy-learning enabling or leading actors to examine their orientations vis-à-vis actors, institutions, procedures or substantive policy-contents.

The main argument in this paper is that the impact of diverse interests has 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 in 1965, 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. But, in the overall procedural policy mix this truly European procedure represents only one alternative, limited to the most innovative part of the medicinal products market.

In the following subchapter, I will briefly describe the problem situation, rationales behind this regulation and the political dimension of regulatory decision-making in this

[1] See the analytical framework of actor-centred institutionalism in Mayntz/Scharpf (1995: 39-72) and Scharpf (1997: chapter 2).

policy field, before outlining and structuring the development of regulation and trying to categorise the type of institutional change encountered as well as the modes of European integration applied. In a further step, attempts are made to interpret this development in light of policy-related learning processes and 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 will be analysed.

The inductively derived 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.

1.2 Rationales for and politics of market-entry regulation for pharmaceuticals

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 and, later on, knowledge creation through scientific and technological advances, at first led to forms of professional self-control which became more and more legalised through procedural regulation (see Schmitz/Kuhlen 1998; Ridder 1990: 22). This form of professional 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 2000). Scientific and technological advances increased the knowledge base not only for developing and producing pharmaceuticals but also for the capacity to control medicinal substances. 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 any 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.

The regulatory advances in drug approval and pharmacovigilance by the 1960s and 70s – in a few countries such as the US already before[2] - were reactions to dramatic

[2] In the 1930s the US had institutionalised quality and safety-oriented marketing authorisation procedures

accidents in pharmaceuticals consumption, the most important being the so-called thalidomide catastrophe of the late 1950s/early 1960s.[3] The thalidomide affair has since been classified as "the single most important event to influence our attitudes to the unwanted effects of medicines" (McEwen 1999: 269). For practically all the countries in Europe it had become evident that effective pharmaceuticals regulation, 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-decision or purely symbolic politics was forestalled and risk-averse politicians had every incentive to create regulatory regimes and systems which would help to avoid or delegate blame if accidents should occur despite regulatory precautions.[4]

Regulatory rationales

In welfare-economic thinking, product-oriented risk regulation in the pharmaceuticals sector 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 product-qualities than the producer. 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 healthcare 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. Daniel Carpenter goes a step further, maintaining that an information problem exists also for industry itself, "the inherent uncertainty that firms themselves have about the quality and safety of their products," concluding that "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 by economists that governmental regulatory policies generally produce sub-optimal outcomes, J. 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"[5] and that, secondly, regulatory policies are legislated and implemented just because policy-makers have preferred the imperfections of regulation against the imperfections of markets (Wilson 1974: 135-136, 145-146). Applying Lowi's and Olsen's categories,

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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; Silverman/Lee 1974).

[3] There are many accounts of this catastrophe; see for example Silverman/Lee (1974), Abraham (1995), Kirk (1999) and Luhmann (2000). 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 (1989) and Vogel (1998).

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

[5] 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 1995)

he distinguishes different types of cost/benefit constellations for concerned parties and the consequences of these constellations for politics. Risk regulation, as found 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 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 most European countries. Wilson maintains that a change in politics occurred through shifts in "national mood," [6] 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 (Wilson 1974: 146, 165-1966). Such a policy–politics constellation also fits the political rationale 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 industry fears detrimental public reactions.

There is also 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 – even though it might be difficult to recognise the normative content of scientific/technical assessments.[7] The refusal of national authorities to mutually accept one another's regulatory decisions even on the basis of extensive legal harmonisation is just such a consequence of the discretionary space in regulatory decision-making (Feick 2000).

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. The Thalidomide scandal gave rise to either fundamental legislative reforms in European and other industrialised countries or to a tightening of already existing regulation.[8] The Thalidomide scandal marked a regulatory starting point for both the

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

[7] 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), and Hall for the field of economic policy (Hall 1993: 289).

[8] See eg, 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

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. They surfaced when it came to design regulations for the control of the pharmaceutical industry and to prescribe the regulatory action to be taken by implementing administrations with the effect of influencing the availability of pharmaceuticals in national markets and medical care. In fact, the EC Commission was well aware from the outset that national differences could always jeopardise the desired effects of legal harmonisation.[9]

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 achieved without hindering "the development of the pharmaceutical industry or trade in medicinal products within the Community," (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) was meant to maintain or strengthen the EU region as a competitive research, development and production site (Liikanen 2002). The increasing importance of these further goals are linked to the perceived decline of the internationally oriented and research-intensive European pharmaceutical industry especially vis-à-vis its US-competitors – with, maybe, the exception of UK and Swiss companies.[10]

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 (Silverman/Lee 1974).

[9] 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, the Commission made clear that their complete abolition might necessitate not only legal harmonisation but also EC implementation measures (Kommission und Gemeinschaften 1970: 127).

[10] See for example van den Haak (2001), Halliday/Walker (1999) and MacInnes/Lumley/Walker (1994). The changes seem to be dramatic eg, for Germany, once known as the "pharmacy of the world": While American companies gained 13% of world market share in the last decade (from 17%-30%), German pharmaceutical companies lost 8%, from 14% to 6% (Balser 2004). There is also the observation of a more general "innovation deficit" in the whole pharmaceutical industry (see Drews 1996).

This complex goal structure contains partly conflicting goals. 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 jeopardise patient safety and public health.

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.[11] Even 25 years after the first Council Directive of 1965 had established the basic regulation, and after many more Council Directives, Commission Guidelines and Communications had followed (see 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).

The first Directive of 1965 had made approval procedures obligatory in the Member States, controlling for the quality, safety and efficacy of pharmaceutical specialties, but leaving the transformation and implementation of this generalised 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. But all these measures still left the authority of regulatory implementation at the national level. The most important institutional changes occurred in 1993, effective from 1995/1998, introducing 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 2001-2004, dealt with only marginally in this paper.[12]

[11] 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 (see Hancher 1990: 104, 112-117).

[12] It is the topic of another project (see http://www.mpi-fg-koeln.mpg.de/review/index_en.html).

Table 1
Major regulatory steps in EC marketing approval regulation concerning medicinal products for human use

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	Directive 75/319/EEC - Detailed requirements for application dossier (technical contents, eg, analytical and test results); - Details concerning controls to be performed by national implementing authorities; - *Community-Procedure* for parallel applications in at least 5 Member States as an option; establishment of the Scientific Committee (CPMP, 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 Pharmaceutical Committee for participation in the preparing of legislative measures
1983	Directive 83/570/EWG, slight procedural modifications of the *Community Procedure*, becoming the *Multi-State Procedure* (now optional with parallel applications in at least 2 Member States; still national marketing authorisations)
1987	Directive 87/22/EWG, *Concertation Procedure* for the most or more innovative pharmaceutical products; obligatory pre-decision involvement of CPMP, but without binding opinion (still national marketing authorisations)
1993	Regulation 2309/93/EEC, Directive 93/39/EEC (in force 1995) - Introduction of the *Centralised Procedure (CP)* emanating from the *Concertation Procedure* but with regulatory decisions taken at the European level and for the whole Community (EC-wide marketing authorisations); - Introduction of *Decentralised and Mutual Recognition Procedure (DP/MRP)* emanating from the *Multi-State Procedure* (still nationally based but with the option of centralised, binding arbitration in case of diverging national assessments and/or evaluations) - Creation of the European Agency EMEA for coordinating the evaluation of the application dossiers in the *CP* and, eventually, in the *DP/MRP*
1998	Complete replacement of parallel national applications by the *Decentralised or Mutual Recognition Procedure*
2001	Directive 2001/20/EC: Standardisation of clinical test requirements
2004	Regulation 726/2004/EC: Amendment of the *Centralised Procedure*: increase of scope, some efficiency measures (deadlines) and organisational changes (EMEA, now EMA; CPMP, now CHMP)
2004	Directive 2004/27/EC: Amendment of *DP/MRP*: obligation of binding arbitration at the European level in case of dissent among national authorities (but, formally, still national authorisations)

2.2 The strategies of European regulatory integration

The goal of creating a Common Market for pharmaceuticals has been pursued by basically two different strategies over time (see Figure 3):

a) **Legal Harmonisation**: Increasingly detailed legal harmonisation expecting congruent national implementation which should lead to the mutual recognition of national regulatory decisions.

b) **Procedural Centralisation**: Institutionalisation of regulatory decision-making at the European level in order to prevent national regulatory disparities through institutional design.

Legal harmonisation and mutual recognition versus institutional centralisation

There have been discussions about these two conflicting institutional strategies since the early 1960s (Hancher 1990: 103-117 and Hart/Reich 1990: 14-36). Most Member States (at that time the six founding states) and their regulatory authorities were not willing to give up regulatory and especially implementation 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 opted to pursue the strategy of harmonisation and mutual recognition anticipating insurmountable national resistance in the Council, who had to decide unanimously, at the same time being mindful of its own administrative limitations.

The first Directive of 1965 (European Council 1965) prescribed formalised national regulatory procedures for all its Member States, a "minimal" harmonisation demand, which left substantial discretion in the transformation and implementation of this European requirement 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. 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). These 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 Common Market for pharmaceuticals remained out of reach (Collatz 1996: 48-50).

Attempts at procedural coordination

With the aim of fostering mutual understanding and cooperation among national authorities two procedures were introduced between 1975 and 1987: first, the so-called *Community Procedure* in 1975, transformed into the *Multi-State Procedure* in 1983, which could be chosen voluntarily in case of parallel marketing applications in several Member States; second, the *Concertation Procedure* in 1987, which was limited to the more innovative medicinal products,[13] and came into effect in 1987 (Council of the

[13] Appendix with list of "technologically high-quality pharmaceuticals" (Council of the European Communities, 1987b); the procedure was obligatory for category A pharmaceuticals, derived from certain

European Communities 1987a). This was the institutional result after the Commission's futile proposal to introduce automatic mutual recognition at least for pharmaceuticals with new active substances in 1980 and the mid-1980s again. Although the latter procedure obliged national authorities to wait for the opinion of the Scientific Committee (Committee for Proprietary Medicinal Products, CPMP[14]) before deciding on an application, 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.[15] The *Concertation Procedure* was comparatively successful insofar as it actually resulted in national evaluations being quite close to the CPMP's position. But even there the Scientific Committee's recommendations were not automatically adopted at the national level, as the innovative industry and the EC Commission had hoped. Nor did the procedure lead to efficiency-gains – quite to the contrary: 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" integration 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 for the completion of the Single Market in the European Community, 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 desist from stopping the free movement of goods across their borders (for the service sector see Schmidt 2002: 937-938). For the Commission the practically unmanageable task of maximum harmonisation seemed avoidable and mutual recognition finally attainable as a reliable mechanism of integration based on minimal framework harmonisations that left regulatory transformation and implementation to the national level. The task was to draw "a clear distinction … 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 Commission established task lists and timetables, including one for "pharmaceuticals and high-technology medicines" envisaging 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 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

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biotechnological research and production methods, and optional for category B ("other technologically high-quality pharmaceuticals, " especially those containing new chemical entities (NCE)).

[14] The CPMP is made up of representatives from the implementing national regulatory authorities. The Pharmaceutical Committee, which was established also already in 1975, is made up primarily of representatives from national ministries and is concerned with more general policy questions. Both committees are institutionalised alongside the EC Commission in the comitology framework.

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

protection arrangements. Their conclusion: in policy fields of special complexity the old approach of maximum harmonisation could not be abandoned. They criticised the Commission for overstretching the applicability of the new approach beyond fields such as rather simple product quality controls or technical norm setting. 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 marketing approval as the main policy field in the EC, so far – 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 – with two consequential innovations: the separation of medicinal products into groups treated differently in the regulatory framework, and the increase in importance of the European evaluatory body, the CPMP.

Towards partial centralisation of regulatory power

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 and the Commission 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 automatic mutual recognition, 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). Further development was expected to be of an incremental nature. Improving "coordination procedures" was seen 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 … [and] 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 … 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 patchwork of procedures in the EU: distribution of decision-making power, opportunity structures and implementation behaviour[16]

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. In 1995 the procedural landscape 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)*[17] 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 13).

National procedures were neither covered by the reform legislation of 1993 nor replaced by it, except for category A pharmaceuticals. Although restricted to less innovative medicines and to single-country applications, they still represent a substantial, in some countries even the largest part of market entry applications. To date, this procedure is by no means a residual alternative.

In the ***Decentralised*** or ***Mutual Recognition Procedure***, also, 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. There are communication and cooperation obligations incumbent on the national authorities affected, but a formally institutionalised coordination infrastructure at the European level does not exist.[18] In this respect, it is rather similar to the previous *Multi-State Procedure* (see above). The important changes of 1995 have been 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 until the

[16] The analyses in this paper mainly reflect the institutional and regulatory situation until the legislative Review of 2001-2004. Where it seems useful for the analysis changes through this reform are included.

[17] 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-procedures belong to the same category because the decision-making processes are identical.

[18] This has been changed to a certain degree through the legislative Review of 2001-2004.

legislative reform of 2004 there was no obligation to take this path in any event.

The fundamental innovation of 1995 has been the introduction of the ***Centralised Procedure***, which - for the obligatory medicinal products - deprives pharmaceutical companies of the chance to strategically select their target countries and, as a procedure, takes away regulatory autonomy from the national regulatory authorities in that regulatory decisions are taken by European institutions and are valid for the entire EU. However, this 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 has been extended by the 2004 reform.

Institutional description of the *Centralised Procedure*

The ***Centralised Procedure*** (see Figure 1) transfers the final assessments, evaluations and regulatory decision-making to the European level, but complements this transfer of regulatory power with an extensive participation of national regulatory agencies in the scientific assessment and evaluation phase (agency level) and of national governments in the regulatory comitology phase (ministerial level). In practice, the degree of centralisation is further strengthened by the fact that the assessments and evaluations conducted by the Scientific Committee (CPMP) at the European Medicines Evaluation Agency (EMEA), almost without exception, anticipate the final regulatory decisions at Commission level. 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.[19] Institutionally joint decision-making[20] does take place, but in practice with clear overall features of central direction.

The Scientific Committee (CPMP)[21] assesses and evaluates the incoming applications for EMEA, the latter then formulating an opinion for the Commission's decision draft, which itself is 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

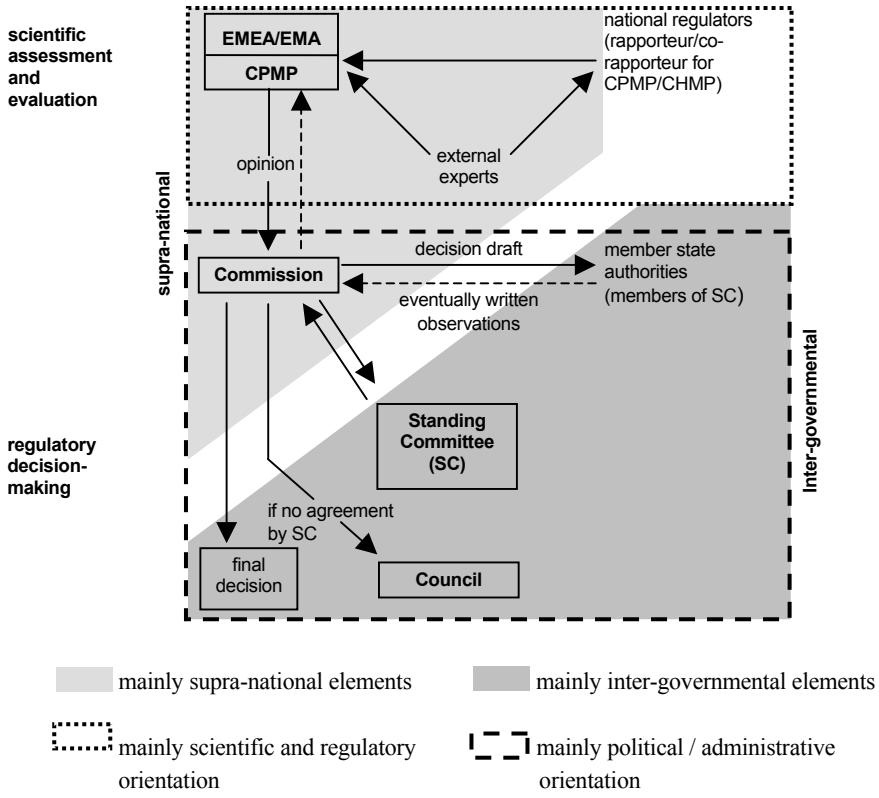
[19] Edoardo Chiti uses the term "decentralised integration" for this institutional configuration (Chiti 2002).

[20] 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).

[21] The CPMP (CHMP since 2004) was composed of two representatives from each national authority. The legislative Review changed this to one per national authority in order to accommodate enlargement. CHMP may co-opt 5 further members on the basis of their scientific specialisation.

EMEA/CPMP for further clarifying discussions on specific scientific/technical issues. This happened only twice between 1995 and 2001 and was resolved in the sense of the initial evaluation.[22] 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. Within this rather centralised framework the national authorities can introduce their views and interests, but no simple veto is possible; "coalition-partners" are needed.

Figure 1
Centralised Procedure (simplified)



EMEA: 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

Institutional description of the *MRP/DP*

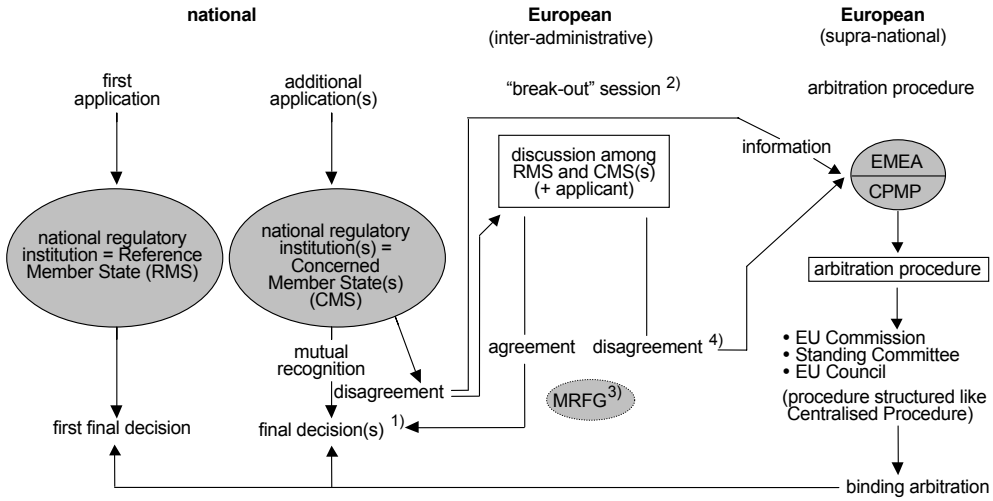
The ***Mutual Recognition*** or ***Decentralised Procedure*** (see Figure 2) is nationally based but contains a component of European centralisation even though it has rarely been applied until 2004. The national authorities have been able to maintain their autonomy at the core of this procedure. And it offers the companies strategic flexibility in selecting the countries where they would like to market their products. They pay for this

[22] Information through personal communication with EMEA (EU 2001 – 10).

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).

The *MRP/DP* differentiates Member States that are chosen for applications by pharmaceutical companies 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

Figure 2
The Decentralised and Mutual Recognition 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 of national regulatory 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 organised 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.

model evaluation and regulatory 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 RMS and the CMSs are

supposed to resolve eventual differences of opinion in so-called "break-out sessions," and c) a binding supra-national arbitration procedure activating the EMEA/CPMP and the Commission 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). The MRFG works as a multi-national network (Perkmann 1999) of national regulatory authorities 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 *MRP/DP* 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

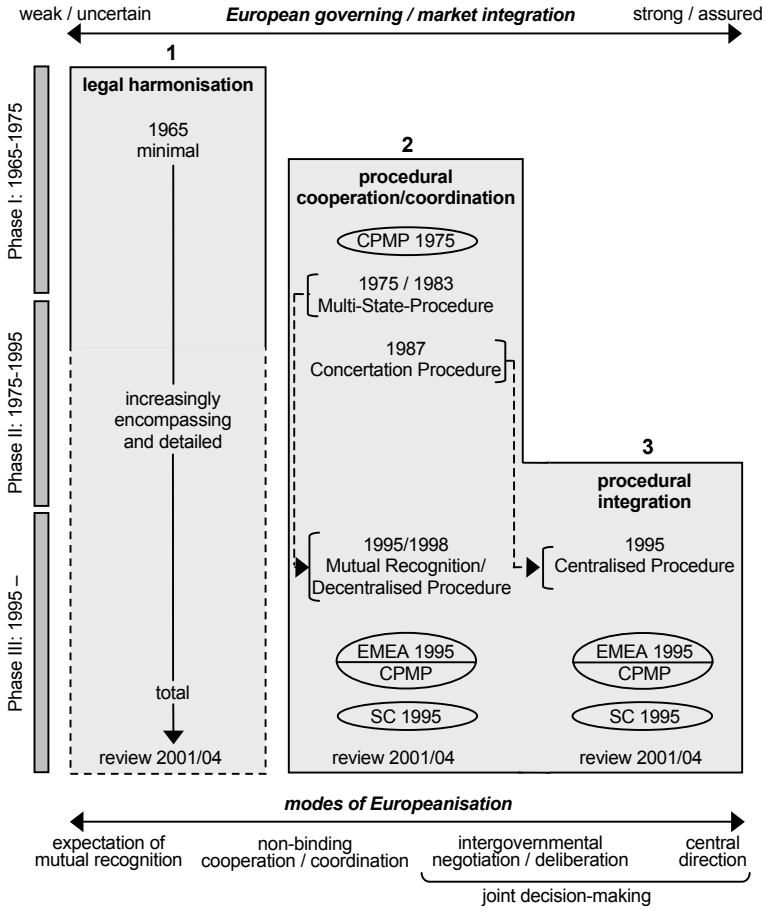
The four decades between 1960 and 2004 have witnessed different types and mechanisms of institutional change ranging from incremental steps to structural transformations. The procedural mix or institutional diversity to which this policy development has led and which we have described above combines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

Three "critical junctures" of different importance can be observed.[23] 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 with the expectation of voluntary mutual recognition by national authorities. This can be regarded as a weak

[23] For an explication of the concept of "critical juncture", see Collier/Collier's study of the regime dynamics in whole countries and societies (Collier/Collier 1991: 27-39).

mode of political Europeanisation and an equally weak and uncertain form of market integration.

Figure 3
EC pharmaceuticals authorisation - Integration strategies and stages



EMEA: 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 for Medicinal Products for Human Use)
SC: Standing Committee (participation in comitology procedure)

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 EU Member States, institutionally guaranteeing a Single Market for these products. The national level is extensively integrated in this *Centralised Procedure*, but the Member States have lost their singular decision-making autonomy.

A third structural change occurred with the legislative review of 2001-2004. 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,[24] then the *MRP/DP* would be deprived of the exit option for applicants and become truly European in the third phase. Thus, starting as a nationally based procedure, the national level would loose its autonomy if the Member States 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, but also turn into a European joint decision-making mode if mutual recognition fails. In the phase of binding arbitration, the regulatory decision-making process would resemble that of the *Centralised Procedure*. As, on average, applications in the *MRP/DP* are targeted at less than half of the Member States (Feick 2002: 40-42) this procedure leads only to partial market integration.

In between the more or less profound structural changes, different incremental modifications and extensions were introduced within the harmonisation and mutual recognition framework. 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.[25] Other incremental steps were 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. The institutions which were created in 1975 to facilitate the attainment of common positions were instrumental in this respect – the Scientific Committee (CPMP) as well as the Pharmaceutical Committee.

After the structural transformations in 1995 with the introduction of the *Centralised Procedure* and the *Mutual Recognition and Decentralised*, 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 (EMEA) and of its supervisory administrative Management Board, as well as a more formal position of the Mutual Recognition Facilitation Group (MRFG) in the *MRP/DP*.

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

[24] 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.

[25] 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/Harron (1992); Sickmüller/Throm (2001); Franken/Kroth (2004)).These are voluntary agreements between the regulatory agencies and industry associations of the EU, USA and Japan , adopted also by countries like Australia and Norway, and are integrated into regulatory implementation by the respective agencies.

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 arrangement 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).

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 the different modes of integration and different degrees 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. The development of this institutional variety, incorporated in the three different regulatory procedures, can be understood 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. These changes did "not push developments further along the same track, …" but opened up the possibility of new structural paths (Thelen 2003: 226-228). And, to a certain degree, "institutional conversion" took place also insofar as relative priorities in the hierarchy of goals had changed in the 1980s. Patient and public health protection was not abandoned, but lost in relative importance to the policy goals of industrial innovativeness and competitiveness through reorientations that stressed regulatory efficiency and regulatory costs. We will take up this perspective when discussing the accommodation of interests. The encountered fundamental structural changes can be interpreted as evolutionary results of incremental processes, where "l'accumulation d'une série de transformations apparémment mineurs peut déclencher une transformation d'ensemble de l'architecture institutionelle," (Boyer 2003: 197), and as voluntary decisions after experiencing the limits of a given approach or policy paradigm (Hall 1997).

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 object of policy-related learning can be the development and implementation of such policies as responses to defined problem situations. It can include substantive and institutional-organisational elements of such policies, as well as interactional orientations relevant for behaviour in the policy process. Learning for policy can occur in very different ways. It can be "lesson-drawing" (Rose 1991) through "learning from abroad" (Dolowitz/Marsh 2000) or through being based on internal comparisons perceiving "failings of a previous policy" (Heclo, 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 Daniel Moynihan termed the "professionalization of

reform" (Moynihan 1965),[26] 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).

Peter Hall distinguishes three types of changes as results of "social learning" (Hall 1993: 278-279). The highest level of learning leads to third order changes concerning basic policy goals and "paradigmatic" policy approaches. Second order change relates to the choice of policy programmes as derived from the more fundamental policy approach and goals and the choice of the main instruments employed. First order change concerns the operational level of implementation requirements such as directly applicable norms and standards.

These policy-related learning 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 behavorial 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 1978), or "between learning within a frame of reference and learning a new frame of reference," (Huber 1991: 93).

Policy decisions are not only, and probably most often to a lesser degree, the result of learning processes. 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 The case of European pharmaceuticals approval

Fundamental policy changes in the 20th century as learning from drug accidents
The 20th century witnessed fundamental changes in the control of pharmaceutical specialties, the single most important factors or motives behind these initial basic changes having been dramatic drug accidents. These experiences lead to a fundamental switch of policy concepts from industrial self-regulation to the establishment of state-based approval systems with increasingly comprehensive approval 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

[26] See also his 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 (Moynihan 1995).

was taken as a justification for corrective governmental action. Regulation was seen as providing the public good of medicinal quality, safety and efficacy.[27]

All regulations in the pharmaceuticals sector after the Second World War, national or European, were based on these fundamental changes of regulatory ideas, which were meant to learn from and 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.[28]

EC policy learning: recognition of discrepancies between goals and achievements
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 evident that the goal 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). Europe was perceived as becoming less attractive as a site for the development and production of pharmaceuticals. The reasons which were cited for this unsatisfactory situation 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 causes for missing out on these and other policy goals.[29] 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 – partly second, partly first order changes in Hall's terms – can be interpreted

[27] 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 at least be mentioned, see for example Weidenbaum (1981), Argyris et al. (1978), Schultze (1977), Weidenbaum (1997), Feick (1980). 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 once characterised as a fiction (Shepsle 1979).
[28] For Germany, see Hasskarl (1978); this has been confirmed by participating policy-makers (see D 2000 - 1); from a comparative perspective, see Mayntz/Feick (1982) and Gephart (1990).
[29] Not only marketing approval regulation influences economic efficiencies, but other regulations maybe more so, such as price, reimbursement and prescribing regulations, which vary among EC Member States.

as a dynamic evolving from the regulatory policy programme itself, whose missing parts have become progressively visible and have had to be inserted, and, also, as a reaction to the non-attainment of the espoused policy goals. The substantive policy development towards total legal harmonisation can be understood as a learning process. After various incremental policy changes especially the EC Commission as the main driving force, but also Member States, had to acknowledge that minimal harmonisation and even the quasi-total harmonisation of substantive rules had been insufficient to achieve equivalent regulatory implementation conditions and results at the national level, a precondition for mutual recognition and market integration via such a strategy.

Institutional-organisational changes 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 establishing institutional supports such as the introduction of two European bodies – the Pharmaceutical Committee and, especially important for implementation, the Scientific Committee (CPMP) – and the installation 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 important 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 lead 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 "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 institutionalised, a procedural mix that cannot be understood solely as the result of a learning process.

Changes in the goal structure

The radical change of the integration approach has only been partial, restricted to the more innovative parts of the pharmaceuticals market. Both Europeanisation or 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 or Decentralised Procedure*, nor the still existing *national procedures* are advancing the integration of the pharmaceuticals market. It is only the *Centralised Procedure* which contributes fully to this goal. In cognitive dissonance terms the regulatory modifications can be interpreted as an 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 impact of interests (chapter 4).

Interaction learning and the acquisition of trust

Besides learning from failures at the policy-making 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.[30] It would be imprudent to understate the importance of this kind of learning via interaction experiences as a prerequisite for the kind of joint decision-making foreseen in procedural centralisation. Practically all national and European regulators interviewed have confirmed this.

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 in the comitology phase of the *CP*) remains 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 joint regulatory decision-making could 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 introduced 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.

[30] It is 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), 30 years later increasingly large groups of regulators can be found in the national regulatory agencies who are not only able and willing to communicate in English as 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).

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 repeated failure to attain espoused policy goals such as the creation of a Single Market for pharmaceuticals. These experiences have led first to incremental procedural improvements short of abandoning national autonomy, but, ultimately, also to the structural institutional changes of 1995/98. Positive learning effects 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

The development of consecutive policies, including procedural-institutional implementation requirements, has not just been the result of learning processes. The regulatory patchwork of marketing approval policies for medicinal products in the EC can also be interpreted, very generally, as an "isomorphic association" (DiMaggio/Powell 1991) of interest and regulatory constellations or as a relative institutional 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 integrates a requisite a variety of influential interests in this policy field. A variety of 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.[31] There are multiple points where

[31] For a general discussion on this issue, see Nelkin (1979) and Jasanoff (1986).

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). And even 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, 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,[32] are of the utmost importance for the distribution of regulatory costs and benefits among pharmaceutical companies, patients and healthcare providers, and – further down the impact chain – for the financing of medicinal supply through healthcare 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.

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.[33] We can roughly distinguish four major groups of actors as being directly or indirectly affected by marketing approval regulations for pharmaceuticals[34]:

- the *pharmaceutical industry* as the main target and the *interest associations* that represent it;
- EU and national *regulatory authorities* at policy-making and implementation levels;
- affected *"user groups"* such as patients and healthcare professionals and their *associations*;
- *"internal and external experts"* of different background, with different motives and liaisons.

The pharmaceutical industry

Because regulations "represent important sources of competitive advantage and disadvantage for firms" (Vogel 1995: 12) *pharmaceutical companies* – and the *interest*

[32] The distinction between "risk assessment" and "risk management" is discussed in Breyer (1993).
[33] For a detailed discussion of the concepts, see Scharpf (2000: 116-122).
[34] These simplified characterisations of the interests of different corporate actors or actor groups, summarised in Table 2, are based on primary documents, secondary literature and interviews.

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 – eg, approval criteria, standards of control and implementation procedures – can vary substantially among groups of pharmaceutical enterprises and also 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 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 strengths are predominantly innovative medicinal products and which are generally the bigger players in the industry.[35] 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, should especially suit the interests of the second group of companies, which might even derive competitive advantages from a more demanding regulatory environment.[36] 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 (eg, 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 entail, first, the reduction of regulatory costs whatever the concrete institutional regulatory situation might be and, second, the preference of the highest possible procedural flexibility within the European regulatory framework, meaning freedom of choice among the different procedural alternatives. This general preference of flexibility

[35] 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.

[36] This is the experience gained from interviews with large and smaller pharmaceutical companies evaluating the regulatory reforms of 1976 in Germany (see Mayntz/Feick 1982). 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 (Lindblom 1977: 178).

Table 2
Authorisation procedures in the EU and actor interests/preferences
- a simplified taxonomy (based on documents, interviews and secondary literature)

procedures / actors	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	- European. uncertain - no Single Market	- influence of national authorities
national governments (ministries)	- national autonomy - protection of industry	- national autonomy - protection of industry	- participation in comitology - industrial policy goals
	- - -	- loss of autonomy	- loss of autonomy
national regulatory authorities (mainly agencies)	- organisational survival and autonomy	- organisational survival and autonomy	- organisational survival - organisational participation
	- - -	-	- loss of control
		regulatory competition among implementing authorities	
Industry	flexibility of procedural choice adapted to product range of enterprises		
product 1 - research-intensive - innovative - international market	- - -	- - -	- regulatory costs - regulatory behaviour - market size
	- - -	- - -	- - -
product 2 - less research-intensive - less innovative (e.g. generics) - international or multi-national markets	- selective choice of market	- selective choice of markets	- regulatory costs - regulatory orientation - market size
	- - -	- inefficient procedure - lacking mutual recogn.	- demanding requirements (documentation, fees etc.)
product 3 - not research-intensive - traditional medicines - mostly national or regional markets	- regulatory environment - market protection - economic survival	- regulatory environment - market protection - economic survival	- - - (no access)
	- length of procedures	- inefficient procedure - lacking mutual recogn.	- - -
medical profession/ patients	guaranty of variety of medicinal products		
	medicines adapted to national/regional medical traditions/ demands		- fast availability of innovative medicines
	- - -	- - -	(- fast-track lacking)
medical profession/ external experts/ consumer groups ("pharmaceutical and medical critics")	- - -	- - -	- improved transparency - comparatively strict
	- less transparent at national level - national variation in regulatory behaviour		- still not transparent and strict enough
	too much influence or consideration of industry interests		

positive for actor | negative for actor

in procedural choice has to do with the above mentioned fact that even large multinational pharmaceutical conglomerates whose strength are innovations generally produce a variety of product lines. Direct or indirect activities in the generics and OTC (over-the-counter, self medication) markets can be substantial.[37]

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 EU level, the EFPIA), the generics industry (at EU level, the EGA) and the companies producing more traditional medicines for the non-prescription, partly even non-pharmacy, market, also referred to as OTC-medicines (at EC level, 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 the most resourceful and powerful of the European associations (see Greenwood/Ronit 1992; Greenwood 1995). But as the recent Review (2001-2004) has shown, the other two European associations have had quite some impact on different aspects of the legislation, too.[38] 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 (eg, 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 inside industry, with the existence of important adversaries and a professional, public and political environment, which is partly characterised by suspicion of an industry whose trustworthiness has often been questioned.

National and European regulatory authorities

The *regulatory authorities* at the national level comprise the competent *ministries* and *implementing agencies or administrations*. At EC level it is the *European Commission* as the most community-oriented political actor and, since 1995, its evaluating agency, the *EMEA* with the *CPMP* (now *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 facilitating a joint European policy decision 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 joint 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). Its role in previous legislations had been

[37] Large multinationals may even concentrate strategically on less innovative medicines, an example being Bayer, Germany, which is planning to buy the OTC-sector from Roche with the aim of becoming a world leader in the self-medication market (Wassener 2004).

[38] See research project on the Legislative Review 2001-2004 (http://www.mpi-fg-koeln.mpg.de/review/).

purely consultative. In general, 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 (Deboyser 1991: 171). Even in the late 1980s it would have preferred a more courageous step towards regulatory centralisation than that which was finally realised in the legislation of 1993.

Although substantive topics of European regulatory harmonisation have been very 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, especially, the implementation levels. Regulatory internationalisation or even supranationalisation can be assumed to run 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. On the other hand, countries with an important innovative and internationally oriented pharmaceutical industry have had an interest in overcoming 'regulatory nationalism' for the product range of these companies in providing easier access to larger markets. Most governments, like industry, were in a mixed-motives position which demanded and allowed for differentiated compromises.

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, the latter sharing with most Member State governments. In this framework, the *Commission* has shown an interest in establishing or expanding regulatory competences. With the introduction of the *Centralised Procedure* in 1995, the enlargement of its scope in 2004, 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. Furthermore, the *Commission, EMEA* and the *CPMP* have been eager to demonstrate their abilities as capable regulators.

'Users' and 'experts'

'Users' are a very heterogeneous group and normally not directly involved in the policy-making or implementation process. Their importance and potential impact 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 or possess strong qualities as multipliers.

There are *consumer protection organisations*, on the European level in particular the European consumer organisation BEUC (Bureau Européen des Unions de Consommateurs), which has been an advocate of institutional Europeanisation for many years and, as such, a supporter of respective proposals by the Commission (Sermeus/ Adriaenssens 1984). Favouring strict safety controls and demanding transparency with respect to data and procedures, BEUC was also 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 sponsored by industry and have played the role of policy-coalition partners for them (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 'users'. Their 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 and regulatory authorities. This is a rather small world considering the differentiation into highly specialised disciplines and the scarcity of supply of excellent specialists. If not already tied to an institution, they are 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 some *outside experts* who are not 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 health and safety 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 1980s

For roughly 25 years the idea of regulatory centralisation at the 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 BEUC 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 decision for 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 and, especially, the 1990s . In the light of rising international competition and the perception of a 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.[39] The disparities in innovativeness and competitiveness, especially between Europe and the United States, and the industrial advantages of a large single market for pharmaceuticals were emphasised.[40] This changing perception of the policy problems in the late 1980s increased the prospects of 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 healthcare 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, it 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 European 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

[39] See, for example, Kaufer (1990), Ager (1996); Sauer (1997: 3); Majone (2002). 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 2002).

[40] See Burstall (1985); Economists/Group (1988); Cecchini et al (1988); REMIT (1997); Gambardella/Orsenigo/Fabio (2000).

(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 in 1999 – 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 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. … [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 endorsed the differentiated procedural approach of the Commission, did not want full-blown centralisation, nor any large-scale European regulatory bureaucracy, but preferred the flexibility of procedural choice, a step-by-step approach towards Europeanisation and, operationally, efficient, ie, cost-minimising, approval procedures.

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 Council[41] 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. Its procedural policy-mix represented the institutional accommodation of a wide variety of interests, which facilitated unanimous adoption of the respective Regulation and Directives in the Council in 1993.[42]

[41] Although 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 this case because of the transfer of the operative regulatory sovereignty from EC Member States and the establishment of a new European institution (Thompson 1994: 4-5); the Commission was surprised by the "bombshell" of its legal service when this advised that, not Art. 100a, but Art. 235 would be the correct legal basis (House of Commons: Health Committee 1992, March: XII).

[42] See the observation of an "accommodation of diversity" in EU environmental policy by Héritier (1996).

4.3 Interest accommodation in the institutional structure of the three procedures

The 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 procedures might be interpreted as an isomorphic constellation (DiMaggio/Powell 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 these 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 *healthcare 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.[43] At the same time, national approval procedures guarantee the organisational existence and regulatory autonomy of *national regulatory authorities*.

The Mutual Recognition or 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* or less innovative ones 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 advantages of the *MRP/DP* apply 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 in very rare cases, so

[43] 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 (Murswieck 1983). From the UK it is known that there are prominent supporters of these 'soft' medical therapies – for example in the Royal Family.

far. Thus the *MRP/DP* protects the interest of *national authorities* in regulatory autonomy and organisational continuity. Most of them are therefore in favour of it, actually even more so than *pharmaceutical companies*, which are not so satisfied with its overall regulatory and organisational inefficiencies (European Commission 2000).

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 can be completely 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 to medicines in the EU Member States (Feick 2002: 38-42; see also Table 4). In the legislative review of 2001-2004, therefore, the *Commission* and the *European Parliament* 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 obligatory binding arbitration in the *MRP/DP*. With respect to the first aim, there was strong opposition from many *Member States* and, partly, *industry* too before a compromise was reached limiting this further obligation to take the central route to new medicines for four indications. As to the second aim, obligatory binding arbitration was introduced in case of disagreement, against the opposition of some Member States.[44]

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)

[44] It should be noted that for these decisions of the legislative Review of 2001-2004 no longer unanimity in the Council was applied – against the futile opposition of some Member States.

Table 4
Diversity in the European medicines market
Mutual availability of active ingredients: country 1 → country 2 (%)

Country 2 / Country 1	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 categorised according to ATC code (anatomical, therapeutic, chemical).

Sources: EURO-Medicines Database; Folino-Gallo 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 for approved medicinal products. 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 large parts of industry but also by most other concerned or interested actors. 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. Nevertheless, industry did not really favour the extension of the scope of the *Centralised Procedure* in 2004 and would have preferred complete flexibility of choice between the *CP* and the *MRP/DP*. 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. [45] Among these critics there are also those who would argue that regulatory competition among increasingly fee-

[45] See, for example, Abbasi/Herxheimer (1998) and the reply from the then director of the European agency (Sauer 1998).

financed regulatory agencies and the race for regulatory efficiency could jeopardise the strict application of safety and efficacy standards.[46]

The variety of procedures accommodating a plurality 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* had 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 the implementation of the *Centralised Procedure* requires intensive regulatory participation on the part of *national authorities* at agency and ministerial level. At the same time the *CP* satisfies largely the institutional interests of the *European Commission* and the industrial policy interests of *national governments, EU* and important parts of *industry*. For the *pharmaceutical industry* the "flexibility" of procedural choice has been crucial, satisfying different parts of it. The same perspective can be applied with respect to the 'users'. The variety of procedures allows for the supply of a variety of medicinal products adapted to heterogeneous medical demands.

5. Asymmetries of influence and interest accommodation

The fact that a plurality of interests are embedded in the established regulatory policies, providing direct participatory access to the policy-making process and implementation procedures or assuring their indirect consideration in the deliberation, negotiation and decision-making processes at EC and national levels, does not exclude asymmetries of influence and in the consideration of interests. 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 evidence suggests that, in general, industry is in a privileged position. This is in accordance with Lindblom's more general hypothesis 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." In this system "business simply needs inducements, hence a privileged position in government and politics, if it is to do its job." As a consequence "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).

Although this appreciation relates to policy-making and implementation alike the following part will concentrate mainly on the latter phase of the policy process. There are specific factors and conditions in implementation which put industry in such a privileged position. These relate to

- informational supremacy;
- institutionalised or de facto 'secrecy' of regulatory procedures and data;

[46] This is a highly contentious issue; for voices anticipating the risk of reduced safety, see Abraham/Reed (2001) and Abraham/Lewis (1999), for opposite views, see Vogel (1998) and Vos/Hagemeister (2000); critical from a not only European but also US-angle see Griffin (2002).

- dependence of regulators on regulatees' cooperation for successful implementation and
- organisational implementation arrangements and the orientations of administrators.

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 outcomes, 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.[47] As the investment in drug development up to the point of marketing approval can be tremendously high,[48] 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 this threatens to backfire sooner or later and can put the economic future of companies at risk. But there are margins of discretionary interpretation.

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, but it also reinforces the above mentioned asymmetrical influence structure. 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 (see note 45). 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 reforms of 2004 therefore contain further transparency requirements at the European level, on the insistence of the European Parliament.

[47] For a critical discussion of these issues, see for example Quick (2002), WHO (2002), Davidoff et al (2001), Medawar (1997), Abraham (1994).

[48] Estimates of drug development costs in the innovative pharmaceuticals sector show that they have increased roughly tenfold within about twenty years (Sykes 1997: 6) 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 2004: 21, note 3).

5.2 Regulatory dependence on cooperation and changes in administration
Especially in complex regulatory policy fields, successful implementation depends on the 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 such regulatory domains 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). In pharmaceuticals this close "co-operation between agencies and the industry" has been applauded also by industry. (Sykes 1997: 6) Nevertheless such a necessity of and actual practice of cooperation opens 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.

Furthermore, 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 now supposed to deliver a service which guides applicants as efficiently as possible through the procedures and over regulatory hurdles (Feick 2000: 244-246). Different mechanisms translate this client-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 each side get to know one another quite well. Furthermore, regulatory agencies have become increasingly open to the enquiries of applying companies, even during the assessment phase – a behaviour which was almost unthinkable two decades ago. And it is intentional policy today, at EU level and national levels, to provide active pre-application guidance for future applicants, partly in order to 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 comitology system at EC-level would suggest.

These features add up to a separation of regulatory decision-making from closer political and public 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 means of influence.

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, possible majority decisions being the exception. And the opinions delivered to the Commission via EMEA, which are the basis for the final approval decisions, 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 (see figure 1). 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.

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" (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,[49] 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.[50] In contrast, the interests of *pharmaceutical 'users'* are much more difficult to organise and can be mobilised only under extreme attention-grabbing conditions (see

[49] For overviews, see Baldwin/Cave (1999: 24-25); Hood (1994: 20-26); Feick (1980: 49-50).
[50] Olson (1968), Wilson (1980); for an estimate of the political strength of the pharmaceutical industry, especially the European association, the EFPIA, see Greenwood (1995).

the Thalidomide scandal).[51] 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 motives.[52] 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 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 EMEA 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 data and examples, showing that the Food and Drug Administration (FDA)'s post-marketing withdrawal rate on safety grounds has gone up since 1992, the year when user fees were introduced at the US 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.[53] Whether it was the pressure of industry itself, of patient groups, politicians, administrative heads of the Agency or an alliance of several actors 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 frame, 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).

[51] 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 demand compensation for drug damages has made pharmaceutical companies more prudent when it comes to avoiding economic damage due to bad publicity and liability claims.

[52] 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).

[53] 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).

"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 and national context stems from a rather complex constellation of institutional and orientational factors whose interplay allows industrial forces – in their heterogeneity, 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, generally, is in a privileged position in policy making and implementation.

6. Conclusion: Learning and 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, which are able to provoke public demand for stricter controls. 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. It is also worth pointing out again 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, the type of medicinal product along the novelty- and innovativeness-dimensions has been an important factor for the acceptability of procedures, especially for Member States. Up until now, the *Centralised Procedure* has largely lived up to expectations (see European Commission 2000). In the legislative Review completed in 2004, the Commission and the European Parliament had proposed to enlarge the scope of this procedure, making it obligatory for all new active substances. Most Member States 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 Procedure*. The result has been a compromise with the scope of the obligatory *Centralised Procedure* being extended to all new active substances in four indications and the legal obligation to reconsider the Commission's initial position after four years.

The development of this astonishing procedural mix over three decades has been described as sequences of incremental and structural change 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 cooperation in the European procedural framework of policy implementation. 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 (in force in 1995) with respect to the *European Centralised Procedure*, 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. 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* (see figure 2) – which transferred exclusive 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 implementation.

The main conclusions of this paper are that the evolution of marketing authorisation in the EC and the resulting procedural variety is a product of learning processes at both policy making and implementation level in this European multi-level and multi-actor system and of the influence of a plurality of interests in the European pharmaceutical policy domain which, somehow, had to be accommodated. Without such a relative isomorphism of interest and institutional structures, the hurdles, especially the unanimity constraint in the European Council of Ministers in 1993, could 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 jeopardising the regulatory goal of patient and public health protection, namely by neglecting high safety and efficacy standards in medicines

approval – and in pharmacovigilance. Conversely, there are other observers who would maintain that an already overly precautious control of medicinal products threatens to hamper pharmaceutical and medical innovation as well as industrial competitiveness and economic success.

To analyse systematically the distribution of influence and of interest consideration is a difficult task if it goes beyond 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) in the political process. This outlook opens a different debate – that of the democratic control and legitimation of regulatory decision-making in policy sectors of high substantive complexity, a complexity which is institutionally intensified by the European multi-level 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 1999).

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