

**MARKETING AUTHORIZATION
FOR PHARMACEUTICALS IN THE
EUROPEAN UNION**

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D) Introduction

As a result of thirty years of policy evolution in European pharmaceuticals regulation, culminating in the regulatory reforms of 1993 (implemented in 1995), the European framework for marketing authorisation of pharmaceuticals is a complex mix of regulatory regimes in the same policy domain. We are witnesses of the co-evolution and, today, co-existence of three distinct regulatory procedures in the same regulatory domain:

A The purely national procedures based on harmonised legislation;

B Quasi-European Procedures, also based on this harmonised legal framework, but in a partly co-operative, partly coordinated European context with the expectation of mutual recognition (**Mutual Recognition Procedure - MRP**) or via parallel authorisation based on the expectation of mutual adaptation and compromising (**Decentralised Procedure - DCP**);

C The **European Centralised Procedure (CP)** in which assessments and regulatory decisions are established at the European level – with centralised oversight by the Commission and scientific appraisals conducted by national regulators, organised through the European Medicines Agency (EMA) and its Scientific Committees (CHMP for medicinal products for human use, CVMP for veterinary medicinal products) and embedded into a joint decision-making framework which binds together national regulators and obliges them to arrive at a European decision valid for all member states.

What is particularly noteworthy about these regimes is that they are applied according to the type of medicinal product for which, and the number of countries in which, a pharmaceutical entrepreneur seeks marketing authorisation. Although purely national procedures still outnumber the two other categories and have therefore not lost importance for national agencies and their pharmaceutical clients, we might neglect them in this paper for two reasons. First, the products dealt with in this procedure are either mainly of regional or national interest or the procedure is chosen only as a first step before application in other member states and, thus, a triggering of regime **B**, the MRP or DCP. Second, these are generally not medicines containing new active substances or establishing an otherwise innovative medicinal product.

This leaves us with regimes **B** and **C**, where the **Centralised Procedure (C)** is required for especially innovative and other defined categories of medicinal products and is available for other medicines which can be defined as innovative. The scope of the CP was enlarged by the review of the pharmaceutical legislation in 2004, which

even stipulates a further automatic enlargement of the CP's scope for May 2008. Although there is intense debate over what constitutes pharmaceutical and, above all, diagnostic or therapeutic medicinal innovation, there can be no doubt that the medicines which pass the European Centralised Procedure represent the more advanced medicinal products. They are generally of greater importance for and in health care, therapeutically as well as financially. At the same time they tend to be of great economic value to the license holders, and they may represent scientific and technological frontiers of medicinal research and development.

Regime **B**, the **Mutual Recognition or Decentralised Procedure**, in contrast to the CP, leads to national marketing authorisations and has to be applied whenever the Centralised Procedure is not obligatory or optionally chosen whenever a medicinal product shall be marketed in more than one member state. In the meantime, the **MRP/DCP** has become the main authorisation route for generics which are of increasing importance for national health care systems under the strain of cost-containment.

Being able to investigate and to discuss these two (more or less European) procedures puts us in the position of discussing the relative efficacy of different institutional arrangements with respect to a variety of legally stipulated and officially espoused or more latent though not less relevant objectives:

- protecting patients as consumers on the one hand and assuring expedited access of patients to innovative medicinal products on the other;
- creating a single market for medicinal products in the EU;
- providing the basis for a viable diversified European pharmaceutical industry and at the same time providing incentives for research-intensive companies to innovate;
- reducing the regulatory costs to industry in terms of approval times, avoiding red tape and unnecessary doubling of laboratory and clinical tests;
- setting up a stable implementation framework which strikes a balance between substantive harmonisation, centralised oversight and co-ordination on the one hand and the input and co-operation of decentralised institutions at national or even regional levels on the other; and
- institutionalising procedures which are transparent and credible.

It is difficult to draw conclusions based on hard evidence not only because it is principally extraordinary difficult to specify causal connections and conclusive measures, but also because this policy field is so complex. It would be irresponsible to take into account only institutional variation in marketing authorisation in explaining outcomes which rely on a variety of interrelated factors, many of them having to do with the delivery and financing of healthcare for which national governments remain responsible.

Yet, looking at the institutional variance in marketing authorisation, the tentative conclusion this paper will point to is that while the different institutional mechanisms all appear to have been rather satisfactory in protecting consumers – and the reforms at the European level, especially since 1995, certainly have contributed to this goal as well as to most of the objectives mentioned above – the contributions of the regulatory mechanisms to the creation of a single market in pharmaceuticals have been quite different. In short, historically, the introduction and extension of the Centralised Procedure can be regarded as a major step towards a single market, while the decentralised mechanism remains, by design, more selective depending largely on choices at the company level.

The historical and present motivations of most member states in objecting to a plain centralisation of marketing authorisation – such as establishing a European FDA in the American tradition – seem to be difficult to explain in terms of the generally-agreed-to policy objectives and the technical and scientific basis of regulatory decision-making. But member states and their regulatory institutions have been reluctant to transfer authority to the European level, not only because they are not prepared to give up regulatory sovereignty or to endanger organisational survival, but also because they fear the loss of regulatory expertise and capacity. After all, national politicians and regulatory authorities have to take the political blame in the case of major pharmaceutical accidents or catastrophes, which cannot be predicted. And from a regulatory and professional perspective, one can argue that decentralised expertise remains necessary at least to ensure pharmacovigilance, to control clinical trials, etc. A centralisation which eradicates decentralised expertise at the national and regional level might even prove counterproductive as far as patient protection is concerned. Nevertheless, even accepting these arguments, there remains quite some room for institutional design which meanders between the poles of centralised and decentralised authority.

II) Marketing authorisation in the context of pharmaceuticals regulation

The complex area of pharmaceuticals regulation

Marketing authorisation is only one regulatory domain in the large and complex field of pharmaceuticals regulation. Indeed, one can argue that pharmaceuticals or medicinal products are among the most regulated goods with an already long history of increasingly close regulation, for many reasons. Firstly, pharmaceuticals can be not only helpful but also highly dangerous. Secondly, market transparency for consumers – and even for most medical professionals – practically does not exist and probably cannot exist in its entirety. Thirdly, pharmaceuticals are of enormous economic interest not only to inventors, producers and sellers but also to whole regional, national or even transnational economies. Fourthly, their distribution to patients and their financing pose specific problems due to medical traditions, the cost of medication and the specific welfare state arrangement or health care system of a country. Lastly, even ecological questions arise, not only in the context of production but also with respect to consumption and digestion or the disposal of left-over pharmaceuticals.

All the points mentioned above can be translated into policy problems of their own, warranting one or the other kind of collective action in the form of policies whose

shape can differ enormously between jurisdictions. Although these policy problems as well as their outcomes and impacts are often interdependent, we will concentrate here on the question of market entry, i.e. on the policy of marketing authorisation. We can justify this approach on two grounds:

- **Institutional:** The Treaty of the European Communities provides the EU with regulatory and judicial competencies concerning product regulation with an impact on the free movement of goods; but the subsidiarity principle leaves the regulation of social protection and health care with the member states (Art. 14, 28, 29 TEC; Art. 30 TEC).
- **Epistemological:** For reasons which cannot be discussed here industry and regulators in most developed countries have succeeded in keeping marketing authorisation regulation within a sphere of scientific and technological reasoning, seemingly leaving aside any financially or economically motivated considerations – even those of comparative therapeutic advantage. This is partly a make-believe world as can be easily shown.³ On the other hand, it is this professionalised discourse and its partly successful immunisation against politics and economic reasoning which has allowed the degree of harmonisation, co-operation, centralisation and joint decision-making which has been achieved at the European level in the meantime.⁴

III) Conflicting goals and interests

The declared policy objectives can be categorised as follows:

Patient protection and public health contain two interrelated, and in practice potentially conflicting, goals which consequently require regulatory mediation. One goal is protective, namely to avoid or limit the risk of distributing qualitatively inferior drugs, those with unacceptably severe side effects and those with nonexistent or unacceptably low therapeutic efficacy. The complementary health goal is supporting, namely to allow market entry for promising medicinal treatments as fast as possible.

The creation of an internal or single market is targeted at two groups. From the point of view of the pharmaceutical industry this means potential access to all European consumers for a medicine authorised within the EU; and from the point of view of patients it means potential access to all medicines available within the EU.

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

³ There is a vast amount of literature which shows how much political and economic consideration flows into these decision-making processes, but the literature also shows that inevitably normative decisions shape this kind of technically- and scientifically-based discourse and its regulatory outcome.

⁴ See Feick (2000) for a discussion of this historical development.

Behind these partly conflicting goals stand stakeholders and interest groups possessing more or fewer resources to make themselves heard in the political process and to influence the implementation of stipulated legislation. The well-organised and in different respects resourceful, though not homogenous, pharmaceutical industry has much more power and influence than consumer protection groups, for example. Member states, also heterogeneous with respect to their interests and preferences, complete the picture in that they pursue their own particular goals in this policy domain. Their goals are linked partly to genuine institutional self-interest and partly to the specific structure of a national industry, health care system or more general regulatory and medical culture.

In addition to institutional and legal constraints, the Commission has to take this variety of interests and preferences into account when pursuing the genuine European Community goal of promoting and ensuring a common or single market, also in the pharmaceutical sector.

Table 1: Diversity in the European medicines market

Mutual availability of active ingredients: country 1 → country 2 in %

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 *	71	69	58	-	75	68	58	63
GER	68	54	43	42	-	50	42	49
NL	80	76	65	56	84	-	61	69
S	79	71	74	59	83	72	-	70
UK	68	62	55	60	73	62	53	-

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

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

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

The single market goal

As Folino-Gallo et al. showed for practically all medicinal products available in at least one member state (see Table 1; (Folino-Gallo et al. 2001)), and as the EURO-MED-STAT Group (EURO-MED-STAT and Group 2003) showed for 2002 with respect to lipid lowering medicines: Medicinal products are by far not equally

available in all EU member states. With respect to the latter pharmaceuticals category, 21 serum lipid reducing agents are licensed and available in Germany, 17 in Italy, 11 in both Sweden and France, 10 in the Netherlands, Finland and Belgium, 9 in Denmark and 8 in both Ireland and Norway. To look at it from a different angle: the first 5 active ingredients were available in all 15 member states in that year, and 9 in more than 10 member states. Of the 37 active ingredients on the list, 18 are licensed and available in only 1 member state.

This kind of data is often cited as proof that a single market for medicinal products does not exist in the European Community. But what do we understand a single market to be? Does it mean that every product has to be actually available in every place? Certainly not. Spatial differentiation of markets is a well-known marketing strategy of companies. What is closer to the definition favoured by the Commission and industry alike is that there should be no trade barriers via tariffs or technical regulations. Ideally, companies should have the right to sell where they want to sell and at a price which they determine. Due to the potential negative externalities of the development, production and distribution of pharmaceutical products, and due to the lack of transparency for consumers, this is a highly regulated field in which, as mentioned above, regulatory competences rest largely with the member states. This has created a regulatory patchwork within the European Community setting up direct and indirect barriers against the free flow of goods which cannot be a dominating value in itself in a sector like pharmaceuticals.

Marketing authorisation represents only one of these regulatory barriers, but one which was thought to be surmountable due to its concentration on specific scientifically- and technically-based standards: pharmacological quality, toxicological safety and medical efficacy. The history of European marketing authorisation for pharmaceuticals shows how difficult this has been and still is.

IV) The development of European marketing authorization⁵

A catastrophe, national action, Commission awareness and first steps

From the very beginning – the discussion of the first Directive of 1965 – **mutual recognition** has been on the Commission's agenda as the preferred mechanism of market integration in the pharmaceutical sector. A medicinal product authorised in one member state should be automatically tradable in another member state, thus avoiding a situation in which a pharmaceutical entrepreneur would have to apply for marketing authorisation in each member state in which he wanted to sell this medicine and shoulder the accumulated regulatory costs (national fees, preparation of different application etc.). Until 1995, with the start of the Centralised Procedure for a limited part of the pharmaceutical spectrum (mainly biotech medicinal products), this situation did not change formally. (See Appendix 1 for an historical overview.)

After the Thalidomide catastrophe in the late 1950s and early 1960s, national regulations concerning the marketing of medicines became more stringent, controlling for the quality, safety and efficacy of medicinal products, with the US paving the way.

⁵ There is a large amount of literature on the development of market entry regulation for pharmaceuticals, in general, and the development in the EC and EU, in particular. We would like to cite two critical accounts of these developments by John Abraham and colleague: (Abraham 1995); (Abraham and Lewis 2000); see also (Feick 2002).

Its regulation, along with that of more advanced European countries like Sweden, became a kind of model for quite a few European national governments. Countries which already had obligatory licensing procedures strengthened them, and those without them introduced marketing authorisation procedures which went beyond mere formal registration.

The Commission of the European Communities was well aware that this development in the national legislations presented the danger of enlarged national regulatory hurdles in the way of the creation of a single market for pharmaceuticals. It therefore proposed a Directive, which the Council approved, whose aim was to approximate provisions in the member states 'laid down by law, regulation or administrative action relating to medicinal products' (Council Directive 65/65/EEC of 26 January 1965). This first Directive, which was held in rather general terms, required member states to apply licensing procedures before the marketing of medicines and to withhold medicines from the market which did not meet the criteria of quality, safety and efficacy after they had undergone documented controls which a competent national authority had to assess and evaluate.

Under the specific circumstances at the time, the espoused goals of this directive were, first, 'to safeguard public health'; but, second, this had to be done without hindering 'the development of the pharmaceutical industry or trade in medicinal products within the Community'. The overall goal of this directive with regard to the EEC was to remove hindrances 'to the establishment and functioning of the common market' – if necessary by way of 'approximation of the relevant provisions' – i.e. legal harmonisation, as laid down in Art. 94 TEC (formerly Art. 100). The EC institutions anticipated that this might be achievable only 'progressively' (preamble of Council Directive 65/65/EEC). In Article 3 it was also made clear that

the provisions of this directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions.⁶

These summarizing quotations from the first Directive mention all the basic difficulties the Commission has been struggling with over the years in trying to create a common or single market for pharmaceuticals.

Co-evolution of different regulatory and European logics

The regulatory development in this field can be described as the co-evolution of different regulatory strategies employing a mix of regulatory instruments in order to arrive at the Europeanisation⁷ of marketing authorisation for pharmaceuticals (see Figure 1).

The **first attempt** of the Commission in the early 1960s to arrive at (automatic) mutual recognition with a minimal degree of **legal harmonisation** failed; furthermore, ever more extensive harmonisation did not guarantee such behavior on the part of national

⁶ This despite several attempts in the 1980s and 1990s on the part of the Commission to liberalise, deregulate or Europeanise national regulations in these areas, which basically failed.

⁷ Europeanisation policies can be defined in different ways. Here the term is introduced as the main category comprising legal harmonisation, mutual recognition of national decisions and procedural integration at the European level as strategies or instruments of Europeanisation.

authorities. The **second attempt** was to provide **procedural incentives and support** by setting up non-obligatory and non-binding **multi-state procedures** and establishing a Scientific Committee (CPMP), composed of representatives of national regulatory authorities, whose aim it was to arrive at consensual regulatory recommendations and to encourage mutual recognition without actually requiring it. Thus, between 1975 and 1983 several pseudo-European approval procedures were introduced, providing for enhanced communication and co-operation between national authorities without interfering in their final decisions.

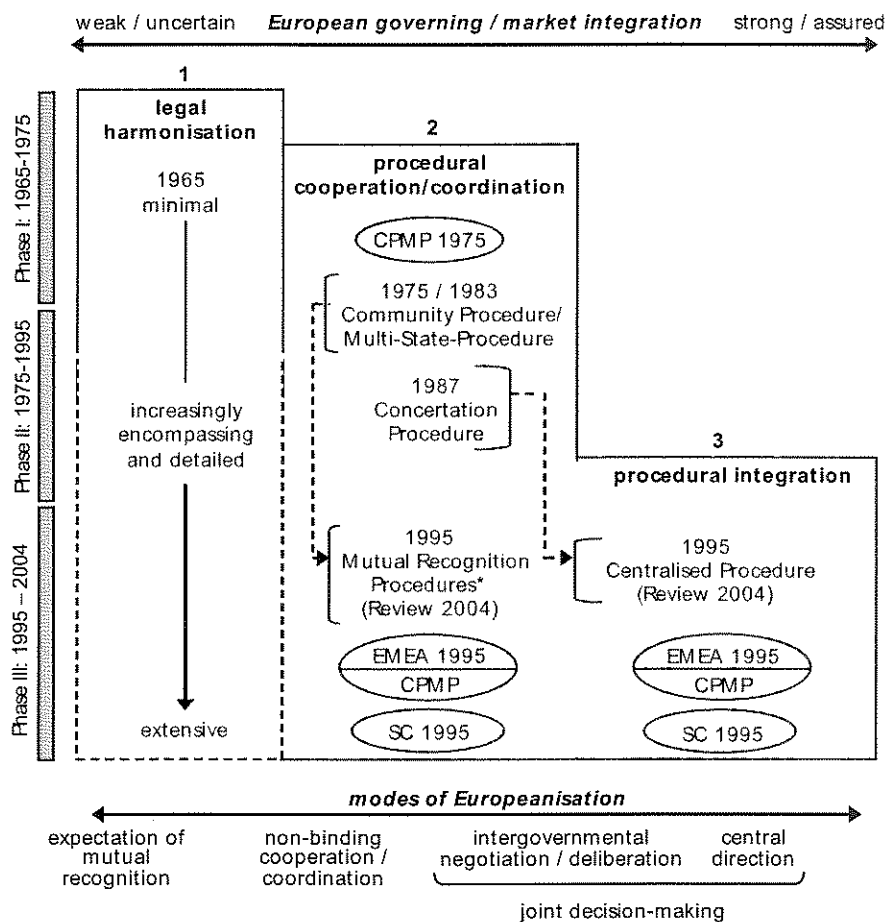
The **Concertation Procedure** of 1987 was another evolutionary step, with national regulators obliged to consult the Scientific Committee CPMP with regard to a subset of especially innovative drugs before making their final decisions at the national level. However, while the Concertation Procedure resulted more often than not in similar national assessments – largely due to the fact that the medicines assessed using this procedure were completely new products which did not carry with them national regulatory histories – national differences still often surfaced and there were efficiency losses as national authorities insisted on the conducting of national assessments in addition to the assessment by the CPMP (see (Vos 1999: 206-211); (Macarthur 1993: 25-28); and the European Commission (European Commission 2000, October), 2000). This second attempt at procedural integration largely failed as well, although the Commission rightly considered this procedure a first step towards the procedural integration of regulatory decision making at the EU level (Deboyser 1991).

In general, there was too much mutual distrust in the national implementation of the harmonised legal provisions. Even in 1989, when the Commission was proposing further steps towards centralisation after 24 years of harmonisation and limited regulatory cooperation, governments in such countries as Germany – which tried to fend off the centralisation of regulatory competencies in Brussels and explicitly favored mutual recognition – were not willing to apply mutual recognition until a certain level of control was ensured for each member state. This was the position of the Ministry for Labour (BMA) put forth in an internal governmental paper on April 3, 1989, on the occasion of the amendment of the German Drug Law (Arzneimittelgesetz, AMG). The weakest state in terms of regulatory compliance should not be the entrance gate into the whole European market. As one scholar of European integration remarked: ‘Until regulators can trust each other to avoid ... selfish strategies, centralisation of regulatory authority is the only practical way of correcting transboundary externalities, or preventing the local regulation of a local market failure from becoming a trade barrier’ (Majone 1998: 32).

The reforms of 1993 in fact introduced, in particular, the **Centralized Procedure (CP)** to replace the Concertation Procedure. They established a truly European regulatory regime leading to EU decisions. However, the CP was mandatory only for biotechnologically produced medicinal products and optional for some other subsets of innovative new products. Applications in these fields were rather limited at the time. In other words, whatever their other motivations, the Member States agreed to this new procedure for fields where the distributional consequences for existing national producers was, so far, not very important. Similar to the Concertation Procedure, the CP was based on assessments by the CPMP (called, since 2004, CHMP), but the final regulatory decision was now made by the Commission, subject to the regulatory comitology procedure, and not by the Member State authorities.

Member State authorities, however, were included in the decision-making process through their representation in the CPMP in general and their significant role in providing the basic assessments for the CPMP through a rapporteur/co-rapporteur system in particular, and their participation in the comitology procedure at Commission level via the Standing Committee.

**Figure 1: EC pharmaceuticals marketing authorisation
Integration strategies and stages**



- EMEA: European Agency for the Evaluation of Medicinal Products; since May 2004: 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)

* In 2004 the Mutual Recognition Procedures became legally split into a Mutual Recognition Procedure (MRP) and a Decentralised Procedure (DCP).

Institutionally, the creation of a European Medicines Evaluation Agency (EMEA), though not an independent regulator but imbedded into a larger EU structure of regulatory decision-making, was not only of symbolic importance but it has become the coordinating centre within a cooperative, decentralised network for regulatory assessments and evaluations on which regulatory decision-making is based at

Commission level. What EMEA recommends, following the opinion of its Scientific Committee, generally passes the comitology procedure without amendments.

The second new authorization procedure applied to all medicines to be introduced in more than one member state for which the Centralized Procedure was not obligatory: the **Mutual Recognition Procedure (MRP)**. The MRP applied to most drugs intended for multi-national distribution. Once a favourable decision was made in one Member State, clearance was required in all Member States, unless the initial clearance was challenged by another national authority. The 1993 Directive restricted the grounds on which Member States could reject another Member State's assessment (only potential risk to public health constituted an acceptable ground, though the concept was not sufficiently defined). The Directive provided for mandatory EU-level arbitration if a Member State rejected the decision of another: such arbitration was to be conducted by the European Medicines Evaluation Agency (EMEA).

Table 2: Marketing authorisation in the EU since 1995/1998 - medicinal products for human use

Procedure	Legal Basis	Scope
Centralized Procedure leading to Community authorisation applicable in the whole EU	Council Regulation (EEC) No. 2309/93	Mandatory for biotechnologically produced medicines (Part A of the Regulation Annex) and optional for innovative medicines (Part B of the Regulation Annex)
Mutual Recognition Procedure leading to national authorisations	Council Directive 75/319/EEC as amended; national harmonised law	Mandatory for all medicines introduced in more than one MS and for which the CP is not mandatory
National procedure national authorisations	National harmonised law	Mandatory for all medicines not authorised by the CP and introduced in only one MS

Table based on (Broscheid and Feick 2005: 10)

The legislative review of 2001–2004 and its outcomes

We will not dwell on the rather complex politics of this legislative reform process (see (Broscheid and Feick 2005)) which had been stipulated in the legislation of 1993 and which stood under a certain pressure due to the accession of 10 new member states in May 2004. By then at the latest, the regulatory bodies at the European level were expected to be adapted to the larger size of the community and to have introduced some harmonisation measures, e.g. of the protection period for application data. Not meeting the deadline might have endangered the whole reform enterprise.

The Commission's reform proposals (1 Regulation and 2 Directives, one of them dealing with veterinary medicines) were sent to the Council and the European Parliament in 2001, after extensive consultations with stakeholders in which the pharmaceutical industry, especially the European Federation of Pharmaceutical Industries and Associations (EFPIA), played a prominent role, and after an extensive evaluation by external consultants (European Commission 2000, October), whereby the latter partly concentrated on the details of implementation which could not be dealt with in the Review. We will concentrate here on the points which seem to be especially important in terms of the institutional balance between the European and national levels in the regulatory procedures, the overall weight of the individual

procedural alternatives, the smoothness of the co-operation within networks of regulators, the probability of arriving at European decisions – especially mutual recognition in the Mutual recognition and Decentralised Procedure – and, of course, the probability of advancing a single market in pharmaceuticals.⁸

The **Centralized Procedure**, reserved for the most innovative products and the pet procedure of the Commission and EMEA, received generally positive evaluations with respect to procedural speed and the (technical/scientific) quality of its decisions. Several companies, a number of member states and, above all, the Commission supported an extension of the scope of the procedure to additional products or product categories. There were complaints by many pharmaceutical companies about the efficiency of decision preparation and decision making in the post-assessment phase and in the comitology procedure after EMEA's/ CPMP's opinion had been forwarded to the Commission.

Review outcome concerning the CP: Despite highly controversial discussions in the Council, the result of the Review was a substantial extension of the scope of the CP with respect both to obligatory and voluntary participation; though, it was not as far-reaching as the Commission had hoped. However, an automatic extension will take place in May 2008 (inclusion of two further indications for which the CP will be obligatory) with the option for the Commission to propose further extensions to the Council. Of less importance seems to be the shortening of deadlines at EMEA after the CHMP has delivered its assessment and for the comitology procedure after EMEA has sent its opinion to the Commission.

The Mutual Recognition Procedure: This procedure was in for greater criticism. The main problem was still an insufficient application of mutual recognition by Concerned Member States (CMS) of assessments and evaluations made by a Reference Member State (RMS). There was a feeling that some member states abused the opportunity to claim a 'risk to public health' as a precondition for the denial of mutual recognition. Pharmaceutical companies especially criticised the fact that binding arbitration procedures at EMEA (CPMP) lasted too long and prevented the introduction of medicines in member states which were prepared to approve them based on mutual recognition before the completion of the arbitration procedure. On the other hand, there were complaints that applying companies could evade European binding arbitration by simply withdrawing their application from the dissenting national authority. Companies regarded the MRP as rather cumbersome, time consuming and more costly than it needed to be.

Review outcome concerning the MRP/DCP: It comes as no surprise that the weakest and most criticised part of the marketing authorisation procedures in terms of Europeanisation and efficiency was strengthened in the end, even though the procedures remain essentially national still resulting in national authorisations, but asking for and supporting close co-operation between national authorities and incorporating negotiations, deliberations and even binding arbitrations at EU level.

⁸ Only at the margins we will mention questions concerning a speeding up of application processing time, and we will not discuss the harmonisation of data protection or the question of direct information to consumers (Direct-To-Consumer Information, DTCI) with respect to prescription drugs at all, which were also part of the reform package. Due to insurmountable controversies about the character of the information, the proposal was removed from the reform package so that the May 2004 deadline would not be jeopardised.

There is now a **clear distinction** between the Mutual Recognition Procedure (MRP, for products already authorised in at least one member state) and the Decentralised Procedure (DCP, for products not yet authorised anywhere in the EU). Concerning the latter the **sequencing** of the procedure has been substantially changed: Now RMS authorities discuss their assessment and planned evaluation decision with CMS authorities in parallel before establishing their official position. The **denial of mutual recognition** is now allowed only for 'serious potential risk to public health', tightening the existing language somewhat (a Commission Guideline is supposed to make its application more straightforward). The CMD(h) (Co-ordination Group for Mutual recognition and Decentralised Procedures - Human; formerly the Mutual Recognition Facilitation Group, MRFG) composed of representatives of the national authorities, has become formally institutionalised and embedded in the procedures. Thus dissenting opinions are referred to the CMD for non-binding discussions and potential referral to the CHMP for binding arbitration. Selective withdrawal by applicants after the RMS has formulated its final opinion (day 120) no longer prevents **binding arbitration** in case a CMS rejects the decision of the RMS. However, the applicant whose product is in the process of binding arbitration is allowed to market it in all member states which accept the RMS's evaluation. The Directive asks the CMD to set up lists of products whose **Summary of Product Characteristics (SPCs)** should be harmonised in order to facilitate mutual recognition of evaluations where one or more similar medicinal products have already been authorised.

Institutional bodies and procedural formalities: There have been propositions with respect to EMEA's Management Board and the Scientific Committee(s) – mainly originating from the Commission and industry – to reduce the participation of national representatives and to increase the importance of stakeholders, on the one hand, and to select Scientific Committee members more with respect to specialised expertise and less with respect to equal representation of the national regulatory authorities. Practically everybody agreed that the size of these bodies should be kept within manageable and functionally acceptable limits. In view of regulatory efficiency and regulatory costs, a shortening of deadlines was proposed – with respect to assessment as well as administrative processing time.

Review outcome concerning institutional bodies and procedural formalities: By and large, the interests of member state governments prevailed. Their equal representation in the regulatory bodies – of special importance: in the CPMP (now: CHMP) – was maintained although it was reduced to one per member state in order to keep the size of these bodies reasonable. Industry associations did not succeed in being represented on the Management Board, but patient groups, health care providers and the European Parliament were offered seats, adding mainly transparency and accountability. Nevertheless, the Commission (and EMEA) succeeded in getting some more focused expertise into the CHMP (5 members co-opted by CHMP on the basis of specific expertise); obtaining the right to establish more expertise (additional therapeutic advisory groups such as the one for cancer diagnostics); and establishing standing working parties for every committee with the aim of providing scientific advice to companies (Title IV of Regulation(EC) No 726/2004). The member states largely succeeded in preventing the reduction of deadlines for assessments but accepted marginally reduced deadlines for the administrative procedures at EMEA and at Commission level. But for medicinal products for which there is a major public health interest, an accelerated evaluation procedure, which reduces the net assessment time from 180 days to 150 days, was introduced. The Council insisted on maintaining

the regulatory comitology procedure (Art. 87 of Regulation(EC) No 726/2004) which gives member states a kind of last-resort influence on the final regulatory decision.

V) The structural importance of the changes, initial experiences and projections for the future

It is too early to provide a conclusive evaluation of the changes effectuated by the legislative review. This is especially true of the Directive dealing with the MRP and the DCP (see Appendix 1), which took effect in November 2005. We are offering only tentative conclusions based on: the available process-produced data; deductive reasoning taking the dynamics of the existing structures and orientations as well as their changes into account; and nine interviews with participants in the regulatory procedures and stakeholders about their initial experiences with the regulatory changes.

Initial experiences in looking at the quantity of new applications over the years (Table 3), we can observe a general upward trend in the **Centralised Procedure (CP)**, though with some important fluctuations. These fluctuations probably have more to do with general innovation fluctuations and specific coincidences of innovation pipelines than with regulatory environments. 2006 saw a tremendous upswing which might be linked to the extension of the scope in 2004 and to other legal changes which we will discuss below.

The frequency of the utilisation of the **Mutual Recognition Procedure (MRP)** and the **Decentralised Procedure (DCP)** has increased steadily over the years – certainly on the basis of their legal requirement and despite their less-than-satisfactory performance from the point of view of mutual recognition expectations. There was an artificial upsurge in 2004 and 2005 because many pharmaceutical entrepreneurs wanted to apply before the legal changes of the review took effect at the beginning of November 2005. But what is especially remarkable are the figures for 2006 and 2007 (see Table 3). Differentiating between the MRP and the DCP shows that the latter is almost as important, in quantitative terms, as the former already in 2006, and it has more than doubled it in 2007. This is due to the fact that the DCP has basically become the preferred marketing authorisation route for generics. (It should be noted that for generics the application needs not be a centralised one even if the original name-brand version has been authorised via the CP.)

The Centralised Procedure (CP) closest to the Single Market concept and growing in importance. The CP procedure, with one centrally established marketing authorisation for all markets in EU member states, clearly corresponds to the concept of a single EU market, at least as far as market access is concerned. And the CP is growing in importance, not only due to extensions of its scope over time but also due to its acceptance by pharmaceutical companies. Approval times are internationally competitive, regulatory decisions are respected as high-quality and EMEA's service orientation vis-à-vis applying or application-preparing clients are regarded as increasingly helpful. By and large, acceptance has also been achieved with respect to those companies – mostly smaller and medium-sized enterprises – who had preferred the MRP and the DCP, both of which allow a more selective targeting of markets. With the possibility of reducing application fees for these companies, EMEA could counter their uneasiness with the high regulatory costs of the CP, including the

requirement to provide product information in all languages of the European Economic Area (EEA) countries - they include the 27 EU member states as well as Norway, Iceland and Liechtenstein - or to market a centrally authorised product in each member state.⁹

There has been another regulatory change outside the Review which will, to an even more decisive degree, contribute to the increasing importance of the CP: pediatric regulation (1901/2006; 1902/2006). The new regulation requires that practically all new active substances be tested on children. The pediatric investigation plan must be submitted to and evaluated by EMEA's Pediatric Committee, the most recently established Scientific Committee of the Agency. Normally, the results of the test must be available in advance of the marketing authorisation application and be part of it, be it a national or a European application. There is an additional incentive which practically drives applicants to the CP: applicants can get six months of additional patent protection (extension of the Supplementary Patent Certificate) on the condition that their new active ingredient be available, if authorised as a medicinal product, in all member states. If companies want to take advantage of these opportunities, they have two options: either to apply in all member states via the DCP or to take the CP path. But since the companies by this point have already had preparatory discussions with the EMEA, at least as far as pediatric studies are concerned, and since the processing of 27 applications – despite the rationalisation within the DCP – is more cumbersome and expensive than one European CP, it is rational for companies to opt for the centralised alternative in those cases where the CP is not mandatory..

Table 3: New applications in the Centralised, the Mutual Recognition and Decentralised Procedures

=- number of applications

	CP ¹	MRP/DCP ²		
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	separated since November 2005	
2004	51	935	MRP	DCP
2005	41	857	826	31 (Nov-Dec)
2006	78	1046	596	450
2007 ³	80	1212	337	875

1) CP = Centralised Procedure (applications by medical product).

2) MRP/DCP = Mutual Recognition Procedure (applications = number of procedures irrespective of the number of products or countries involved).

3) January to October

Sources: EMEA Annual Reports 1996-2006 (always most recent and revised data); EMEA/CHMP, Monthly Report, 27th November 2007, London

⁹ It should be noted though that the European Commission considers a medicine to be available in all member states once it is actively marketed by the authorisation holder in at least one member state - the rationale being that it can be imported EU-wide and that product information is available in all languages.

(<http://www.emea.europa.eu/index/indexh1.htm>[Press Releases]);
 CMD(h), Reports from meetings from January to November 2007
 (<http://www.hma.eu/180.html> [Press releases]).

The Mutual Recognition and Decentralised Procedures

Changes which have directly impacted the position, responsibilities and alternatives of action of the regulatory bodies as well as other concerned actors have been of great importance. The following three are especially important:

1 The formal institutionalisation of the Coordination Group (CMD; formerly MRFG) and its integration into the regulatory procedure as a body with specified responsibilities

The CMD has become an institution to which unresolved questions between the RMS, the CMSs and the applicant up to day 120 are referred. Although the CMD, which is a body of representatives of national regulatory administrations (agencies), has no right to decide but has to strive for consensus; its importance is enhanced due to the automatic referral to the CHMP for binding arbitration if questions cannot be resolved within the CMD.

2 Strengthening the instrument of binding arbitration and making it an automatic procedure and weakening the impact of withdrawals

If an applicant does not withdraw before day 120 and if the CMD does not arrive at a consensus after that day, the applicant can still withdraw the application from a dissenting country but he can no longer avoid binding arbitration through this step.¹⁰

3 Changes in the sequentiality of the procedure

CMSs no longer have to wait for the RMS to complete its assessment (day 120 in the DCP; see Art. 28 (3.) of the Directive), but rather the involved national authorities now discuss important and potentially critical points before the RMS has arrived at its final position. This allows for mutual adaptations and the resolution of issues well in advance. It should be noted, though, that much of this is possible only because national authorities – keep in mind that the MRP and the DCP lead to national marketing authorisations – are prepared to utilize the maneuvering space provided by the legal changes in a more or less informal way.¹¹

Other changes, but of seemingly slighter impact, are:

4 The strengthening of the wording which allows national authorities to reject an RMS's position

The national authorities are allowed to refuse only if the case for 'a potential serious risk to public health' (Art. 29 (2.) of the Directive) can be made. This is still very much a matter of interpretation despite the Guideline which the Commission has published. But the regulators interviewed here nevertheless insist that sensibility and

¹⁰ Even though not obliged to do so, the CMD has established the informal practice to discuss dissenting opinions of member state authorities even if the applicant has withdrawn his application before day 120 from the respective CMS.

¹¹ As one regulator remarked: 'Without goodwill, national authorities could still kind of sabotage the MRP/DCP'. But national authorities by and large seem to co-operate with a view to running these procedures as smoothly as possible. So if an authority sends a regulator, responsible for a certain application, to a break-out session or a CMD meeting and he or she 'behaves a bit like a martyr' and is unwilling to compromise at all, national authorities are likely to replace him or her with someone who functions better in an environment requiring discussion, co-operation and compromise.

awareness have increased, which makes it improbable that just anything could be taken as a pretext to reject another authority's assessment.

5 Article 30 (2.): Harmonisation measures

Not directly linked to the authorization procedure but nevertheless part of its regulatory environment and, furthermore, stressing the increased role of the CMD is Art. 30 (2.) of the Directive, which asks the CMD to propose to the Commission a list of products whose Summary of Product Characteristics (SPC) should be harmonized. (It should be remembered that differing SPCs have been the main reason in the past and are still an important ground on which mutual recognition is rejected.)

The experiences with these changes seem to be quite encouraging, especially as far as the DCP is concerned, where no preceding national regulatory decisions exist. As we noted before, the DCP has become the procedure of choice for generics and is becoming increasingly popular with regulators as well as with applicants. The latter seem to be especially fond of its flexibility and smoothness as well as of the compliance with approval times. But there is also criticism which indicates that this procedure might fall victim to its success. Some RMSs encounter capacity problems which the applicants experience as increases in waiting time until a Decentralised Procedure starts and the clock starts ticking.¹²

There have been other visible improvements. Withdrawals are no longer a problematic issue in the sense of the strategic behaviour of firms. They still occur before day 120 when an applicant has the impression of absolutely no chance in one or more countries and does not want to take on the burden of binding arbitration. Binding arbitrations have increased substantially in the last two years (see Figure 2). From 1995–2005 there were about 2,5 referrals per year; in 2006 alone, there were 23; and from January to October 2007 there were already 17. The major reason for this development is the referral-automaticity in the case of remaining disagreements after day 120. Another factor might be that the reforms have made it less costly for (rather confident) applicants to risk binding arbitration as they are now allowed to market a product in MSs which are willing to authorize products on the basis of mutual recognition while arbitration is still going on.¹³ It is also reported that applicants are sometimes even eager to go into binding arbitration if they want an issue to be resolved authoritatively for the whole EU.

In this context, it is worth noting that of all referrals to the CHMP for binding arbitration, in 2006 and Jan-Nov 2007, only 3 out of 40 emanated from the DCP. This confirms the point made above that medicinal products which have not obtained isolated national authorisations before, facilitate consensus in assessments among national regulatory agencies. And these figures illustrate also the important impact of the changes in sequentiality discussed on the preceding page.

¹² A non-representative survey of the German BPI with member companies shows that the waiting time runs between 2 and 15 months and seems to be mostly due to problems of personnel capacity.

¹³ It should also be noted that applicants no longer have to pay fees for CHMP arbitration. These costs, as well as some other costs, now must be paid by the EMEA, which might put budgetary strain on the European agency.

Referrals to the CPMP / CHMP for binding arbitration 1995 - 2007
 Mutual Recognition (MRP) and Decentralised Procedures (DCP)

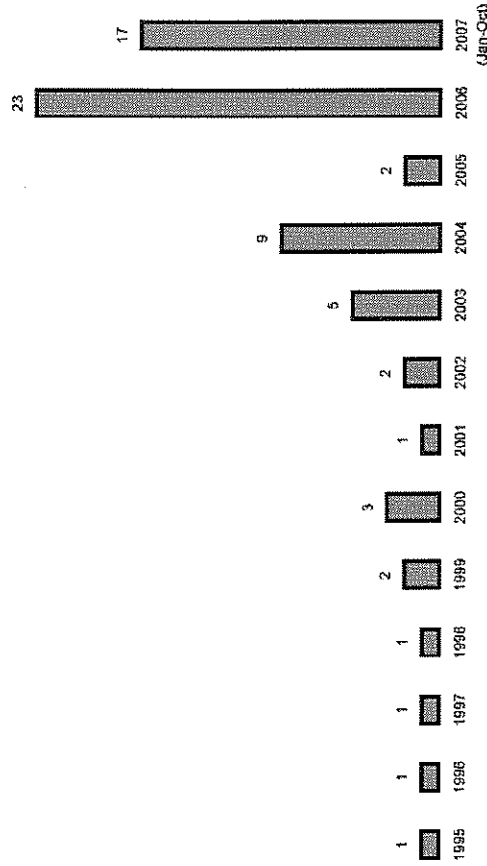
1995	1
1996	1
1997	1
1998	1
1999	2
2000	3
2001	1
2002	2
2003	5
2004	9
2005	2
2006	23
2007 (Jan-Oct)	17

Note: Practically all referrals in 2005-2007 concerned the MRP, only 1 in 2006 at MFRG, Monthly Reports; CMD(h), Reports from CMD(h) meetings

Sources: (<http://www.hma.eu/180.html> [Press releases]).

CPMP = Committee for Proprietary Medicinal Products.
 CHMP = Committee for Medicinal Products for Human Use; CMD(h) = Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human; MFRG = Mutual Recognition Facilitation Group.

Figure 2: Referrals to the CPMP / CHMP for binding arbitration 1995 - 2007
 Mutual Recognition (MRP) and Decentralised Procedures (DCP)



Note: Practically all referrals in 2005-2007 concerned the MRP, only 1 in 2006 and 2 in 2007 the DCP.

Sources: MFRG, Monthly Reports; CMD(h), Reports from CMD(h) meetings (<http://www.hma.eu/180.html> [Press releases]).
 CPMP = Committee for Proprietary Medicinal Products.
 CHMP = Committee for Medicinal Products for Human Use; CMD(h) = Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human; MFRG = Mutual Recognition Facilitation Group.

There is also a large number of referrals to the CMD – i.e., applicants who have not withdrawn by day 120 – which indicates that pharmaceutical companies have developed some trust in the national authorities' preparedness for and capability of finding a consensus in the CMD. If CMS(s) still disagree, binding arbitration by the CHMP is the next step. There were 105 referrals to the CMD(h) in 2006 – 104 in the MRP and 1 in the DCP – and 35 from January to June 2007, of which 13 stem from the newly established DCP. The 2006 figures also show clearly which kind of products go to the MRP and DCP by now. In 2006, almost all referred applications (102) were chemical substances, and only 3 were biological. And 80 of them were generics.

Roughly the same quantitative relations can be derived when analysing all new applications **finalised** in 2006: The total number was 592, of which 572 were chemical substances and 17 biological (among them 9 blood products and 3 vaccines). 419 of the 592 were generics (EMEA/CMD(h): , MRP/DCP and CMD(h) referrals – Statistics for 2006).

It is also noteworthy that of all the procedures finalised in 2006 in the MRP/DCP, new active substances (NAS) were concerned in only 11 cases; and of these applications only 4 were initial applications, the other 7 repeat use or multiple (copy) applications.

The reasons that the CMSs do not agree with an RMS's suggestions have changed over time. While more than half of the withdrawals from 1995–2000 happened because national authorities rejected mutual recognition due to differing, i.e. non-harmonized SPCs (57%; see MRFG – 23/01/01), the reasons for the refusal of mutual recognition – and the subsequent referral to the CMD(h) – are now above all differing views about bioequivalence (37 of 102 referrals in 2006). Lack of harmonization of SPCs ranges now second with 26 out of 102 (EMEA/CMD(h): MRP/DCP and CMD(h) referrals – Statistics for 2006).

VI) Preliminary evidence in view of three goals: Europeanisation, creation of a single market and European attractiveness for pharmaceutical innovation and production

On the basis of observations regarding the long-term evolution of marketing authorisation for pharmaceuticals in Europe, generally, and preliminary evidence concerning the impact of the newest reforms in 2004, specifically, we might draw the following tentative conclusions:

- There is a clear trend towards the **Centralised Procedure** regarding practically all more or less innovative medicinal products which are of specific scientific, medical and economic importance. Thus, this regulatory regime of joint decision making, with its centralising and decentralising elements, can be regarded as the cornerstone of marketing authorisation in the European Union. As this regime, which leads to one European marketing authorisation via one procedure, is, by and large, regarded as effective and efficient and, thus, competitive with the most advanced national procedures, especially the American regime. There is no reason to believe that this marketing authorisation system as such could be a hindrance to the establishment of a single market or to pharmaceutical innovation or production

in the EU. It is also the most Europeanised regime in the sense that it circumvents the necessity of mutual recognition through procedural integration.

- The remaining **nationally based procedures** are either only of national relevance (the purely national procedures which we did not discuss here) or they are embedded into a European co-operative network of national authorities and European bodies – the **MRP** and the **DCP** which have been discussed in this paper. Looking at the products concerned, there is a clear trend towards generics and pharmaceuticals based on chemical substances. Institutionally and procedurally, the reforms of 2004 have strengthened the European element in that binding arbitration has become obligatory in the case of dissent among national authorities involved in a procedure. And with a CMD(h) more formally integrated into the mutual discussions among member state authorities, the attempts at consensus building, and the increasing number of binding arbitrations, these nationally based procedures are becoming increasingly European.
- As the **MRP/DCP** path is overwhelmingly chosen for generics, this procedure is less important for innovations at the scientific and technological frontiers but more important with respect to the affordability of medicines for patients and concerns of cost containment for public health care systems. These types of medicinal products are also of high national or regional economic and political importance as the survival of mostly small and medium-sized companies with an impact on local or regional employment depends on this product market.
- The way the **MRP/DCP** is constructed, as an expected co-operation among national authorities on the basis of national procedures and leading to national marketing authorisation decisions, they do not, by definition, contribute to the establishment of a single market. There are two institutional elements which contribute to this effect. The most important one: Applying pharmaceutical entrepreneurs have the opportunity to choose target countries; it is their selection, in the first place, which determines the size of the market in the EU and which restricts access. Even if mutual recognition were to work, i.e. if it were automatic, it would still be the companies' decision where to apply for marketing authorisation. The second limiting element had been the national authorities' ability to reject mutual recognition for reasons of public health. With the introduction of automatic binding European arbitration, this element has now ceased to be of greater importance. The **MRP/DCP** remains basically an instrument of regional market differentiation in the hands of pharmaceutical companies.

VII) Possible futures, probable futures?

More centralisation?

There are some people, like the author, who observe more or less solid trends towards increasing centralisation by different means but expect that this trajectory does not necessarily lead to a European Food and Drug Administration comparable to the American FDA. There are others, some in national regulatory agencies, who think that, in the long run, this trajectory will lead to such a centralised regulatory agency. And there is a third group – among them the former regulator and industry

representative and now consultant John Griffin – who thinks that such a central European FDA should be created, and the sooner, the better (see Griffin, 2002).

While the regulatory logic seems to speak for such an institutional solution, it is less convincing when it comes to hurdles and constraints which such a decision would have to pass. There are political and administrative obstacles. Most member states, especially those which have established a large administrative capacity in this regulatory field, are not willing to give up this capacity. In the end, national governments will be blamed in the case of drug accidents and eventually pay for it when elections come around. Additionally, the existing national regulatory administrations will fight for their mere organisational existence.

Large parts of the industry would lobby for the continued existence of national regulatory administrations and their continued role in regulatory assessments and evaluations. This is certainly true for those applicants who choose the MRP/DCP, with the requisite variety and flexibility they offer. Companies, for better or for worse, establish ties with specific agencies as their preferred Reference Member State agencies. Even the more research-based and innovative companies appreciate these ties to national administrations. They are therefore not satisfied with a detail of the reform of 2004 which now prevents them from suggesting the rapporteur and co-rapporteur for assessments in the Centralised Procedure. Their argument: After having discussed regulatory questions in the pre-application phase with some national regulatory agencies, they regard it as a disadvantage that rapporteurs – and their respective agency – are now chosen independently by the CHMP.

There are functional, task-related arguments which are brought forward against a radical institutional centralisation: Since pharmacovigilance, site inspections and other such administrative duties must be organised nationally or even regionally, member states depend on local expertise necessary for these tasks. Regulatory administrations cut off from the authorisation system might lose the necessary regulatory capacity and strength.

These are some reasons why it seems rather utopian today to assume that a European FDA is the logical end to which the European regulatory path will lead.

Incremental evolution of a complex status quo?

An incremental evolution of the existing system with further Europeanisation in terms of harmonisation and mutual recognition, on the one hand, and joint decision making at the European level on the other seems more likely. Within such a framework, different options are available; but, essentially, they would have to rely on the existence of national regulatory institutions – whereby work sharing among them could be established in terms of specialisation – and on their co-operation or co-ordination through the European institutions and procedures in which they are embedded.

This regulatory framework depends on an already established – though still improvable – network of ties which allows for increasingly close and smooth co-operation and co-ordination, and which has fostered a co-operative orientation of national regulators developed over the last 40 years of European regulation, and it depends on measures which maintain and increase the regulatory expertise and

regulatory strength of the respective personnel. This includes the willingness, capacity and authoritative independence to co-operate with as well as to confront a highly powerful and competent industry – in order to reduce avoidable regulatory costs, but not at the expense of patient safety and public health. The latter are not only best assured through competent and reliable personnel in regulatory agencies, but they also have to be safeguarded and strengthened through still-improvable transparency measures. In this respect, the authorities of the EU have gone considerably further than most national agencies. Also in this respect, the participation of all national regulatory agencies in the assessment and evaluation process at the CHMP level – in a less formalised environment via discussions in the CMD(h) – and of national regulatory policy institutions in the final decision-making at the Commission level not only provide for national input but also for a variety of views which have to be dealt with and which add to mutual control and to the credibility of decisions made.

Taking the MRP/DCP as a quasi-European procedure resting on a national basis, one could image further steps beyond attempts at improving mutual recognition and towards procedural integration if automatic mutual recognition is not attainable. In this view, the MRP/DCP would come closer to the Centralised Procedure, though without necessarily obliging pharmaceutical entrepreneurs to target all markets.

The trajectory which pharmaceuticals marketing authorisation procedures are on in the EU point towards the **increasing importance of the Centralised Procedure** institutionally and its impact with respect to the product sector it covers, and towards a development which facilitates or even requires a further Europeanisation of regulatory decisions in the Mutual Recognition and Decentralised Procedures (MRP / DCP). An independent scientific base at the EMEA will probably be further strengthened in the future without its counterparts at the national level being ignored. At the national level, a practice of work sharing will probably be developed which makes the most out of existing expertise and specialisation. But all legal measures are only as good as their implementation. And here it is the willingness and capacity of old and new members of the EU to co-operate and strive for common positions and decisions which are credible and regarded as legitimate. This leads us to mention the necessary European orientation of those involved in regulatory processes, which includes the mutual willingness to listen to regulators from other member states and to mutually respect the limits within which everybody is able to compromise when differing views have to be accommodated or resolved. In the past decades, national regulatory institutions and most of their personnel have learned to co-operate in the European context and have acquired the tacit knowledge which is necessary for productive co-operation. As one national regulator put it: The procedures (especially the MRP/DCP) are so complex that influential participants unwilling to cooperate could still sabotage them and eventually drive them against the wall.

The necessity of vigilance: some warnings

This description and outlook has a basically optimistic tone. However, we should not ignore the problems and potential fallacies which are inherent in a system relying on ever closer relationships and co-operation between the regulators and those being regulated, especially when there exists a certain asymmetry of information and other resources favouring the regulated industry and a certain secrecy which has been a salient characteristic of this industrial sector and policy field. There is always the danger of capture ((Bernstein 1955, 1972)) when these relationships become too close

(Griffin 2002) and cosy (Abraham and Lewis 2000). There are many indications that vigilance is warranted.

Counterbalancing forces are necessary. One of these counterbalancing forces is, of course, the fear the industry itself should have of the impact of possible adverse drug incidents or disasters. Obviously industry has become increasingly sensitive to the impact that negative news has on a company's image and financial losses – not to speak of possible liability claims. This situation could reasonably lead to even more secrecy and attempted cover-ups. Public transparency is no guarantee, but it is the main prerequisite for ensuring accountability. In this case, public health should rank above the protection of commercial secrets in the hierarchy of values. EC policy and legislation towards a better-informed public through the establishment of accessible databanks in the context of 'freedom of information' rights points in this direction.

Another prerequisite is the control of the regulators and of the impact the regulated industry might have on regulatory decision making, directly or indirectly¹⁴. Here, too, public transparency and the opportunity for critical outside experts to blow the whistle is of utmost importance. The specific European institutional construction of marketing authorisation might add to the safeguards against the corruption of regulatory practice. It is the cumbersome and organisationally costly requirement of co-operation and co-ordination between independent national regulators and regulatory authorities within a network setting which might provide the necessary and fruitful variety of inputs and mutual checks which reduce the danger of regulatory failure.

Marketing authorisation is only one element

When it comes to regulatory impact on the creation of a single market and, additionally, the attractiveness of the EU as a place for research, development and production in the pharmaceutical sector, it is not only the regimes for marketing authorisation and their implementation which play a role. Other regulations and circumstances might be even more important.

As mentioned above, member states are free in the regulation of their health care systems, including direct or indirect price controls, reimbursement schemes, and quality controls with respect to cost-effective diagnoses and therapies. All this, of course, influences the calculations of pharmaceutical companies and their willingness to serve a national market in a way compatible with a single market concept which expects every medicine to be available everywhere.

For attracting especially innovative companies, market size is important. Market size is at least indirectly affected by marketing authorisation. Since the European CP is the procedure of obligation or choice for most innovative products and since this procedure is regarded as rather efficient by companies, it is certainly not a hindrance in attracting investments of pharmaceutical companies. Much more important are here, again, national health care system regulations with their impact on entrepreneurial decisions and thus, indirectly, on market size. Additionally, the general political and social environment can be more or less restrictive or open vis-à-vis research and innovation, in general, or in specific areas. Certainly, in this sector

¹⁴ For various reasons, there is still a worrying informational asymmetry in favour of the pharmaceutical industry. Also, strong ties between the industry and pharmaceutical and medical specialists serving as reviewers and experts can bias assessment and evaluation results. For a recent study of this problem, see Yank, Rennie and Bero (2007).

the relationships between universities, public research institutions and industry play a formidable role, including more or less hidden subsidies e.g. in the form of research grants, the availability of tax reductions, etc.

VIII) Appendix 1

Major regulatory steps in EC marketing approval regulation concerning medical 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, e.g. 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/ EEC, 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/ EEC, *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
- Introduction of the *Centralized Procedure*: emanating from the *Concertation Procedure* but with regulatory decision taken at the European level and for the whole Community (EC-wide marketing authorisations);
 - Introduction of the *Mutual Recognition Procedures* emanating from *Multi-State Procedure*, still nationally based but with option of centralised, binding arbitration in case of diverging national assessments and/or evaluations (national marketing authorisations)
- 1998 Complete replacement of parallel national applications by *Mutual Recognition Procedures*, based on Directive 93/39/ EEC
- 2001 Directive 2001/20/ EC: Harmonisation of clinical trial requirements

- 2004 Regulation 726/2004/ EC amending Regulation 2309/93/ EEC: Amendment of the *Centralised Procedure*: extension of scope, some efficiency measures (deadlines) and organisational changes (EMA, CHMP)
- 2004 Directive 2004/27/ EC, amending Directive 2001/83/ EC: Amendment of *Mutual Recognition Procedures*: in addition to the *Mutual Recognition Procedure* , introduction of a *Decentralised Procedure*, still national authorisations but strengthening the possibility of binding arbitration in case of dissent among national authorities and formalising as well as strengthening cooperation among affected national regulatory authorities; strengthening pharmacovigilance
- 2004 Directive 2004/24/ EC (regarding traditional herbal medicinal products): introducing quasi-automatic mutual recognition for these traditionally utilised medicines
- 2006 Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/ EC
- 2006 Regulation (EC) No 1901/2006, amended through Regulation (EC) No 1902/2006 on medicinal products for paediatric use: Companies are obliged to test new medicines on children

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JOINING-UP EUROPE'S REGULATORS

**HOW NATIONAL REGULATORS IN ENERGY,
FINANCIAL SERVICES, PHARMACEUTICALS
AND TELECOMS ARE COMING TOGETHER IN
EUROPEAN NETWORKS AND AGENCIES**

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