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Mutual Transformation and the Development of European Policy Spaces: The Case of Medicines Licensing

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Abstract:

This article pleads for a systemic approach to European policy spaces formation. The term “mutual transformation” is used to underline three observations concerning how European policy spaces are formed: 1) influence among the “levels” composing the Union runs simultaneously from “Brussels” to the “lower” levels, from the lower levels to the EU authorities, and from country to country; 2) sources of change are both exogenous and endogenous; 3) the nature of the policies under study and the issues and interests associated with them evolve over time, affecting the identities of the different-level actors and their ties. The case of drug licensing is used to illustrate the usefulness of this approach. To come to grips with the complexity of the processes explaining the creation of a “European policy space for medicines”, we emphasize the role played by three closely interrelated mechanisms: competition, cooperation and the transformation of relations between expertise and policy-making.

0. Introduction

In the last several years, studies of public policy in Europe have brought to light the entanglement of policy levels within the European Union (EU). Notions of “multilevel governance” (Marks and al., 1996) or administrative “fusion” (Wessels 1998) were developed to describe this reality. But few studies have used adequate empirical means for understanding how exactly the different echelons fit and work together (Le Galès 2002). Moreover, theories on the *process* by which European policy space gets formed have tended to neglect level intertwining and its effects on conceptualizing EU dynamics. The quest for linear causal mechanisms linking national and EU levels has worked against our recognizing complex interdependencies.

The understanding in this article is that it is important to come to grips with this complexity if we are to account in full for the formation of European policy spaces. We use a particular case to show the usefulness and fecundity of the concept of mutual transformation for understanding how a European space is constructed in a given public policy sector.

We studied the regulation of pharmaceutical products, specifically the delivering of marketing authorizations (MAs) aimed at ensuring the safety and efficacy of drugs. In this area, the European Medicines Evaluation Agency (EMA), which began operating in 1995, and EU procedures which gradually supplanted most national procedures, mark the creation of a European policy space for medicines licensing. This space may seem to have been constructed merely through delegation of national competences to a “supranational” authority. In fact, the new European system is the last stage in a nearly forty-year history involving profound changes in the activity of evaluating and registering medicinal products; transformation of sector actors’ identities and strategies; and constant interpenetration of national changes and EU initiatives and reforms. That system thus corresponds not so much to any sudden transfer of competence as to a new way of organizing medicine evaluation in Europe that affirms and consolidates (in the sense that it manifests and strengthens what made it possible) the formation of a European space for evaluating and authorizing medicinal products.

The article first discusses the fact that not much is said about mutual transformation in research on European Union dynamics (section 1). After presenting the main stages in the development of what we call a European policy space for medicines (section 2), we explain that full reconstitution of this process requires taking into account three closely linked

phenomena: the emergence of medicine evaluation as a focus of competition among EU Member States (section 3); the development of cooperation among national authorities (section 4); and the ascendancy of scientific expertise in market authorization decisions at both national and EU levels (section 5).

1. Conceptualizing mutual transformation

Researchers seeking to account for how European policy areas are formed have two wide avenues clearly open to them. The first corresponds to “classic” studies of EU integration, whether (neo)functionalist/institutionalist or intergovernmentalist. In the vast majority of these studies, the development of European policy spaces is conceived as the increasing capacity of EU institutions to govern.¹ This understanding, and the fact that those studies focus on transfers of policymaking competences, means that the studies are particularly interested in, and likely to emphasize, oppositions between Member States and trans/supranational levels caught up in what looks like a zero-sum game.

The second avenue, opened more recently, uses the notion of Europeanization to obtain a broader view of EU formation (Featherstone and Radaelli 2003). Studies using this approach highlight the “national” dimensions of European Union advancement, thereby complexifying the panorama of European process conceptualization (Radaelli 2006). However, the broad definitions of Europeanization proposed² are at odds with the restrictive use often made of them: these studies have a tendency to focus on national transformations brought about by the existence of EU-level policies.³ Admittedly, this research program has evolved away from strongly “top-down” approaches, symbolized by the “goodness of fit” program (Borzell and Risse 2003), toward approaches that begin at the national level and integrate a variety of transformation mechanisms (Radaelli 2006). But most of the related empirical studies continue to use “causalist” and linear logic: national structures/policies A at Time 1 were transformed by what is understood as autonomous EU policy/dynamic B at Time 2 and ultimately take form C at Time 3. Though Claudio Radaelli does say that national and European levels can “co-evolve,” he still affirms that the first rule for conceptualizing the Europeanization process is to start with the idea that “in order to produce domestic change Europeanization must precede change” (Radaelli 2006: 66). He also specifies that his study does not encompass questions of policy transfer from one EU country to others (Radaelli 2003: 27).

Without calling into question the productiveness of these two approaches, which are complementary rather than in competition, we would like to suggest a “third” way, one that offers the advantage of being consistent with current emphasis in the social sciences on the systemic complexity of most macrosocial transformations. This requires to apprehend European “policy spaces” in line with N. Elias “figurations” (1978), i.e. as networks of interdependent individuals and institutions (belonging to national and/or European levels). As entities embedded in figurations are linked along several dimensions and because their ties are also constitutive of their identities, figurations are continually in flux, undergoing changes of many kinds (Elias 1978). In deed, as in football games, any transformation/act in a part of the figuration changes the figuration itself, generating other acts/adaptations. In this context, the term “mutual transformation” involves the following three observations concerning how European policy space is formed: 1) influence among the “levels” composing the Union runs *simultaneously* from “Brussels” to the “lower” levels, from the lower levels to the EU authorities, and from country to country; 2) sources of change are both exogenous and endogenous and their impact is at times comprehensive, affecting all national and European organizations, at other times partial; 3) the nature of the policies under study and the issues and interests associated with them evolve over time, affecting the identities of the different-level actors as well as the balances among them.

Taking into account this mutual transformation has several analytical consequences when it comes to explain (and even describe) the formation of European policy spaces. The analysis shouldn’t be based on essentialist and fixed conceptions of social actors (for example “Member States”) nor use simple linear cause: it should adopt several angles and be attentive to their “reciprocation.” To do this, it is important simultaneously to research from a comparative perspective what is occurring at the national level, and to analyze how Union policies are being shaped. This method makes it possible to identify a series of historical sequences and to conceptualize the different *social mechanisms* that explain their succession.

The case of medicines licensing can be used to illustrate this approach. Scholars studying the European developments in this field have focused on the “steering” of the creation of a European system. Two main explanations have been put forward : one insisting on the role of the pharmaceutical firms lobbying (Abraham and Lewis 2001, Greenwood 1997) and the other stressing the political entrepreneurship of the European Commission (Permanand and Mossialos 2005). We favour this second vision (Hauray 2006), but this paper will underline that analyzing the European “steering” is not sufficient to understand how, and *why*, a European “Medicine space” has been formed. Relying on empirical research conducted in

France, Germany, the United Kingdom and the EU level⁴, we will try to account for the 40 years mutual transformation of this field. In the interests of clarity, this paper is structured analytically, emphasizing social mechanisms (competition, cooperation, change in relation between expertise and decision making) rather than sequences.

2. The formation of a European medicines licensing

One of the first aims of the representatives of European countries assembled in 1961 to promote a common market for medicines was to create the conditions needed to establish European-level control over what medicinal products got onto the market. It made sense to give priority to market authorization because this regulation not only acts as a filter but defines the product (specifying indications, counter-indications, etc.) and permits it to be marketed. Moreover, the strong technical-scientific dimension of medicine evaluation suggested that this might be a matter in which national specificities and interests could be overcome, in direct contrast to economic controls, closely indexed on nations' specific social insurance systems. Also of crucial significance was the breaking of the thalidomide affair, which put the issue of medicine evaluation firmly on the policy agenda that year. Thalidomide was causing thousands of abortions and malformed babies in Europe and the United States. This traumatic event had the effect of *synchronizing* the histories of national drug registration systems, at least in North America and Europe. Whereas before then national systems had reflected the regulation histories specific to their nations—France's "visa," devised by the Vichy government; the German system inherited from the Nazi regime (Abraham and Lewis 2001), industry self-regulation in the United Kingdom (Hancher 1990)—the countries now, at the same moment, all found themselves having to rethink their respective approaches to registering medicines.

Negative integration; i.e., abolishing trade barriers and setting up automatic recognition of other countries' MAs, was clearly impossible in such an area. No state was willing to delegate to its neighbors the entire responsibility of protecting its population against such dangerous products. Moreover, since each approval involved making a "critical decision" on the basis of a specific evaluation, procedures had to be set up (above and beyond application of shared standards) that would allow for formulating identical judgments on drugs on the basis of distinct national scientific evaluations. This is why the formation of an European policy space for medicines involved first and foremost the development of a European system for evaluating medicines and granting (or refusing) permission to market them.⁵

The European Union's hold in this domain as an area for policy action was consolidated through a process that continued for more than 40 years and that can be accounted for synthetically by the following four criteria:

1) *The construction of scientific knowledge, practices and standards common to EU countries.*⁶ These worked at first to enrich (and in some cases to bring into existence) the bases for national-level evaluation, while going some way toward aligning those bases. A European Economic Community (EEC) directive of 1965 proposed a legal definition of a medicine—an innovative, European definition—and established the principle of a medicine approval, to be compulsory and based on three criteria: efficacy, safety and quality. Two 1975 directives indicated what an application for marketing authorization was to consist in, i.e., the tests and clinical trials that industrial pharmaceutical firms were required to conduct before applying for access to a national market. Then, starting in the late 1970s, European-level working parties were created that brought together representatives of different national administrations. The joint work done in them has fostered expert judgment convergence and made it possible to develop numerous guidelines specifying the criteria and knowledge to be used in drawing up and handling application files. With the predominance of European procedures came the diffusion of new relational modes between these expert authorities and the drug companies.

2) *The development of EU authoritative bodies specific to medicinal products.* The first authority of this type, created in 1975, was the Committee for Proprietary Medicinal Products (CPMP), charged with evaluating requests for mutual recognition and reflecting at the European level on all problems related to the pharmaceutical sector. Working parties were regularly formed alongside this body and on the basis of it. The European Commission administrative apparatus developed its own medicine section. At first no more than a secretariat of the CPMP, it grew in size and competence, eventually becoming a full-fledged unit within the EU's Directorate-General for Enterprise and Industry. The decisive turning point in instituting a European space for medicines, however, was the opening in 1995 of the European Medicines Evaluation Agency (EMA), encompassing the CPMP (now called CHMP⁷) and its groups. Headquartered in London, the EMA today employs over 350 persons.

3) *The strengthening and combining of medicine MA procedures.* Until 1975, there was no coordination whatsoever of national-level decisions. Then the first mutual recognition procedure was instated: as soon as a firm obtained a marketing authorization for its medicinal product in one country, it could apply to have the authorization recognized in at least five

other countries. If one of these countries refused to recognize the initial authorization, the national bodies came together to present and compare their diverging positions in the CPMP, which would then give a non-binding opinion. This procedure was seldom used at first, and when countries did start to use it, it proved inefficient. It was improved in 1983 but to no avail. Then in 1995, as the EMEA was being set up, two new procedures were designed that revolutionized the whole arrangement. In the first, a firm applied for marketing authorization to a national body; once the application had been evaluated, this body coordinated with the other national administrations that the firm wished to receive an authorization from. States reluctant to recognize the first approval could no longer simply remain on the sidelines, because if this mutual-recognition procedure, occasionally called “decentralized,” failed, an arbitrating procedure was triggered that transformed it into a “centralized” one—i.e., the second new procedure. The centralized procedure was at first compulsory only for biotechnological products, optional for innovative ones. In the centralized procedure, managed by the EMEA, two Member States (through their representatives in the CPMP) acted as rapporteurs. On the basis of their reports, applications were examined by the Committee; that body’s recommendation was then adopted by the European Commission. These two procedures were partly modified in 2005; those recent reforms are not discussed here.⁸

4) *A change in the strategic orientation of pharmaceutical market actors.* Pharmaceutical firms once anxious to construct national niches or adjust themselves to the demands of the various national expert bodies are now using European Union procedures and developing their products in accordance with those procedures. The firms’ European orientation is reflected in their opening of *European* structures (in London and Brussels) whose job is to get their products registered for Europe, and in the growing power of the European Federation of Pharmaceutical Industry Associations (Greenwood 1997). Meanwhile, national health administrations, once concerned to protect their national pharmaceutical industries, have turned into agencies concerned to compete successfully for a good reputation as medicine evaluators, since this both attracts pharmaceutical firm applications and increases individual agency influence in the European-level bodies.

A Europe in which each state sovereignly decided what medicinal remedies would be allowed onto its national market has thus yielded by successive moves to a European policy space for medicines where individual member states can at most exert influence on collective decision-making of a sort where no single voice has anything like a right to the last word. How can we most accurately analyze this development?

3. The emergence of evaluation as a focus of cross-national competition

Competition implies strong interdependence among the entities engaged in it. Norbert Elias went so far as to consider competition an essential integration mechanism, explicative of the development of modern states out of smaller units (Elias 1982). In our area, the fact that evaluation quality became an autonomous focus of competition among states was decisive in the formation of a European policy space.

In the early 1960s, interdependence among national entities with regard to medicinal products was weak. Pharmaceutical markets were primarily national, and national administrations did not have highly specialized units for handling issues arising around pharmaceuticals. States understood the interest of their countries to lie in protecting their national pharmaceutical industries. In the German Federal Republic (GFR), for example, there was no state system for controlling medicinal drugs. And the country's delegates threatened to block all moves to align the content of clinical trials that would involve stiffening the related requirements unless German products were institutionally granted automatic recognition and allowed them to be sold throughout the EEC. The German position effectively blocked EEC work in this area until the early 1970s.

At that point the landscape changed. The development of clinical pharmacology and the beginnings of randomized, double-blind clinical trials in both the medical field and pharmaceutical industry radically changed drug evaluation conditions. The spread of Evidence Based Medicine (Marks 1997), combined with the development of new laboratories and therapy supply, moved national administrations to realize that competence in medicine evaluation was an important resource. The first priority was to ensure protection of the population. This concern was not new, but it now brought with it entirely new challenges: the number of new medicines was rising, their strength as well; the proportion of foreign products on national markets was growing, and the competence needed to evaluate drugs had taken a qualitative leap. And there was a new concern: acquiring the ability to control medicines was now imperative if a country was to defend the interests of its national industry. No one believed that the experts were neutral. In the understanding of national leaders, if the nation did not have the competence needed to effectively promote the quality of its evaluation work and get that quality recognized, then the products of that nation's industry would be subjected to evaluation by countries that *had* acquired such a reputation, and those countries that would then be free to slip the interests of *their* national industries into their expert opinions. Meanwhile, drug evaluation became the focus of envious comparisons. As some of them told

us, French and German health policy officials and pharmacologists, for example, were furious at being ranked by the English, who had created a Committee on Safety of Medicines as early as 1968, and the Americans at the same level of incompetence as the Italians and Spanish. The prospect of evaluation conducted at the EEC scale, a prospect opened with the adoption of the first European procedures, was an incentive to each of these countries to set up genuinely specialized administrations. In 1975 the GFR created the Institut für Arzneimittel; France set up its Direction de la Pharmacie et du Médicament in 1978. As indicated, however, the policy space for medicines remained national.

In 1985-1986 several factors worked to increase the importance each country attached to its own capacity for checking and controlling medicines. First, the increasing number of MA applications and the fact that the amount of data required for them was also continually increasing meant that evaluation was taking an extraordinarily long time (up to five years), creating a serious backlog. This was a problem not only for the pharmaceutical industry but also for patients, especially when AIDS began affecting developed countries. Second, in the wake of the 1985 White Paper, and on the initiative of the European Commission departments, a series of negotiations got under way to create stricter European-level procedures and a European-level agency. The national authorities tried to stall this development at the same time as they began preparing for a potentially integrated system, thus increasing the probability that the change would occur. Increasing talk of a future European medicine evaluation space, and the understanding that such a space could bring about the disappearance of some national administrations, led Member States to begin looking more closely at their own expertise capacities and international reputations. Third, the pronounced internationalization of pharmaceutical companies meant that the point was no longer for a country to defend its national industry but rather for it to attract international research and get multinational companies to open subsidiaries on its territory. A country's reputation with regard to marketing authorizations, the influence it could claim to have in future European-level decision-making thanks to its experts and ways of working, and the image the pharmaceutical industry had of its administration were now understood as decisive for getting foreign concerns to set up there.⁹ The result was that countries engaged in this competition began to create independent agencies in place of specialized administrations: the UK's Medicines Control Agency (MCA) in 1989; France's Agence Française du Médicament in 1993; Germany's Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in 1994. These independent agencies had greater management and financial autonomy, and owing to a sharp increase in licensing fees paid by the companies, they were able to hire new experts.

The agencies were a means of acquiring greater competence and international credibility (Majone 1996), but also of accelerating evaluation work, a development obviously consistent with pharmaceutical firm wishes. From the mid-1980s, then, the point was no longer for a country to ensure that its national administration had the competence required to defend the national drug industry, but rather for it to acquire a strong position in the competition now on among national regulation agencies.

Competition centered on evaluation quality worked strongly both to improve national arrangements for registering medicines and bring them closer together, and this in turn facilitated adoption of the 1993 European acts founding the European agency and specifying the two aforementioned new procedures. When these went into effect in 1995, the nature of competition among national authorities changed. On the one hand, competition now takes place within an interaction system involving collective decision-making procedures; on the other, to use Elias' terms, individual countries' struggle to protect "the chances" of their respective national territories yielded to a struggle to appropriate some of the opportunities available in the common territory (Elias 1982); i.e., to acquire or hold onto a place within the European system. These authorities are either more or less able to attract firms' authorization applications and defend their evaluation work in European procedures. This ability has direct effects on what products are ultimately put up for sale on a country's own markets, but it also conditions their own resources, since most of an applicant firm's licensing fees go to the country that reports on its application or the one that first granted it an MA. In the mutual recognition/decentralized procedure, firms can choose that country, and in the centralized procedure their requests for particular rapporteur countries are extremely likely to be taken into account. In this way a truly strategic space has opened up, in which, to put it schematically, national authorities can either work to speed up the evaluation process so as to attract a high number of industrial applications (external strategy) or use their ability to impose their views within the system to obtain a particularly privileged position in Europe and become an actor the firms have to reckon with (internal strategy). Competition of this sort and its effects on how evaluation work gets distributed has once again facilitated the diffusion of particular action models. The "English" style of handling relations between regulator and the regulated (Hancher 1990), for example, wherein cooperation between those two sets of actors is readily accepted, won out in the European space, namely because the UK was most frequently chosen by pharmaceutical companies. Germany, whose style of relating to drug companies was very different—relations restricted to written exchanges—had no choice but to temper its ways. The German agency gradually ceased to think of itself as a "fortress" and

came around to accepting, like its European counterparts, the principle of direct exchanges with the companies.

With the system implemented in 1995, evaluation came to be realized and recognized as an autonomous focus of competition. Today, regardless of whether the decentralized or centralized procedure is used, all new significant MAs are European. Firms develop European-level strategies for getting their drugs registered; e.g., preparing a single application and using identical clinical trials for all countries. Consequently, in order for evaluation done by a given national authority to count, that authority must take into account the evaluation ways of the other national expert bodies; it must anticipate their reasoning and arguments and be ready to counter those arguments in collective deliberations. Cross-national interdependence, integrated into an interaction arrangement that requires both coordination and cooperation, may be said to have reached maximum intensity.

4. European cooperation

The second essential mechanism for understanding the formation of a European policy space is cooperation among national delegates working on EU committees. For our case, it may even be said that the mid-1970s creation of working parties played the role of a “critical juncture,” as that term is used in historical institutionalism (Pierson 2000). At a period when European integration seemed doomed to fail, this initiative put national authorities on a new track, and this in turn partly explains the relative success of Europe construction in this area. For ten years, from 1975 to 1985, the CPMP was in danger of becoming a deliberating body with nothing to deliberate. Pharmaceutical companies were not seeking mutual recognition of their medicines and the states were not using their option to consult the Committee on current problems. It had so few matters to handle that some of its meetings were cancelled. But at the urging of its president Léon Robert of Luxembourg, the body reacted by setting up specialized working parties to study the main problems involved in evaluating medicines. Their assignment was to determine and formalize the necessary knowledge and appropriate demands for handling specific practical problems. The working parties defined clinical criteria for various pathologies, for instance, and various methodological requirements to be followed in conducting clinical trials.

Since evaluating medicines is an art as well as a technique, these guidelines played a central role in developing European-level practices. On the one hand, national authorities, that had few formalized norms at that time could immediately define and adopt European-level

ones via their representatives on the Committee. On the other, pharmaceutical laboratories began to follow those guidelines more attentively in developing their products: their very existence was leading to convergence of evaluation conditions by aligning industrial practices “upstream” of the evaluation process. Admittedly, this dynamic was fostered by the specific conditions of the period in which the working parties were instituted (Pierson 2000): in 1970s in Europe, “modern” medicine was taking hold thanks to a new generation of professionals who, before becoming leaders of the respective national authorities, became involved in running European forums. The Committee was one of the most prominent meeting places for top national experts; it was also a privileged place for developing new knowledge for evaluation purposes and above all for diffusing that knowledge from the Netherlands and the United Kingdom toward the southern European countries.

But the fact that national authority representatives were regularly meeting within the CPMP also triggered socialization mechanisms (Checkel 2005). Delegates learned to work together, developed deliberative norms (see 5.2), mutual trust and even interpersonal relationships. Trust was needed due to the difficulty of checking both the quality of the know-how used and the probity of the evaluators, difficulties due to the fact that the Committee was only examining the results of the evaluators’ work (the evaluation report). But trust developed only gradually in each committee. A former member of a biotechnology working party recalls the mutual wariness that characterized the first months of cooperation:

At first ... Actually we were suspicious of the other countries’ ways of doing things. Then by working together we came round to respecting each other and trusting each other’s abilities. We knew that we were working in the same direction, if not in the same way.

(Interview with a former member of the CPMP’s biotechnology working party, UK)

The fact that Committee members were increasingly able to support positions that went against the interests of their country or the opinion of their national committee was also crucial. Lastly and quite simply, the repeated meetings were conducive to the development of personal ties, friendship, mutual esteem, all of which later facilitated cooperation. Today’s national-European regulators are part of a network that got structured around members of the initial working parties and grew stronger as national structures shifted their sights increasingly toward Europe and as European cooperation became a greater part of their work, increasing from approximately 10 meetings a year in the 1980s to 50 in 1995 and more than 400 today.

5. The transformation of relations between expertise and policy-making

To understand and account in full for how the European policy space for medicines was formed, we need to examine the question from a third angle: changes in the relations between scientific expertise and policy decision-making. In fact, the European dynamic facilitated greater autonomy in MA decision-making and a growing “absorption” of political decision-making by scientific expertise. This development facilitated the setting up of a national authorities network and fostered changes in modes of national representation in European committees.

5.1 Policy decision-making absorbed into scientific evaluation

There is no logical requirement that medicine evaluation have only one dimension, i.e., the one involving application of the experimental method, and public authorities were in fact likely to consider at least two other dimensions before granting a marketing authorization. The first was economic: a national government could refuse to grant a marketing authorization for a medicine that had passed efficiency and safety tests but was judged too costly for its health insurance system. Another concern was public health. The “quality, efficacy, safety” criteria do not exhaust means for assessing how a drug may impact on public health. The recent case of a drug that reduces flu duration by half raised the following questions: Does such a drug, while meeting current MA requirements, have enough therapeutic value? Isn't there a danger that it will undermine a country's vaccination policy? In the period when expert evaluation and the decision to grant an MA were clearly distinct and deemed complementary, the MA decision-making process could and did take such aspects into account. At that time, MA decision-making was in reality controlled by national administrations and policy officials (the relevant minister and his or her cabinet), and they would add their own evaluation to the experts' opinion, an evaluation based on broader criteria than the experts' three. But another conception of the MA ultimately prevailed, wherein economic considerations and policy concerns may only come into play in decisions on drug reimbursement and possibly price determination. Those considerations now fall outside the domain of the MA proper.

The increased autonomy of medicine approval furthered the “absorption” of policy decision-making by scientific expertise. In concrete terms, the expert committees’ opinions, once formulated, are not really re-debated before becoming policy decisions. In the centralized European system, the EMEA (that is, its scientific Committee) is an organization charged with presenting scientific opinions of the best possible quality for European Union institutions and Member States. These opinions are then turned into decisions by the Commission, after a complex “comitology” procedure that allows for *a posteriori* oversight by the Member States through a Standing Committee on Human Medicinal Products. In fact, the European Commission and the national representatives do not really question CPMP (now CHMP) opinions or discuss their fundamental content. Moreover, those opinions are made public the day the Committee adopts them, i.e., *before* the Commission makes its final decision. The absorption phenomenon is not specific to decision-making in the framework of the EU centralized procedure; it may also be observed in national-level decision-making in France, the United Kingdom or Germany (Hauray 2006).

European dynamics strongly propelled the processes of autonomization and absorption. As early as 1965 the framework directive on medicines explicitly rejected allowing additional criteria to be taken into account in MA decision-making (Hankin 1996: 9). With each framework directive reform, the European institutions successfully defended this choice, and the texts adopted since the early 1990s have clearly bolstered it. National arrangements that did not clearly separate MA issues from price and reimbursement problems have had to modify their legislation. At the European-level, making the MA process autonomous was a means of clearing the way for position convergence: in situations where convergence is already difficult, it is preferable to reduce the number of points that may be considered. Because drug reimbursement systems and price-determining modes are so different from one country to the next, integrating the question of cost for national health insurance systems into medicine evaluation would have meant introducing extremely heterogeneous interests into European-level discussions. Similarly, the drawback of medical and public health evaluation that extends beyond risks-benefits analysis—i.e. analysis in terms of “therapy need” or “benefits to public health”—is that it uses less readily formalized notions and introduces a range of different ways of viewing public health. Lastly, the strengthening of European-level judgments based on national-level expertise further facilitated absorption of policy decision-making by scientific expertise: it was no longer legitimate to call those judgments into question for reasons exogenous to European compromise.

But national changes also played a crucial role in these dynamics. For example, the creation during the 1990s of independent agencies, itself a result of intra-European competition, obviously modified the existing tie between medicine evaluation authorities and the state ministries they were attached to. France provides a particularly clear illustration of this, though it is not an isolated case. In 1989, the French health minister still categorically refused to grant a French MA for the drug Sumatriptan, a powerful anti-migraine medicine because of the high burden it would represent for the health insurance system. In fact, the firm, leaning on the media, was trying to impose an extremely high price for it,¹⁰ and the number of patients likely to use it was both high and undetermined. The French blocked the MA for two years, and this gave the state a chance to negotiate the price. However, in the early 90's, modernization of French evaluation arrangements and the quest to get those arrangements recognized internationally gave decisive weight to the idea that market authorization should be strictly "scientific," unburdened by economic considerations and protected from any discretionary intervention by official policymakers so as to guarantee its credibility. This concern was dramatized and symbolized by transferring the "signature" of MAs from the national health minister to the director of the independent agency, a switch that encountered a certain resistance.

The formation of a European policy space has fostered a progressive absorption of political decision-making by scientific expertise and MA growing autonomy. But, no doubt the transformation of MA decision-making, by limiting the interests at stake and the taking into account of "exogenous" considerations, has, in turn, facilitated the strengthening of European coordination. These two dynamics are thus closely linked.

5.2 The transformation of relations between expertise and representation

The work that national experts do in the CPMP (now CHMP) and its working parties is of a different nature than what they do as civil servants or commission members in their respective countries: at the European level, the function of representation is added to that of expertise. CPMP members have always been appointed by the Member States, which might suggest that they are supposed to express the views of their governments. When the Committee was created in 1975, the representation function was actually an explicit component of its members' official status, and it was maintained as such in 1993 when the status definition was revised upon integration of the Committee into the EMEA. Members no longer represented their states, however; they now represented the national licensing authorities. In the

decentralized procedure, too, all parties to the discussion are national representatives named by national authorities. But representation cannot be satisfactorily conceived in terms of official status; it is an activity, a function. More or less directly, and depending on the period, experts have “represented” national positions by orienting their action within the collective evaluation body in a way that is consistent with the results of the preliminary evaluation done in their national authority body.

During the first decade that the CPMP was in operation, internal and external constraints on collective decision-making regarding mutual MA recognition were weak. Internally, disagreement amounted to refusing mutual recognition and had no serious drawbacks. The substance of agreement was always minimal, and agreement did not significantly inflect national positions because each state could introduce its own provisions, a fact which significantly undermined the very idea of mutual recognition. Externally, no CPMP opinion could be imposed on Member States. In this context, the dominant type of representation enacted by CPMP experts corresponded to the *mandate* theory (Pitkin 1967): they were spokespersons for the evaluation results and positions that had been established in their countries before CPMP meetings, and when there was unanimity, it was reached only by glossing over the biggest problems or attaching national conditions to the joint decision (Hankin 1996).

In the mid-1980s this began to change. Two apparently minor procedural modifications actually had a major impact. First, pharmaceutical companies began to be invited to defend their products to the CPMP. For the first time, the Committee’s national experts had to collectively examine drug firm arguments and debate with the firms; this meant that they acquired information and were able to examine applications in a way that their national administrations before them had not done. Second, in the *concertation* procedure set up in 1987 for highly innovative products, CPMP discussions took place at the same time as national ones rather than after them, meaning that the two levels could inform and affect each other. The effect of this for CPMP members was a change in how the expertise and representation functions fit and worked together: the experts were now practicing *trustee*-type representation (Pitkin 1967), where the representative, while acting in the “interest” of his or her constituents, is not tied to a specific mandate. CPMP experts could now develop an idea of what was in the interests of their administration only as discussion progressed at the European level.

Yet another new period began in 1995 when the European agency was set up in London and the centralized procedure got under way.¹¹ Committee members now sit in their own

name and instructions from national bodies that are in any way “incompatible with their tasks” are forbidden. For each MA application examined by way of the centralized procedure, a “rapporteur” and “co-rapporteur” are appointed from among Committee members. The rapporteurs’ evaluation determines whether or not the pharmaceutical company will be auditioned and provides the basis for Committee deliberations, which lead to a decision confirmed by a vote. Committee decisions are now binding on all states. Clearly our direct observation of the Committee deliberations confirms that the ability to convince other members of the strength of one’s arguments is a decisive condition for getting one’s viewpoint across and accepted. Moreover, the normative framework of Committee debates has evolved in favor of a strictly “European” view of what is involved in medicine marketing authorizations. It has become increasingly less legitimate for Committee members to invoke a national specificity or to request that a national program be taken into account (vaccination, for example). But can we say that Committee experts now exercise what Pitkin called *Burke*-type representation?¹² That is, do they now only conceive of their work as serving a superior European-level interest? If this were so, we could say they have moved from “strategic interaction to problem-solving by deliberation” (Joerges and Neyer 1997). In our view, however, that would be going too far. Empirically, individual Committee members still rely heavily on the work of their respective country agencies; they are still concerned to defend “their” agency’s way or “style” of evaluation, which is of course, for each country, the committee member’s own. However, above and beyond these reservations, Joerges and Neyer’s assertion poses a conceptual problem. In keeping with Habermas’ vision and with studies of deliberative democracy, that assertion is based on an opposition between deliberation and negotiation (Neyer 2004) wherein deliberation is conceived as a means of reaching European solutions by ignoring national interests. In fact, this opposition is not relevant for describing and analyzing human interactions, even in a discussion context where normative argumentation requirements dominate. Deliberation, i.e., a situation where arguments can have effects and preferences can change, does not necessarily imply impartiality or preclude tactics, negotiation or coalitions (Urfalino 2005). Deliberation cannot follow on strategic interaction because strategic interaction is a component of deliberation.

The change in modes of “representing” national expertise has of course increased the level of competence required if Committee members are to correctly exercise their role. The further representation is from the mandate mode, the greater the representative’s responsibility and maneuvering room and the more important is it for him or her to be able to influence the decision-making process by means of his/her competence and knowledge. This requirement

has changed the profile of members appointed to represent their country. Whereas CPMP members used to be top officials of their national agencies, they are now more likely to have more strictly scientific profiles. Concomitantly, they have become increasingly concerned to surround themselves with and obtain support from their national agency's experts. No doubt this evolution has in turn worked to further weaken mandate representation.

We said that the effects of cross-national regulatory competition and the cooperation among experts that began in the 1970s were essential in explaining the formation of a European policy space for medicines. The transformation of relations between expertise and policy decision-making is a new key for understanding this process and the resulting European system. If political or administrative authorities had continued to intervene forcefully in MA decision-making and if national delegates had continued to play a “mandate”-type representative role, the network of national authorities could not have developed—i.e., precisely the network headed today by the EMEA (Dehousse 1997).

6. Conclusion

In approximately 30 years, from 1965 and the first directive on medicine markets to the 1993 creation of the European Medicines Agency, the conditions for authorizing marketing of a medicine have radically changed. Whereas the MA used to be a purely national decision, today it is in large part European. We have shown that this development cannot be understood as a mere transfer of competence, nor adequately grasped by studying the impact of European models on pre-existing national practices. The European policy space that has been formed in this sector is best apprehended by studying the transformation of the involved actors and their relations. The three characteristics justifying the use of the mutual transformation notion (see the first section) prove crucial in the European dynamics analysed in this article.

- 1) Influence among the various actor levels operates in all possible directions, takes all possible paths. “Brussels” initiatives have of course duly made their weight felt at different moments in this history. We did not have sufficient space to describe how a segment of the European Commission attempted to steer this development—and at certain key moments succeeded in doing so (Permanand and Mossialos 2005, Hauray 2006). But European Commission steering had to rely constantly on other impetuses and changes that were developing by way of other paths. First, EU bodies had constantly to subordinate their initiatives to changing national state arrangements and provisions, these in turn linked to the condition of particular national setups for evaluating medicines. Behind the labels “national

administration” and “Member State” were actors with ideas, ties and differing practices who expressed preferences on how the system should evolve and accepted the gradual strengthening of arrangements. As we have emphasized here the institutionalization of this European space was strongly conditioned by phenomena of competition, learning, and cooperation between national administrations and their experts, though these phenomena themselves depended on the existence of European-level forums and procedures. This means that the states’ mutual influences on each other were crucial, and here we see the full relevance of the notion of mutual transformation.

- 2) The sources of change were not only endogenous—that is, activated and kept in motion by the tightening of interdependence among national actors—but exogenous. Certain external impetuses for change manifested themselves in diffuse, overall manner, affecting all actors; examples are the ascendancy of evidence-based medicine and the “gold standard” of randomized clinical trials. Others took the form of exogenous shocks, strong but circumscribed in time: the arrival in the early 1980s of medicines developed through biotechnical research worried the Member States, which had been shaken by the AIDS epidemic and were therefore quite willing to coordinate with each other in this area. This development was the basis for setting up the concertation procedure, which prefigured the centralized procedure.

- 3) Lastly, we have shown that as the interdependence among national-level entities grew, the issues and concerns on which they were either united or divided changed. In bringing to light the transformations in relations between expertise and policy-making, for example, we showed how the very nature of MA decision-making evolved. Meanwhile, the institutional bases on which national actors operated were also changing: in the 1960s they worked in non-specialized health administrations; in the 1970s, specialized administrations; in the 1980s, agencies became their institutional base. In the course of this development, national entities’ representations of their interests and mission changed several times. With these various changes—issues, interests and institutional bases—the very identity of the actors was profoundly transformed, as were relations among them.

Given the diversity of mutually affecting processes, presenting the transformation at work in the formation of European policy spaces is a complex undertaking. Here we have chosen to emphasize three closely interrelated mechanisms: competition, cooperation and the transformation of relations between expertise and policy-making. We hope to have convincingly demonstrated, using the particular case of the drug licensing, that the

multiplicity of influence and impetus vectors and the evolution of identities plead for a systemic approach to European transformation¹³.

Notes

¹ See (Stone Sweet, Sandholtz, Wayne and Fligstein, eds. 2001: 1) and (Moravcsik, 1998: 1).

² The most commonly used definition is Claudio Radaelli's (2003).

³ Risse, Cowles and Caporaso state clearly their choice to emphasize the downward causation from Europe to domestic structure (Risse, Cowles and Caporaso, eds. 2001: 12).

⁴ The analysis that follows is based on more than 100 interviews with sector actors (pharmaceutical industry representatives, members of national authorities and EU institutions, consumer advocate association representatives), direct observation of the EMEA and national health agencies, and archive study.

⁵ For an overall analysis of European-level developments in the medicines area see (Permanand, Govin and Elias Mossialos 2005).

⁶ It is important, however, not to confuse the formation of a European policy space with convergence.

⁷ Committee for Human Medicinal Products. "CPMP" and "CHMP" are hereafter often abbreviated "Committee."

⁸ Briefly, the reforms were as follows: the list of products requiring use of the centralized procedure was extended to include several pathologies, including AIDS, cancer, diabetes, rare diseases; the mutual recognition procedure was changed to allow Member States to exchange opinions before any national decision was made.

⁹ It is in a country's interest to have a recognized MA procedure because pharmaceutical firms will then develop their products in response to its demands, often by doing their clinical trials and research in that country.

¹⁰ Drug prices in France are determined by the state following negotiation between public authorities and pharmaceutical firms.

¹¹ The representation mode of the decentralized process was still "trustee": a state makes a decision which it must then defend against criticism from the other states. Representatives must therefore choose which contentious components of their national agency's position they will defend intransigently and which they can accept to sacrifice.

¹² The reference is to Burke's renowned speech to Bristol voters: "Parliament is not a *congress* of ambassadors from different and hostile interests, ... parliament is a deliberative assembly of *one* nation, with *one* interest, that of the whole."

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