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Philippe Gorry, Matthieu Montalban, Andy Smith

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**Reinstitutionalizing the evaluation of medicines:  
EU-national complementarities, competition and contradictions**

**Philippe Gorry, Matthieu Montalban and Andy Smith**

Paper presented at the ECPR conference, Reykjavik, Iceland, 25-27th August 2011

**Introduction**

At least throughout developed countries, the pharmaceutical industry is in the midst of a period of doubts, reflexion and propositions for change concerning the inextricable link between its economic structure and its political ordering.

- From the angle of industrial economics and the business models of firms, the end of the 'blockbuster era' -caused by a plateau in scientific innovation and increased competition from generics- has yet to give rise to a replacement wherein biotechnologies, personalized medicines and preventive clinical practice might eventually herald a new set of parameters;
- At the same time, this disruption of the economy of pharmaceuticals has in part of course been caused by decisions by collective and public bodies that have led to greater competition through the lifting of barriers to international trade and encouraging the substitution of off-patented drugs by generics. Whether these measures have been the result of neoliberal ideology, or simply of a drive to cut the ever-rising costs of health care, the consequence has been a challenge to the capacity of large pharmaceutical companies ('Big Pharma') to demand that public and collective bodies reward all the 'innovations' they seek to put on the market (Montalban, 2007 & 2008).

Nevertheless, such companies and their supporters also clearly still possess a capacity to generate public support through underlining the profits they make and the skilled jobs they continue to provide within developed countries. At least within the member states of the European Union (EU), lines of argument about the 'competitiveness' of the pharmaceutical industry are developed in order to counter those of other actors more concerned with 'the sustainability' of health systems. Indeed, the middle ground of general political debate over the future of pharmaceuticals in Europe invariably contains rhetoric about the need to combine 'competitiveness' and 'sustainability' as two complementary goals.

The difficulty of actually reconciling these objectives during commercial activity and government of this industry thus provides the first dimension of this paper's object of study. It is supplemented however by a second set of questions concerning the scale of this government and the scope of the institutions it encompasses. Between 1965 and 1995, instruments were progressively built for authorizing the commercialization of medicines at the scale of the EU. Indeed, this process seemed to culminate with the establishment of the European Medicines Authority (EMA), the organization which is responsible today for the majority of market authorizations (MAs) in Europe (Hauray, 2006). However, neither a European market for pharmaceuticals, nor its government at the scale of the EU, has been completed: formally health care remains a national competence, national MA systems still exist, and pricing and reimbursement (P&R) continue to be conducted on a national scale. Consequently, the government of pharmaceuticals in Europe entails intricate compromises, notably between states' representatives trying to maintain their sovereignty and the sustainability of public finance, pharmaceutical firms attempting to loosen MA and P&R rules, and European Commission representatives seeking to enlarge their role in both these issue areas.

The puzzle which arises from this twofold concern for the politics of the pharmaceutical industry and change in its scale thus concerns the emergence of a form of European government that despite being fundamentally incomplete (due to the persistence of the national scale and range of issues it aspires to govern), nonetheless has had considerable and largely unstudied impacts on health systems in Europe. In more concrete terms, we have therefore set out to answer the following questions:

- what evaluation instruments have been established and are being proposed at the scale of the EU?
- to what extent have they been institutionalized and even replaced national rules and practices?
- who has participated in these developments and how?

The responses related here pertain essentially to two key issue areas within the government of pharmaceuticals:

- the according of MAs to medicines following ‘assessment’ of their safety and efficacy – what one interviewee called ‘the scientific definition of the market’<sup>1</sup>;
- the P & R mechanisms through which health systems and their varying sets of protagonists (taxpayers, insurers, patients) ‘appraise’ and pay for medicines – the socially and politically defined market.

Over the course of the 1980s and early 1990s, at the national scale in Europe a concerted attempt was made to separate assessment and appraisal by setting up agencies and procedures to this effect. As will be shown, actors, norms and instruments from the scale of the EU participated only marginally in this process (part 1). However, as of the beginning of the 1990s the scale of the EU increasingly began to have an impact on the pharmaceutical sector and this essentially around the issue of MAs and the establishment of the EMA. At that time, this was presented as the simple addition of a level of authorization which would respect, and even enhance, the separation between MAs and P & R that then existed at the national scale. Over the course of the last decade, however, both the relationship between MAs and P & R in much actor discourse and behaviour, but also the influence of an EU scale of government, have changed considerably. Many MA and P & R systems in Europe systems have (re)developed a more dialectical relationship, whilst many more issues have been debated and legislated over at the scale of the EU.

Contrary to readings of this change around ‘reduced transaction costs’ and rational choice institutionalism (Permanaud, 2006), however, this displacement in the evaluation of medicines is not simply the consequence of the establishment of the EMA. Nor is it just the result of national governmental cost-cutting. Instead a ‘constructivist-institutionalist’ (Hay, 2007) framework needs adopting in order to uncover the ‘political work’ through which actors have sought to reproduce or change institutions through the making of arguments and alliances<sup>2</sup>. More precisely, by examining the actual *practices*<sup>3</sup> of MA and P&R in two member states (France and the UK) and at the EU scale, their relationships with pharmaceutical firms and the links between both these sets of actors and national or EU administrations, parts 2 and 3 of this paper hypothesize that:

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<sup>1</sup> Interview with French trade association official, October 2010.

<sup>2</sup> This overlapping process entails both the problematization of issues and their politicization or depoliticization (Jullien and Smith, 2008: 19-22).

<sup>3</sup> As François has shown, institutions in the economy exist above all through the practices their injunctions give rise to: ‘There are not on the one hand rules with an independent existence that soar above practices, and on the other practices which are just their more or less imperfect and case by case translation. On the contrary rules can only be grasped by examining practices’ (2011: 51).

- Dominant firms, and their collective representatives have consistently worked to reduce uncertainty about MAs (by promoting the EMA) but also to retain flexibility (by maintaining the national scale). This power of dominant firms has not however simply flowed from their ‘structural’ resources (eg. capital, profits and job provision). Instead, the power of such firms is due to their engagement in EU politics via work that has been institutionally more ‘appropriate’ (March and Olsen, 1989) than that of their opponents.
- The unintended and cumulative consequences of member state governments authorizing the initial creation of the EMA, then progressively accepting an expansion of EU competences, has facilitated the political work of dominant firms and their allies in the Commission and the EMA. Indeed, over both the assessment and the appraisal of medicines, since the late 1990s representatives of states have opened a ‘pandora’s box’ from which a flow of calls for more EU-scale government has increased and often been met by positive legislative responses.

Overall, and as part of a wider set of research that is still very much in progress<sup>4</sup>, this case study reveals that in the pharmaceutical industry much convergence on methods and some transfers of authority to an EU scale of government have taken place. However, the EU government of medicines is still very much incomplete and therefore by no means constitutes a ‘common pharmaceuticals policy’. Instead, the evaluation of medicines in Europe is now a field within which EU-national tensions constantly impact upon the government of medicines, and thus of health, throughout Europe.

### **1. The Separation of Market Authorization and Pricing (1985-2000): National agencization without EU influence**

In order to study the accelerated development of an EU scale of government for this industry that has taken place over the last 15 years, it is first necessary to grasp the changes of similar magnitude which took place *within* European states during the preceding 10 to 15 years. During this earlier period, systems of hands on involvement of government ministries in the assessment, appraisal and financing of medicines were largely replaced by the delegation of these activities to specialized agencies. ‘Agencization’ is of course a trend that has been the subject of much research and numerous publications (Pollitt et. al., 2004). This is particularly so in the domain of health where many authors have shown how the establishment of agencies enabled state representatives to deploy the precautionary principle, present themselves as impartial and encourage new ways of managing internal and external expertise (Besançon, 2004: 38-9; Borraz, 2008). Moreover, in most European countries this externalization of ‘the management of risk’ ostensibly facilitated a separation between ‘assessments’ of the safety of a medicine and ‘appraisals’ of its medical effectiveness and economic efficiency. Interestingly, however, this convergence in managing the problematics of risk does not appear to have been driven by European integration and the European Commission in particular. Certainly an initial directive (65/65/CEE) on MAs then another on the transparency of pricing (89/105/CEE), despite occurring 24 years apart, did have some impact upon national practices. However, as the French and British case clearly illustrates, until the mid-1990s the main drivers for change were instead

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<sup>4</sup> This paper synthesizes one aspect of our research on the EU’s government of pharmaceuticals (the others include inter-firm competition and research/innovation policies). In addition to in-depth sectoral analysis of this industry, and that of numerous documentary sources, to date around 25 interviews have been conducted with representatives of firms, interest groups and administrations located in Paris, London and Brussels. Research on this industry is also part of a wider project on the *Gouvernement européen des industries* (GEDI). Financed by the French *Agence nationale de la recherche*, the GEDI project runs from 2009 to 2012 and also encompasses the automobile, wine and aquaculture industries. We thank our GEDI colleagues, Cédric Lomba and Colin Hay for their comments on an initial draft of this paper.

located at the scale of the states and concern their relationships with their respective pharmaceutical firms and national health systems.

### 1.1 France: from statist dirigisme towards some delegation and separation of powers

In contrast to many other industries in France, that of medicines has not been heavily regulated for very long. Nevertheless, beginning in the 1940s the French state did develop and deploy an interventionist approach to this issue area which, through affecting both the authorization of medicines and their price, but also the development of state-owned firms, heavily marked this industry until the mid-1990s. Another specificity of the French government of industry is the role of the social security system and the control of prices. Indeed, when the *Conseil National de la Résistance* institutionalized the Sécurité Sociale in the 1940s, a lot of debates on the level of pricing and reimbursement took place between the industry and the government. The compromise found was to consider that reimbursement would ensure an increase of demand, so firms would not need high prices because they would obtain a high volume of commerce. The Comité Armand-Rueff proposed in 1959 a reform of this pricing system by including more flexibility and attempts to sustain R&D for new products. However, these rules were never really implemented.

The institutionalization of drug regulation and of specific administration in France dedicated to drugs should of course be understood as part of a long historical and international process. Actors in the USA were pioneers: in 1902 and 1906, the « *Biological control Act* » introduced compulsory control over the manufacturing of vaccines because of sanitary problems. The control of drugs became stronger with the Food and Drug and Cosmetics Act of 1938 which created the Food and Drug Administration, prescription drugs and forbade false claims – all this due to the political work of scientists known as ‘therapeutic reformers’ (Pignarre, 2003). In 1962, the Harris Kefauver Act imposed systematic evaluations of the quality, safety and efficacy of drugs, and the benefit-risk balance. In France, the equivalent process was much slower. If a ‘Visa du médicament’ was institutionalized in 1941, and then reformed several times, controls were not as strict as in the US. However, due to several scandals (“poudre de Baumol”, Stalinon, thalidomide...), France finally adopted a genuine marketing authorisation system in 1972.

In 1967 a system had previously been devised to bring French practice in line with the EC’s 1965 directive (Chauveau, 2007: 88). The 1972 system was revised in 1978 and gave rise to procedures essentially based upon the relationship between two parts of the Ministry of Health (*Le laboratoire national de la santé* and *La Direction de la pharmacie et du médicament: DPHM*). Lengthy debates in the 1980s eventually led in 1992 to the merging of these two bodies into the *Agence du Médicament*. A principal concern at this stage was to separate therapeutic evaluation from (national) industrial policy concerns:

‘Until 1992 the DPHM did everything – who examined files in the name of the minister, made decisions about risk-benefit calculations, MAs, who managed a committee called ‘transparency’ (...). The reform fundamentally separated these aspects. It put everything concerning safety regulation into an agency, with the idea that was very clear in the minds of its creators, that one should not mix purely safety-centred evaluations with regulations that were more economic’<sup>5</sup>.

The creation of the Agence du Médicament was accelerated by a number of public health crises (AIDS, contaminated blood) which revealed the weakness of the Ministry of Health’s expertise

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<sup>5</sup>

Interview, senior AFSAPPS official, Paris, October 2010.

and gave impetus to the policy concepts of *'sécurité sanitaire'*, the 'precautionary principle' and, more generally, the notion of 'evidence based decision-making' (Urfalino, 2001). Indeed, in 1998 this agency both widened its remit to become the *Agence française pour la sécurité sanitaire des produits de santé* (AFSSAPS) and deepened its legal base. Other commentators point out that the establishment of this Agency was also a policy response to the need to create a French representative for EU scale exchanges and 'coordination' (Besançon, 2004: 28). Through its own employees but also a network of 2000 external experts, the main stated objective of this agency has been to assess the benefits and risks of new medicines, and thus their relative safety. One of our interviewees, a pharmaco-epidemiologist and ex-expert for AFSSAPS<sup>6</sup>, also underlines the independence of this evaluation and expertise.

Another objective of the creation of the *Agence du médicament* was, however, also to separate questions of safety assessment from those of setting prices and levels of reimbursement by the social security system. As we saw above, until the mid-1990s, prices were set essentially by the Ministry of Health. Towards the end of that period (1990-97) this Ministry undertook a number of experiments in using economic analysis to set prices were made. However, the controversy they sparked led to this approach being abandoned (Benamouzig and Paris, 2007: 15) and replaced instead by the creation of a system built around a *Comité économique des produits de santé* (CEPS). Comprised initially by four representatives of the Ministry of Health, the director general of the Ministry of Industry, a Director General from the Ministry of Finance (head of the DGCCRF) and three representatives from the national insurance fund, the CEPS has been summed up as the place 'where health becomes interministerial' (Besançon, 2004: 27). Although clearly not independent of the state, neither is the CEPS simply a tool that belongs exclusively to the Ministry of Health either.

Indeed, the inter-sectoral negotiating role played by CEPS brings us to that played by representatives of pharmaceutical firms and their interest group (*Les entreprises du médicament*: LEEM) within the regulation of medicines in France. LEEM (ex-SNIP) includes all the companies having activities in France. Between the 1980s and the mid-2000s, the French pharmaceutical industry experienced a lot of changes: first, a high degree of concentration occurred with the creation of Sanofi-Aventis, one of the five largest *Big Pharma* in the world. Second, most of the familial companies declined compared to their competitors. Consequently, CEPS and its policies were envisaged by private and state actors as a means of developing 'national champions' through meso-level industrial policy<sup>7</sup>. Indeed, very often, large (foreign) groups like Pfizer made complaints against the level of prices set and threatened to relocalise their activities. Indeed, the institutionalization of CEPS and SMR/ASMR criteria were tools which allowed more 'open' bargaining between firms, State and other stakeholders (CNAM, Mutuelles etc). Indeed, since 1997 framework agreements between CEPS and the LEEM have been signed each year (or for a longer period).

Overall then, over the period 1985-2000 the French model of regulating the pharmaceutical industry changed significantly due to its reproblematicization by actors within the French state, but also others working for large pharmaceutical companies who anticipated benefits from developing a more distant relationship with civil servants and ministers. Without being totally absent from this process of reproblematicization, EU scale legislation, norms and actors were nevertheless only marginally involved in this change.

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<sup>6</sup> Interview Bordeaux, June 2010

<sup>7</sup> Until the mid 1990s, this policy was often in contradiction with the government's attempt to also attain its macro-economic objectives of controlling inflation by fixing low prices. This often frustrated the LEEM (interview, Paris, October 2010).

## 1.2 UK: from *colbertisme à la britannique* to agency autonomy

British interventionism in the economy is less well known than the French equivalent, nevertheless it has often been much more extensive and profound than is generally recognized. This is certainly the case for pharmaceuticals where, as one British civil servant put it to us: ‘we actually have a surprisingly *Colbertiste* approach’<sup>8</sup>. The causes of the latter stem from a longstanding approach of British civil service to certain industries, the key role played by the National Health Service (NHS) since its establishment in 1948, as well as the existence of several British based Big Pharma players (notably GlaxoSmithKline and AstraZeneca) represented by a powerful trade association: the Association of the British Pharmaceutical Industry (ABPI).

In terms of the authorization of medicines, this approach first gave rise to an NHS committee on ‘prescribing’ which, in 1962, became a formal MA body (The Commission on the Safety of Drugs) which in turn became in 1968 the Medicines Control agency and the Medical Devices Agency. As part of ‘New Labor’s’ drive to inculcate managerial norms within such organizations (Moran, 2003), these two bodies merged in 2003 to become The Medicines and Healthcare Products Regulatory Agency (MHRA).

The most recent Labour governments also sought to spread such norms by modifying organizations and practices in the area of pricing and reimbursement. At one level, this strive for change seems to have been singularly unsuccessful because prices for medicines in the UK continue to be set through a negotiating process –the Pharmaceutical Price Regulation Scheme (PPRS)- who’s basic principles have been rolled forward every five years since their creation in 1957. Each PPRS is the result of lengthy exchanges between the Department of Health, the NHS and the APBI which rather than control the price of each medicine, seek to control public expenditure on pharmaceuticals by setting limits on the profits of the firms concerned and ensuring that excesses are paid back to the public purse (Cohu, Lequet-Slama & Raynaud, 2007). Notwithstanding the continued institutionalization of the PPRS, British practice over pharmaceutical pricing nevertheless changed considerably as of the late 1990s due to the establishment of the National Institute for Health and Clinical Excellence for England and Wales (NICE) in 1999. Charged with evaluating the cost efficiency of medicines through ‘medico-economic evaluations’, Nice not only determines what medicines cannot be purchased by the NHS (‘the black list’) but also the ‘quality’ of each one that makes ‘the grey list’ (calculated in terms of ‘Quality Adjusted Life Years’: QALYs).

Overall then, in the UK assessment and appraisal are clearly separated and considerable autonomy from government involvement has been granted to both the MHRA and NICE to develop their respective mandates.

Indeed, as we have just seen, many reinstitutionalizations to the government of pharmaceuticals were carried out in both France and the UK during the period 1985-95. In both countries there was a concerted attempt to separate assessment, appraisal and price-setting, and to “professionalize” all three of these processes. However, and despite some evidence of indirect policy learning across the Channel, all this occurred with little EU actor or instrument involvement.

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<sup>8</sup>

Interview, Department of Health, December 2010.

## **2. Increases in MA/P & R dialectics and European Government: from a state-led to a corporate-led EU-scale government of the pharmaceutical industry**

Since the early 2000s, a move to reinstate, but also reinvent, the linkage between the assessment and appraisal of medicines has taken on increasing importance within the government of this industry - a government that without replacing national actors, nevertheless increasingly takes place at the scale of the EU. During this period, a certain role has been played by the politicization of issues, notably via the ‘High Level’ EU health policy forum and national counterparts more specifically linked to pharmaceuticals<sup>9</sup>. But most political work in this industry has in fact been carried out in a more technicized vein around the detail of evaluating medicines and innovation. In so doing, a key step has been the establishment then institutionalization of the EMA. Ostensibly limited to the task of assessing the scientific value of medicines, this organization has steadily moved itself to the centre of numerous debates concerning the government of the pharmaceutical industry. This technicization, focused upon issues of expertise, has had at its centre the evaluation of innovation. In general, member states have adopted an almost schizophrenic stance by ardently defending their sovereignty over the field of health for reasons of legitimacy, the defence of public health and controlling costs, while participating in progressive communitarization through the establishment of different mechanisms for sharing competences and information. Nonetheless, the highly technical nature of the debates this has entailed is also highly revealing of the strongly political dimension of health-related issues. Technicization has thus been a method for ‘making progress’ towards communitarization.

It is vital to appreciate that firms have participated fully in this process. Whereas they had previously been reticent as regards European integration, and in particular the institutionalization of rules and of the EMA, as of the mid to late 1990s they instead became pro-active in deploying political work which mobilized both their internal expertise for their argumentation, but also alliances with Commission officials and a certain number of MEPs<sup>10</sup> or patient organizations.

For their part, officials from the Commission who for decades had only be concerned with building a single market for pharmaceuticals production and trade, began to develop a mode of political work that enabled their progressive insertion into health issues. The most obvious examples of this trend have been the transfer of responsibility for medicines from DG Enterprise to DG SANCO in 2010, and increased Commission involvement in pricing and reimbursement issues. A representative of the French national insurance organization (la CNAM) presented this change as follows:

‘Until now states have always kept responsibility for P & R. This has not changed but one can see that the Commission, because of the health crises there have been, tries to insert itself into all the interstices by pushing off from the public health end of things. And it has nevertheless obtained powers that it has more or less given itself. Afterwards it works at what one calls ‘window dressing’: pretending that nothing is changing then pushing as hard as it can to maximize European-scale competences’<sup>11</sup>.

Indeed, this pincer movement by large firms and the Commission has constituted a major challenge for national governments. Although they still retain a great deal of power in the health field, they now find themselves increasing in conflict with both sets of protagonists, notably over issues of price, and this despite all the actors concerned seeming to accept that complete

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<sup>9</sup> In the UK, when prime minister Tony Blair set up a pharmaceuticals task force. A similar entity exists in France attached to the Presidency.

<sup>10</sup> In particular Françoise Grosstête, MEP from the Rhône Alpes region.

<sup>11</sup> Interview, Paris, October 2010.

communitarization here would be impossible. In short, although largely incomplete and possibly even incompletable, the government of this industry that our research has revealed is increasingly European within which large firms appear to be augmenting their power. Here we illustrate this hypothesis by focusing first upon the effects wrought by the initial institutionalization of the EMA (2.1) and then by its consolidation (2.2).

## 2.1 The institutionalization of the EMA and reinstitutionalizations of national agencies

What first needs to be grasped is that the EMA was not created in opposition to national agencies but very much alongside them (2.1.1). Secondly if, during the early years of this process, Big Pharma were not drivers of this project, it nevertheless fitted well with the blockbuster model which then dominated the industry (2.1.2).

### *2.1.1 European and national agencization in parallel*

Indeed, in general terms, the construction of a set of rules and laws for regulating the European medicines market owes as much to national administrations and agencies as it does to Big Pharma and the Commission (Hauray, 2006).

Firstly, as we saw in part 1, the model based on agencies developed progressively. The separation they were supposed to introduce between therapeutic value assessments and industrial policy concerns was achieved without any significant reference to the ‘needs’ of European integration or the ‘demands’ of the Commission:

‘Contradictions between economic logics and health ones will always exist. Regulating them however does not necessarily means raising one or other to the European level (...). The scenario here is that the states have kept control over public health. Its a responsibility where subsidiarity rules’<sup>12</sup>.

Nevertheless, the emergence of a European scale of assessment is seen as advantageous for national authorities because it enabled them to share competence, to exchange information and thus to seek to ‘improve’ decision-making over MAs. Today, national agencies still possess considerable levels of expertises. Indeed, several of them, and notably the French and British ones, often seek to dominate this decision-making over specific applications, not only for reasons of organizational legitimacy but in the name of their respective national interest. Again, the representation of this by an AFSSAPS official is highly revealing:

‘In reality, accountability and responsibility is at the national level. Let’s be clear here, and I’ve often said this provocatively in English : ‘There is no such thing as a European scene in this domain’. i.e., when actors want to intervene because a product has been withdrawn too early or authorized too late or, on the contrary, withdrawn too late, they don’t demonstrate in front of the Commission’s windows but in front of ours’<sup>13</sup>.

In similar vein an official from the British MHRA underlined to us:

‘Nobody would argue that the MHRA is one of the leading agencies in Europe so we do tend to get a high proportion of rapporteurships for centralized products – which also

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<sup>12</sup> Interview with senior AFSSAPS official, Paris, October 2010.

<sup>13</sup> Interview, Paris, October 2010.

brings lots of responsibilities after the licensing has been completed: the safety monitoring. But even when we are not the *rappporteur*, the UK's view has always been that these are products that are going to be on the UK market, so that even if we are not taking a leading role in the assessment, we want to be absolutely confident that they meet the needs of UK citizens<sup>14</sup>.

In other words, socio-political (accountability, ways of life, values, type of health system) but also biological (genetics) reasons have been evoked by a diversity of actors in order to maintain national agencies alongside the EMA. But just as importantly it is these national agencies who provide virtually all the experts that allow the EMA to function at all. As an ex-expert in pharmaco-epidemiology stressed to us on interview: 'The EMA would be nothing without the national agencies'<sup>15</sup>. Indeed, to return to our interviewee in AFSSAPS :

'The function of information is absolutely essential (...). Over pharmacovigilance for example, there are national decisions and centralized decisions. But you need networks of pharmacovigilance in the different countries to produce the signals, and you can't manage that is a centralized logic. You need national mediators'<sup>16</sup>.

### *2.1.2 European agencization not pushed by Big Pharma...but coherent with their blockbuster model*

The initial reticence of large pharmaceutical firms as regards a European agency can in part be explained by the difficulty they had in reaching agreement amongst themselves on this point. As a representative of their European federation, the EFPIA, put it to us:

'25 years ago certain French firms, eg. IPSEN or Fabre, did not cover the whole of the EU. And it was the same for Spanish and Italian firms. These countries, countries from the South, wanted to keep a decentralized system'<sup>17</sup>.

In other words, many medium-sized companies feared that the EMA would introduce stricter controls and simply duplicate national ones, whereas other, often larger, firms simply wanted a centralized European agency so as to have 'a one stop shop'. For a medium-sized company with an essentially national market conserving national procedures that they were used to, and that they thought they could even control, was often seen as being in their interest. However, for companies whose business model was constructed around selling large volumes of 'blockbuster' drugs, European centralization was seen as a means of directly obtaining access to the whole of a much wider market:

'Why did MAs become communitarized? Simply because this was the époque of big commercial blockbusters and medicines whose markets would be worldwide. We realized it was stupid to continue to conduct duplicatory studies, which delayed market entry, for products that needed considerable investment that could only be recovered on a global scale'<sup>18</sup>.

Ultimately, this divergence of interest amongst firms, combined with the schizophrenic attitude of most national administrations, produced a compromise where three levels of MA would co-exist:

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<sup>14</sup> Interview, London, December 2010.

<sup>15</sup> Interview, Bordeaux, June 2010.

<sup>16</sup> Interview, Paris, October 2010.

<sup>17</sup> Interview, Brussels, June 2010.

<sup>18</sup> Interview, LEEM, Paris, October 2010.

- European MAs through assessment by the EMA (and final approval by the Commission);
- National MAs given by national assessment agencies uniquely for each national market;
- Decentralized MAs given by national agencies but recognized throughout the EU through application of the ‘mutual recognition’ principle..

Firms were thus given three options. Nevertheless, this mode of communitarization is also seen by many actors as driven by industrial policy in order for a European scale of regulation to compete with the American FDA and its Japanese equivalent. This interpretation lies at the heart of the viewpoint expressed to us by a senior official from the LEEM. Having directly experienced this whole process, he recalls that the argument in favour of centralization was:

“if we do not act together, if we do not develop in Europe powers in the evaluation of MAs, there will be just two dominant mechanisms for MAs: the American and the Japanese systems (...). So if we didn’t mechanisms for normalizing market entry in Europe, we would have ended up with a totally different system, with the English is the American system... (...). So if we did not want research-based medicine to disappear in Europe we had to have a debate about norms”<sup>19</sup>.

## 2.2 The consolidation of the EMA and a European scale of government

Notwithstanding the way the EMA was created and the formal role it received, since the end of the 1990s a considerable reinstitutionalization of the European government of pharmaceuticals has taken place. Indeed, this process has been driven both by actors within the EMA, but also a number of allies in the Commission and elsewhere.

The key element here has been that despite the limits set upon it in the early 1990s, the EMA has become the centre of a network of all the national assessment agencies in Europe. Through its (Committee for Medicinal Products for Human use), the applications to be evaluated are divided up amongst national agencies (two evaluators per file) in accordance with their respective ‘comparative advantages’. The results of these two opinions are then collated by the principal evaluator before being presented to the committee as a whole. One of the effects of this process is to have created a form of benchmarking designed to ‘improve the quality’ of all EMA’s evaluations. According to the previously cited official from AFSSAPS, for example:

“The existence of a European agency since 1995 has meant that on certain subjects there has been a confrontation of scientific knowledge in certain European countries and amongst groups of European colleagues. This is quite something and provides the system with strength. One is challenged therefore its a factor improving quality. It’s positive. It’s stimulating”<sup>20</sup>.

As stated earlier, the EMA itself has relatively few resources in terms of expertise and instead, has to take support from national agencies, and the four most developed of these in particular (the French, the British, the German and the Swedish). As one of EMA’s employees stated on interview:

‘I confirm that the EMA is not where the assessment is taking place. The assessment is made by the experts in the member states. We may draw on this expertise, and help to finalize the decision. Our role as an agency is as a secretariat co-ordinating the assessment,

<sup>19</sup> Interview, LEEM, Paris, October 2010.

<sup>20</sup> Interview, Paris, October 2010.

and drawing from the resources identified. But the experts come from the member states – and exceptionally from outside it. We now have collaborations with the US, Canada and the WHO. Where we have more of a scientific role is in the areas of orphan drugs and paediatrics. In this area we contribute to the scientific assessment in collaboration with the national experts. So we contribute to the network with slightly different roles, complementary roles<sup>21</sup>.

This said, EMA is nevertheless where nearly all MA applications for ‘innovatory’ products are made, whereas those for generics or ‘me too’ drugs tend to be made via a national agency. As our interviewee at AFSSAPS underlined: ‘nearly all innovation tends to go through the centralized procedure’<sup>22</sup>.

Crucially, this reinstitutionalization of the EMA and its hegemonic role in the assessment of ‘innovatory’ drugs has taken place during a period where firms have experienced decreasing returns for innovation, increasing R & D costs and a decline in the total number of MA applications for new molecular entities. Having framed these trends as a single European ‘problem’, the rest of the political work conducted by large firms and DG Enterprise has ostensibly aimed at improving the competitiveness of individual companies. From this angle, over the last 15 years the following series of directives and regulations has been adopted, each of which in its way has contributed to consolidating the role of the EMA and, more broadly, has legitimized the EU-wide scale government of this industry:

- a directive on biosimilars in 2004 ;
- a directive and a regulation on pharmacovigilance in 2010;
- a directive on counterfeit drugs also in 2010;
- a directive on clinical trials that is currently under discussion;
- a directive on information to patients that despite great controversy, is still being negotiated.

In nearly all of these instances, the legislation, and particular the initial proposal from the Commission reveals a strong level of proximity between the positions of the latter and the EFPIA. Even if many of these legal instruments were ultimately adopted with some amendments due to the political work of actors such as (European Social Insurance Platform), *la Mutualité française*, or the journal *Prescrire*, often within the platform *Europe et médicament*, this has only led to fundamental reproblematisations in the case of ‘information for patients’. In contrast, the firms of Big Pharma, usually via the EFPIA and often via the French MEP Françoise Grossetête, have developed sustained influence over MEPs from the PPE. An official working for a social insurance organization presented this situation in the following way:

‘Big Pharma is extremely powerful (...) they have their own lobbyists, there are lobbyists from consultancy firms that can be mandated by the companies, by advertising agencies or even television channels. There are many arguments about money, or economic power, that are invoked whilst we underline those related to public health. Fortunately we have this argument because in terms of resources we are a bit behind them ! (...) They are really very skilful, they have think tanks etc. to promote ideas, undertake studies in universities which are biased...’<sup>23</sup>.

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<sup>21</sup> Interview, London, December 2010.

<sup>22</sup> Interview, Paris, October 2010.

<sup>23</sup> Interview, Brussels, June 2010.

Similarly, a representative of *La Mutualité française* described on interview how, in their view, firms financed patient organizations as a means of encouraging new legislation that would be favourable to them:

‘At the European level, what concerns us a lot is the European patient forum which presents itself as representative of all the European patient associations. But if one looks a little closer it is 100% financed by the pharmaceutical industry. It is very present within the European Commission as a so-called defender of patients. But it defends pro-Big Pharma arguments a great deal<sup>24</sup>.

It is also important to grasp that the reinstitutionalization of both the EMA and the GEDIP is strongly linked to legislation from the late 1990s concerning ‘orphan drugs’. Regulation 141/2000 institutionalized at the EU scale a category of medicines which, because they concern relatively small numbers of patients in each member state, benefit from derogations from internal market law, and that concerning intellectual property rights in particular. Since the adoption of this regulation, an orphan drug in the EU has been defined when it is destined for less than 1 in 2000 patients. This regulation was the consequence of political work undertaken initially by several researchers within the French health research institute (INSERM), and by Annie Wolf in particular. Having first targeted the French administration, they then proceeded to expand their actions to include the Commission and the Council. At the end of the 1990s, Wolf became a member of Simone Veil, the then French health minister’s *cabinet* and managed to convince her to push for a European regulation on orphan drugs, inspired by the American *Orphan Drug Act*, during the French presidency of the Council. The French administration as a whole then worked to organize a meeting of Community organizations and patient associations, despite the latter being poorly organized at that time. An initially sceptical set of Commission officials rallied to this cause and shepherded a regulation through the Council which gives the EMA a monopoly over the designation of MAs for all orphan drugs. This exclusive competence has therefore given the EMA itself the opportunity to develop expertise in this area, and even an ability to co-design clinical trials. As an EMA official put it to us:

‘For orphan drugs we are much more into the assessment. EMA is still the body that validates the whole exercise like for other AMMs. But we have two assessors – what we call co-ordinators- for each application. One of them is EMA staff and one is a member of the committee. Indeed, the first assesseur is here in the EMA and the rapporteur is commenting on their report. (...) I think the orphan regulation is definitely an example of where an EU interest can be put together and then taken forward. It’s a very good example of successful EU collaboration. And it makes us proud that the EMA has had a role in this and that our staff has acted as a co-ordinator<sup>25</sup>.

This development takes on additional importance when one considers that orphan drugs have shifted from being a minor issue for Big Pharma in the 1990s to a priority for all the firms concerned because of the difficulties encountered by the blockbuster model. **Indeed, a restructuring process has taken place, with some Big Pharma firms trying to develop new business models based on personalized medicine and orphan drugs (e.g Roche Holding with Rituxan, Novartis with Glivec or Sanofi-Aventis, which acquired Genzyme recently).** By 2009, no less than 57 orphan drugs had received a MA and 577 molecules had been given orphan

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<sup>24</sup> Interview, Paris, November 2010.

<sup>25</sup> Interview, London, December 2010.

status<sup>26</sup>. Similarly, products generated by biotechnologies are generally classified as ‘innovatory’ and thus are assessed using the centralized procedure and the EMA.

All this reinforces the legitimacy of the institution, and make it a strategic arena, for the appraisal of drugs, but also as tool for industrial policy. To quote two EMA officials:

A : ‘We are personally very proud to have been involved in the orphan drug situation and to have something for companies – because the success is there. We are big supporters of the orphan drug legislation (...). As regulators we are very happy to see that incentives were made and, furthermore, that they were implemented and used. We are very good in Europe in creating incentives, but as soon as people try to use them there is a problem. Not killing the goose...’

B: ‘There are also ways to breach market exclusivity if something more interesting comes onto the market. So we are not creating a sort of market exclusivity against anything. Market exclusivity has a very clear definition in the regulation – it is not just a blank cheque for the company. But something that incentivizes them’<sup>27</sup>.

More generally, the question of ‘innovation’ and fast access to ‘innovative medicine’ has been important to the reinstitutionalization of the European government of pharmaceuticals because this has also occurred in national cases such as France: AFSSAPS has a tool, the « Autorisations Temporaires d’Utilisation » (ATU), that allow an anticipated access to the market, before the MA, especially for innovative drugs. Most of the time, ATUs are given on average one year before the expected date of the MA. But for orphan drugs, ATU are delivered 34 months before the MA<sup>28</sup> (entretien AFSSAPS). For its part, EMA has provisional MAs. In all those cases, ‘ethical’ arguments are mobilized to justify the adoption of such procedures. Nevertheless, consciously or unconsciously, the actors are aware of the potential role for industrial policy of such tools (see previous quotations from members of EMA, and the following from a representative of AFSSAPS):

‘ATUs were created out of ethical preoccupations in the sense of access for patients, anticipated access for patients who have imperious needs – and this sometimes even before we have completely established the benefit-risk balance... This was clearly the objective. It is also true that, with hindsight, one can see that the existence of more flexible mechanisms in France that this is a plus in terms of attractiveness. Industry is the first to say this. They don’t say it too publicly, but in this office they say ‘we are really happy’<sup>29</sup>.

In summary then, the EMA is not the sole entity around which not only a reinstitutionalization of MAs in Europe have taken place, but also more generally a reproblematicization of the pharmaceutical industry and its government. As a consequence, the tensions between safety issues on one side, and industrial policy and the sustainability of reimbursement systems on the other, are greater in a context where P&R remains national, the control of innovative (and costly) drugs is more and more communitarized and there are increasing pressures on public finances. Not surprisingly, political work has thus more recently become increasingly focused on ‘innovation’ and the evaluation of innovation.

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<sup>26</sup> For illustrations of this see Gorry and Montalban (2010).

<sup>27</sup> Interviews, London, December 2010.

<sup>28</sup> Interview, Paris, October 2010.

<sup>29</sup> Interview, Paris, October 2010.

### 3. Another reinstitutionalization of evaluation in Europe ? Growing contradictions and the ‘solution’ of Health Technology Assessment

More precisely, since the mid 2000s, articulating MAs and P & R systems has been increasingly problematized at national and EU-wide scales.

At the national scale a number of attempts to deinstitutionalize existing methods of MA and P & R and to reinstitutionalize alternatives have been made. The most obvious of these in the UK has been a sustained challenge to the PPRS system and moves to replace it with ‘value-based pricing’<sup>30</sup>. More generally, in this country the practice of appraisal of medicines has been formalized and made systematic, notably through the role of NICE but also through increased emphasis placed on ‘medico-economics’ (pushed in particular by the Office of Health Economics, a think tank sponsored by the ABPI). Meanwhile in France a sustained debate has taken place about the role of both the CEPS and the *Haute Autorité de la Santé* (HAS). In the case of the former, polemical criticisms are regularly made by policy outsiders of its supposed proximity to the interests of Big Pharma (Horel, 2010). But even more significantly, many policy insiders, and in particular insurance organizations, also consider that the CEPS is currently incapable of undertaking economic analysis, and this largely because it cannot obtain the information it needs from the pharmaceutical companies<sup>31</sup>. Founded in 2005, the HAS was pushed for in particular by representatives of the above-mentioned financing organisations. Its *Commission de la Transparence* has a particular responsibility for evaluating the medical utility of drugs and whether the social security systems should reimburse them. However today the latter ‘deplores’ that the *Commission de la Transparence* does not examine medico-economic questions sufficiently, despite this having been added to its functions by the 2008 Social Security Act<sup>32</sup>.

At the EU scale, a third publicized debate has taken place where, despite opposition from large firms and the EFPIA<sup>33</sup>, the Commission’s DG Enterprise has recently concluded an official consultation with a view to updating of the 1989 transparency directive<sup>34</sup>. As is relatively well known, on the basis of information on pricing this directive obliges them to make public, national P & R authorities regularly use ‘baskets’ of prices from other European countries to set their own prices and levels of reimbursement<sup>35</sup>. But despite DG Enterprise’s animation of a Prices and Reimbursement network at the EU scale, little sustained pressure for EU scale change appears to be occurring here, and none that is spilling over into wider issue areas. Instead, however, our research has come across a more fundamental subject of uncertainty and debate which underlies all three: the very separation between MA & P&R policy instruments which has come to be seen by many actors as constraining the management of national healthcare systems and P&R administrations in particular. At least for the moment, this indirect challenge to P & R practices has been problematized around the concept of Health Technology Assessment (HTA) which has recently become a stabilized domain of expertise and administrative competence. Much of its development can and should be attributed to political work undertaken at the

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<sup>30</sup> Importantly, between September 2005 and 2007, the Office of Fair Trading (OFT) conducted a market study of the PPRS and issued a report that was contested by many in the industry. This report recommended a switch to ‘ex ante value-based pricing’ involving pre-launch centralized government price setting based on a cost threshold plus periodic ex post reviews (Office of Fair Trading, *The Pharmaceutical Price Regulation Scheme. An OFT market study*, 2007). The OFT claimed this approach to pricing would not only save the NHS money, but also act as an incentive for producers of pharmaceuticals to invest in appropriate drugs. For sustained criticism, see an article published by the director of the APBI-funded Office of Health Economics, A. Twose (2007). The DOH have proposed this through a public consultation that ran from 16<sup>th</sup> December 2010 to 17<sup>th</sup> March 2011.

<sup>31</sup> Interviews, Paris, October and November 2010.

<sup>32</sup> Interview, *La Mutualité française*, Paris, November 2010.

<sup>33</sup> Interview, Brussels, June 2010.

<sup>34</sup> This lasted from 28<sup>th</sup> March-25<sup>th</sup> May 2011 (see DG Enterprise website).

<sup>35</sup> cite Sanofi interview, but also Marty & DGS

national and global scales. In the case of the former, NICE in the UK and the HAS in France clearly possess national status and legitimacy. Meanwhile a worldwide network of HTA professionals has steadily expanded its membership and activities. Nevertheless, since the mid-2000s, and pushed in particular by the European Commission's DG SANCO, an EU scale of HTA debate has come to accelerate and deepen the challenge to both pre-existing P & R practices and their respective linkages with MAs. The intention of a range of actors here is to challenge and shift institutionalized definitions of the 'problem' of appraisal, but also to revisit that of assessment.

On the basis of our elite interviews, here we successively analyse three causes of this debate over HTA and the tensions it has created with national actors: reproblematisations of 'risk' (3.1), proposals to 'share' scientific knowledge (3.2), and the possibilities offered by the emergence of the specialization, and even the profession, of 'medico-economics' (3.3).

### 3.1 Redefinitions of 'risk'

As summarized in part 1, since the late 1980s the notion of risk has been explicitly placed at the centre of reflexion on the management of health systems, and thence the agencization of pharmaceutical regulation (Borraz, 2008). At that time, the main emphasis upon risk concerned the safety of medicines. But since the mid 2000s this debate has come to be paralleled by two others concerning first the 'increased burden' of clinical trials for 'research-based' pharmaceutical companies and, second, the cost of medicines for public health systems.

The argument put forward by most of this category of companies is that since the demise of blockbusters and the rise of generics, they have had to develop new business models based upon producing more products that cover more illnesses. Consequently they have to make more MA applications, each of which now entails an extensive and expensive period of clinical trials before they get any return on investment. In reaction to this, such companies and their representatives have sought and often achieved provisional approvals for their new drugs through procedures (P2) which have constituted a break with what had hitherto been a relatively standardized and stabilized system of approval and pricing (P1):

P1: Research > clinical trials > MA application > MA authorization > P & R decision > product launch

P2: Research-initial trials-Provisional MA-launch of product-more trials-pharmacovigilance-full MA

Many representatives of pharmaceutical companies see this issue as something that requires 'political' change in the medium to long term:

'Politicians are not becoming less risk averse. If anything they are becoming more risk averse. Regulators become under more pressure – and put more constraints in (...) we need to change political attitudes to this process. The first and most important element is to talk about benefit-risk all the time (...). And this is fundamentally a political judgement. Because they are going to be defending the decisions saying 'this is the right balance between benefit and risk'<sup>36</sup>.

For the moment, however, assessment agencies, notably MHRA and EMA, are now looking more at the concept of the 'relative effectiveness' of drugs (also known as comparative effectiveness) as a means of evaluating benefit-risk quality. Instead of just focusing on the relative

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<sup>36</sup> Interview with ABPI, London, December 2010. For a fully developed version of this point of view, see the recent book by the ABPI's former Director General, Richard Barker (2010).

efficacy of a drug, relative efficiency also brings in the question of the user and their perceptions<sup>37</sup>.

However, change towards the direction of ‘relative effectiveness’ is often seen by its critics as being accompanied by moves to accept medicines earlier by giving them provisional acceptance that also have their roots in EU legislation and Commission advocacy. These provisional MAs are currently causing much controversy, notably because they anger organizations that finance health care:

‘Today EMA’s policy is to give conditional MAs and to rely upon risk management plans. But we want a better balance – a good evaluation upstream under experimental conditions and experiments in the real life of a medicine. It’s not just because more risk management plans are written that one should give more MAs. But Big Pharma is pushing for that!’<sup>38</sup>.

‘Medicines are accepted earlier and earlier. They are not ready and it’s shameful (...) this is a very serious trade-off. The brand image of the pharmaceutical industry is an important part of its capital (...). And us in the insurance sector have to pay and then pay again. It’s crazy : the cost of non-quality that is not covered by the system’<sup>39</sup>.

These criticisms overlap with others concerning the increased emphasis placed by assessment agencies upon post-launch evaluation (‘pharmacovigilance’) as a means of controlling the safety and quality of medicines (what one interviewee called ‘*Gérons le truc au sifflet*’ – ‘let’s manage things like a referee’). Although EMA officials say they do not want more premature applications, their organization clearly supported the adoption of the EU’s recent pharmacovigilance regulation (1235/2010 and directive (84/2010), and this despite reticence in other quarters:

(this legislation contains) ‘une déclaration des effets par les industriels, qui vont coder eux-mêmes cette vigilance... voilà. Bon, on n’est pas sûr que ça favorise un bon fonctionnement de l’agence (the EMA). Et on aurait aimé aussi un comité de décision de retrait des médicaments – comme à la FDA. Ils ont séparé clairement l’évaluation et le pouvoir de retirer’<sup>40</sup>.

To conclude on this point, reproblematisations of the notion of risk which seek to include the cost of developing and authorizing drugs have led to a destabilization of institutionalized modes of decision and practices. Consequently there is currently much uncertainty and conflict over this issue area which has created space for connected debates about the possible mutual benefits of a European-wide system of assessment, but also about how appraisals can also be ‘improved’ through drawing lessons from different national experiences at the scale of the EU.

### 3.2 From ‘pooling scientific knowledge’ to the centralization of assessment?

On one level the proposal to systematically share the data used when assessing the scientific quality of a drug throughout the EU is a ‘no brainer’ which generates widespread agreement and even enthusiasm:

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<sup>37</sup> See reports of EUHPF working group on relative effectiveness (DG Sanco website).

<sup>38</sup> Interview with Mutualité française, November 2010.

<sup>39</sup> Interview with French national insurance organisation (CNAM), October 2010.

<sup>40</sup> Interview with Mutualité française, November 2010.

‘Why should we do this exercise 27 times when it could be done only once? Here the position of the industry, of the EFPIA in any case, has always been clear: we are in favour of one evaluation at the European level, as long as it is not on top of national ones’<sup>41</sup>.

Not surprisingly then, the European commissioner for health, John Dali, has publicly set out the pooling of assessments as an important goal for the current Commission<sup>42</sup>. However, putting in place such a system has already provoked two sets of debate. The first concerns how this scientific knowledge would be brought together and by whom? One option would be to develop a system of ‘reinforced cooperation’ where national agencies would transmit data to an intergovernmental European ‘Transparency committee’. The second option, clearly favoured by the Commission, the EMA and many Big Pharma companies, would be to set up a centralized EMA-led system of pooled data. However, the latter proposition also has its opponents:

‘Nobody wants to stay where they are supposed to be for long. So industry is pushing for an EMA-based system. In my view it’s an error and not the right solution. Because the EMA is too close to industry’<sup>43</sup>.

The second debate concerns how such a system of pooled assessment data would fit with national systems of appraisal. For the moment even the Commission is not proposing that evaluating the social worth of a medicines, and thence setting its price and level of reimbursement, should be transferred to the scale of the EU. Nevertheless, many actors fear that an EU-scale assessment system will inexorably threaten national modes of appraisal. Resistance on this point is therefore already well organized, and this from differing parts of the industry:

*Representatives of pharmaceutical companies* - ‘Including pharmaco-economic criteria in an MA would be mixing up two different entities. National public health and reimbursement policies are about the collective interest (...). But we all know there only four rigorous appraisal systems in Europe (France, the UK, Germany and Sweden). So we are not going to have a quadri-thing that’s going to impose its views on the others. And what we also see is that social actors in the member states (...) all want social policies to remain territorialized’<sup>44</sup>.

*Representatives of insurance organizations* – ‘Each member state has developed its system over the years, depending on the culture of the country and there are a lot of things that are just not transferable practices’<sup>45</sup>.

*Representatives of national ministries of health* – ‘As soon as things slide towards the organization of health care, to domains that are more part of national sovereignty, then we say ‘stop!’<sup>46</sup>.

Notwithstanding this deep reticence or outright political resistance towards the European government of appraisals, technicized political work is nevertheless taking place to develop policy tools that are already destined to lead towards more convergence between national practices, and perhaps even homogeneity.

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<sup>41</sup> Interview, EFPIA, Brussels, June 2010.

<sup>42</sup> See several of Dali’s speeches during autumn 2010.

<sup>43</sup> Interview, CNAM, Paris, October 2010.

<sup>44</sup> Interview, LEEM, Paris, October 2010.

<sup>45</sup> Interview, ESIP, Brussels, June 2010.

<sup>46</sup> Interview, French Ministry of Health, Paris, November 2010.

### 3.3 The rise of HTA and medico-economics

In procedural terms, and building largely upon extra-European examples<sup>47</sup>, moves in this direction at the scale of the EU began only in 2005-8 with the launch of the EUnetHTA joint project. Co-ordinated by the Danish HTA body, this network essentially sought to put other such organizations in consistent touch with each other<sup>48</sup>. But this policy objective has since been extended and made more ambitious in 2010-12 by a ‘joint action’, chaired this time by DG SANCO, that has since been inscribed in EU law within the ‘cross border care’ directive adopted in March 2011 (2011/24, article 15). According to a Commission official involved in this joint action, it has three objectives:

‘1) give patients the best possible service; 2) cost containment – we aim to identify the best products and treatments. The best will be rewarded and disinvestment, in theory, will take place for products and processes that work less well. 3) Reward innovation’ (...). It’s ‘promotion of co-operation’ amongst the member states. This means that HTA is a lot about exchanges over practices, definitions and the implementation of methodologies to avoid duplications between what NICE and the HAS etc. are doing<sup>49</sup>.

Even under the current joint venture, cooperation between national agencies thus remains voluntary. However, there has been increased involvement from national bodies, many of whom are deeply attracted by a focus upon developing and testing criteria and other analytical tools they hope will help them tackle thorny appraisal problems. As one NICE official said on interview:

‘We spend a lot of time looking at methods of research. There is a lot of activity to see what it would mean if we looked at how we value things differently, broadening the perspective<sup>50</sup>.

This focus on methods is also greeted warmly by organizations who finance health systems. For example, a representative of *La Mutualité française* considers that HTA:

‘is a concept of great interest to us and that we think will be decisive in the years to come because we need more analytical concepts in the domain of reimbursement. In France, we are not happy with the SMR and we are constantly asking for a reform of this criterion. We want more medico-economics (...). I think that fundamentally there is reticence here because medicine is seen as something that is noble whereas economics is vile (...). Indeed, the French are very critical of NICE etc, niah, niah, niah, although we are in practice going

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<sup>47</sup> Benamouzig and Paris (2007) mention in passing the pioneering role played by the US Congress’s Office of Technology Assessment as of 1972. They also highlight the Swedish SBU set up in 1987. Australia is a country cited by others as having introduced economic evaluation as of 1993. But to fully grasp how and why the very concept of HTA has grown in political importance it would be necessary to examine the development of a number of networks of actors who have turned the appraisal of health technologies into a profession. Chronologically one would need to examine for example INAHTA (an international network that exists since 1993), HTA international who’s journal is *International journal of technology assessment and health care*, the International society for pharmacoconomics and outcomes research (journal: *Value in Health*) and ‘HTA world’ (an annual conference held since 2008, the next to be in London in December 2011).

<sup>48</sup> The stated ‘strategic objectives’ of the EUnetHTA Project were to: i) reduce overlap and duplication of effort and hence promote more effective use of resources; ii) increase HTA input to decision-making in Member States and the EU and hence to increase the impact of HTA; iii) strengthen the link between HTA and health care policy making in the EU and its Member States; and iv) support countries with limited experience with HTA ([www.eunetha.net/public/home](http://www.eunetha.net/public/home)).

<sup>49</sup> Interview, Brussels, April 2010.

<sup>50</sup> Interview, London, December 2010.

towards more qualitative studies. Today of course public resources are not limitless. So one has to move towards optimization and there is nothing shocking about that<sup>51</sup>.

Notwithstanding all this support for the EUnetHTA initiatives, a number of criticisms of its exchanges over HTA have nevertheless been made. First, certain actors regret that for the moment they do not systematically address the topic of orphan drugs:

‘Where it would be great is in orphan drugs which is just the area that people find very hard, and so don’t touch. I think this could have been one of those areas where you could say that the evidence base is European anyway – if there are only 150 patients in all Europe<sup>52</sup>.

Second, and more fundamentally, other actors point to a problem with the timing of HTA body intervention as regards MA applications. Although there is apparently widespread desire in both Britain and France to conduct appraisals closer to the time of assessments, change here appears difficult to achieve. According to one official from an assessment agency, the main problem is the legally defined mandate or her organization:

‘We in the UK have had several goes at trying to make a better common ground with HTA requirements. But the problem with that is because we are fixed in the medicines legislation, the only people who could move are the HTA people (...) but there must also be separation<sup>53</sup>.

If this issue does indeed have an impact on debates, the mandate and resources of HTA bodies appear to be even more important. The following is the view of *La Mutualité Française* as regards the positioning of the HAS within the French P & R key decision-making arena – the CEPS:

‘We would like it to be in a strategic position and to be able to say that this product is better than that one – so you can encourage it. But we have realized that that’s not what happens in within CEPS. Its chair will say, ‘yes I have the HAS’s opinion, but I also have to take into account other industrial, employment or regional development considerations<sup>54</sup>.

To summarize this point, throughout the developed world HTA is now being advocated as a new approach to the appraisal of medicines. It has been imported into Europe by a set of Commission officials and HTA practitioners who appear to be consolidating their alliance and attracting advocates with more political resources at both the scale of the EU and that of its member states. Technicized political work has dominated, but once again it is already producing considerable effects in terms of its capacity to challenge and change pre-existing institutions that are of major importance to both the pharmaceutical industry and health systems.

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<sup>51</sup> Interview, Paris, November 2010. This representation of the CEPS is shared by an official within NICE: ‘It is very non-transparent. I met a professor in this body and he says they never talk about numbers. It is much more about general things. Maybe with a glass of Chablis!’ (then laughed). London, December 2010.

<sup>52</sup> Interview with NICE official, London, December 2010.

<sup>53</sup> Interview, MHRA, London, December 2010.

<sup>54</sup> Interview, Paris, November 2010.

## Conclusions

Overall our research first leads us to conclude that our hypothesis about the unintended role played by state actors in the development of an EU-scale government of the pharmaceutical industry largely holds true. Of course, there is still much national vigilance and resistance about transfer of powers to the EU scale. To cite a French and a British civil servant speaking about the Commission sponsored HTA initiative:

‘Despite everything, we keep a wary eye on the steam roller we talked about earlier because the smallest adaptation for us can generate extra expenditure which can have considerable consequences (...) I don’t know if they have a strategy but tackling expenditure is a good one. But I don’t know where this will take us’<sup>55</sup>.

‘What we and other member states do not want is a Euro-NICE because decisions about what technology to fund have to be based in a given health system (...). We just want to make sure that this does not go somewhere we don’t want it to’<sup>56</sup>.

Nevertheless, an interpenetrated and interdependent EU government of pharmaceuticals has developed. Although far from common (applying immediately to all member states) or complete (covering all the Institutionalized Relationships of the industry – finance, employment, production and sales: Jullien and Smith, 2008), this scale of government now has considerable impact upon the way medicines are assessed and appraised, and therefore upon how they are produced and sold. Indeed, as the French and British cases clearly bear out, this EU-scale of government is now an intergal and institutionalized component of the European, and indeed global, pharmaceutical industry. Most state actors have not desired or worked towards this outcome. However, their resistance to it has been consistently weakened by their failure to appreciate and anticipate the political work being undertaken by their respective opponents.

Indeed, the second main conclusion of this paper concerns the coalition of Big Pharma, Commission and EMA representatives who have, largely successfully, done this work by combining in EU-appropriate modes technical expertise and carefully calibrated occasional politicizations. Much of the technicized work has concerned the separation between the assessment of drugs, their appraisal and industrial policy concerns. As part 1 underlined, this separation was supposed to have been institutionalized by agencization first at a national scale then at a European one. However, our research has uncovered the porosity of the ‘walls’ that in practice divide assessment, appraisal and industrial policy. Indeed, in the 2000s the word ‘innovation’ has frequently become an ‘open sesame’ for derogations from general rules for reasons of encouraging national and European champions. Actors today rarely use the term ‘industrial policy’, but what we have witnessed often fits with this category. If the political work deployed to justify a drug as innovatory has frequently entailed the depoliticization of issues through encouraging instead a focus upon details and arguments of ‘efficiency’. Indeed, such arguments have been at their most potent when allied to others about ‘the competitiveness’ of firms and ‘the sustainability’ of health systems, and this as if such notions are uncontested and unproblematic. Nevertheless, debates over values have also taken place. Much of our future research should and will therefore be focused upon these debates and/or their burial beneath layers of technicized detail.

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<sup>55</sup> Interview, French Ministry of Health, November 2010.

<sup>56</sup> Interview, UKREP, Brussels, June 2010.

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