

Chapter 4

The EU's Government of Pharmaceuticals: Incompleteness Embraced

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Dans B. Jullien et A. Smith, eds. *The EU's Government of Industries*, London, Routledge, 2015

Introduction

The European Pharmaceutical industry is reputed to be the most intensive investor in research and development (R&D) in the world (around 15.3% of total sales: www.efpia.eu), to have generated more than \$950 billion in sales in 2012 worldwide and currently employs more than 620,000 inhabitants of the EU. Moreover, amongst other such figures (see box 1 below), it consistently features large European balance of trade surpluses (nearly €37 billion in 2009: Eurostat). One might therefore have thought this industry would have been governed at the scale of the EU for years, if not decades. However, this has not been the case. If, after World War II, the pharmaceutical industry grew rapidly in many West European countries due to therapeutic innovations and increased demand fuelled by burgeoning social security systems, its government has until recently been dominated instead by state actors and their respective commercial and societal interlocutors. Over the 1950s, 1960s and 1970s, major producers of pharmaceuticals (known as 'Big Pharma') emerged in each of the EU's larger member states (e.g. Sanofi in France, Glaxo in the UK), accompanied by the arrival in Europe of large US-owned multinationals (e.g. Pfizer). These actors rapidly became the dominant players within each national government of the industry. Representing their industry as 'highly regulated', through their national and European trade associations these companies have developed continuous and multi-scale political work to protect their rents, and this by imposing high prices, sustaining the patent system or trying to limit the controls of drugs that enter the market (Montalban, 2008). Numerous other stakeholders have of course been involved: patient associations, states through different administrations (drug agencies, ministries of health, ministries of industry, social protection systems), doctors, but also health insurers, contract research organizations (firms who conduct clinical trials), biotech companies etc. Nevertheless, all these actors have mostly been dominated by the largest pharmaceutical companies.

Notwithstanding the power of Big Pharma and the durability of national government of the pharmaceutical industry, since the mid-2000s the industry as a whole has experienced several challenges both in Europe and worldwide. First, ministries of health and finance have attempted to limit the growth of pharmaceutical expenditure by promoting generic drugs and, particularly since the onset of 'the economic crisis' in 2008, reducing prices. Second, companies in the industry have suffered from the decreasing productivity of their R&D expenditure. Third, several scandals over drug safety (e.g. Mediator, Vioxx etc...) have raised concerns about the practices of pharmaceutical companies and their regulation. As a consequence, the dominant business model of the industry –known as the 'blockbuster model' based on developing patented prescription drugs that generate more than \$1 billion per year- is widely accepted to have been 'in crisis' for at least ten years (Montalban and Sakinç, 2011).

Alongside this development, what, if anything has been taking place at the scale of the EU? Most accounts focus upon national executives and interest groups as the keys to understanding today's government of the pharmaceutical industry in Europe. Consequently the EU-scale is reduced to a messy 'patchwork' (Hervey & Vanhercke, 2010) within which additional but not causal processes have taken place. In contrast, based upon the GEDI approach to industries and more than forty interviews conducted in Brussels, France, the UK and the Czech Republic, our research has come to a quite different conclusion: in this industry, the EU has become an omnipresent scale of government with which commercial operators and other stakeholders are inextricably engaged.

The first and most evident component of EU government concerns the granting of Market Authorizations (MAs) for pharmaceuticals. As part one of this chapter relates, since the opening of the European Medical Agency (EMA) in London in 1996, and despite the continued co-existence of national authorities, the vast majority of new medicines are approved at the EU scale (Hauray, 2006). Moreover, as part two of this chapter argues, over the last decade, the EU scale of government has also begun to have significant impacts within the Commercial IR of this industry through the extension of the EMA's activities, but also by influencing the pricing of drugs - an area of decision-making that had previously been monopolized by national scales of government.

Nevertheless, to use the terms used throughout this book, despite the significant developments related below the EU's government is far from 'complete'. Many of its instruments - notably its framework for clinical trials or funding of R & D- remain extremely modest¹. Therefore tools of traditional industrial policy structure EU-scale interventions in this industry only at the margins. Moreover, in contrast to the highly politicized character of many national debates on the safety and costs of medicines, discussions and interventions at the EU-scale have thus far been completely depoliticized. However, such avoidance of value-centred debates is no accident. Indeed, the central claim made in this chapter is that this depoliticization, together with the incompleteness highlighted above, have not only fitted with the 'conception of control' (Fligstein, 2001²) imposed upon this industry by its dominant firms (Big Pharma); it has actively reinforced it.

1. Three decades of incremental institutionalization

Until the mid-1970s, the Commercial IR of this industry was almost entirely defined at national scales. It consisted of institutions concerning drug safety, but also set conditions for entering the pharmaceuticals market through rules relating to reimbursements by social security systems, prices and intellectual property rights. In each national case, these sets of institutions reflected compromises at this scale between on the one hand health policy, industrial policy and public finances and, on the other, representatives of producing firms, the State, patients and health practitioners (chiefly

¹ The only EU R&D funding specifically for pharmaceuticals is the Innovative Medicine Initiative (IMI), a joint-action between several Big Pharma companies and the EU, where each 'partner' provided 1 billion euros to fund projects for the whole of the 28 member states. This compares with a French R&D tax credit which generated €650 million of tax reductions for pharmaceutical companies in 2008 alone.

² For Fligstein 'a conception of control is a story about what the organization is and its location vis à vis its principal competitors. It is also an interpretive frame used to interpret and justify actions vis à vis others' (2001: 69).

doctors and pharmacists). Until the late 1990s, the EU scale government of pharmaceuticals was essentially limited to issues of the free movement of goods between member states, co-operation over MAs and a small budget for research. In order to explain this long process of 'incremental' institutionalization (Streek & Thelen, 2005), this section first traces the national origins of this industry's Commercial IR as a means of subsequently explaining the creation of the EMA. This analysis is then supplemented by data on EU scale intervention in the Finance IR through decision-making over mergers and takeovers.

1.1 The institutionalization of a Commercial IR at national scales (1945-1985)

In the Europe of the late 1940s and 1950s, the main objective of national governments of pharmaceuticals was to provide widespread and cheap access to new and efficient medicines for all their respective populations. Because doctors prescribed drugs that were either reimbursed by social insurance mechanisms (in countries like France and West Germany), or provided 'freely' by National Health Services (as in the UK), price played little role in purchase decisions, and therefore encouraged limitless growth of demand. To avoid the explosion of expenditure, rules for controlling pricing and reimbursement levels were institutionalized in most countries. Nevertheless, together with the patent system, the prices set provided firms with high incentives to invest in order to create new drugs. Indeed, even the control of prices was also linked to industrial policy objectives. For example, the UK's *Pharmaceutical Price Regulation Scheme* (PPRS) was seen as an important political tool for developing an indigenous industry. Indeed, a representative of the European Federation of Pharmaceutical Industry Associations (EFPIA) underlined on interview that:

'The PPRS ended up enabling a British industry to develop (laughs). But everyone benefited from this. Indeed, the position of the EFPIA has always been 'if you create conditions that favour research etc., it's normal that a bit extra is given to local firms' (Brussels, June 2010).

At the same time, because of the potential side effects of drugs and information asymmetry between patients, doctors and the pharmaceutical industry, the control of security, quality and efficacy of drugs was progressively tightened throughout many countries. As of 1902, regulators in the U.S. became pioneers in this area (Pignarre, 2003) whereas in Europe an equivalent process occurred much later. For example, in the UK the authorization of medicines was only institutionalized between 1962 and 1968. Meanwhile in France, even after several scandals (*poudre de Baumol*, Stalinon, thalidomide...), a genuine marketing authorisation system was only adopted in 1972. What is also important to underline is that during this entire period, and again in contrast to the US, European Ministers and Ministries of Health retained complete control over MAs.

During the 1970s and 1980s, however, this 'hands-on' involvement of government ministries in the assessment, appraisal and financing of medicines was largely replaced by delegation to specialized agencies. In the field of health, many authors have shown how the establishment of agencies enabled state representatives to deploy the precautionary principle, present themselves as impartial and manage expertise

differently (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. For example, the French system of MAs was revised in 1978 and gave rise to procedures that mediated between two parts of the Ministry of Health which, in 1992, were eventually merged into an *Agence du Médicament*. Crucially, a principal concern at this stage was to separate therapeutic evaluation from (national) industrial policy concerns:

‘Until 1992 the DPHM (a ministerial directorate) did everything – it examined applications in the name of the minister, made decisions about risk-benefit calculations, MAs, managed a committee called ‘transparency’ (...). The reform fundamentally separated these aspects. It put everything concerning safety regulation into an agency, based on an idea that was very clear in the minds of its creators: one should not mix purely safety-centred evaluations with regulations that were more economic’³.

In summary if, as early as 1965, the European Community had adopted a directive on publishing information about MAs throughout the member states which prompted minor changes in national systems (Chauveau, 2007: 88), the latter remained extremely autonomous in their decision-making over the authorization of drugs until the late 1980s.

1.2 The long gestation of EU-scale Market Authorizations

Despite the low intensity of EU-scale influence on this industry until this period, as Hauray has explained with great finesse (2006), the establishment of the EMA in 1995 nevertheless needs to be understood as the culmination of more than two decades of political work at both the EU and national scales. What first must be grasped is that the EMA was not created in opposition to national agencies but very much alongside them (Hauray and Urfalino, 2009). It is thus a good example of incremental institutional change brought about through the ‘layering’ of institutions rather than their replacement (Streek & Thelen, 2005). Secondly if, during the early years of this process, Big Pharma were not drivers of this project, EU-scale MAs nevertheless fitted well with the blockbuster model which then dominated this industry.

Indeed, the initial 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, the national models of market authorization based on agencies outlined above produced organizations for whom a European scale of assessment came to be seen as advantageous for three reasons: it enabled them to share skills, to exchange information, ‘improve’ decision-making over MAs and, more fundamentally, consolidate their professional and political legitimacy. Indeed, it is important to recall that the EMA was initially considered to be ‘ahead’ of most national authorities in terms of the safety standards required to obtain an MA⁴.

³ Interview, senior official from French MA agency (then called AFSSAPS), Paris, October 2010.

⁴ And this even according to a representative of the radically critical journal *Prescrire*. Interview, Paris, October 2011.

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

‘25 years ago certain French firms, eg. IPSEN or Pierre Fabre, did not cover the whole of the EU. And it was the same for Spanish and Italian firms. These countries from the South, wanted to keep a decentralized system’⁵.

In other words, many medium-sized companies who only targeted their respective national markets feared that the EMA would introduce stricter controls and simply duplicate national ones, whereas larger firms simply wanted a centralized European agency in order to apply to ‘a one stop shop’. Indeed, for companies whose business model was constructed around selling large volumes of a limited number 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 epoque of big commercial blockbusters and medicines whose markets were worldwide. We realized it was stupid to continue to conduct duplicating studies which delayed market entry for products which needed considerable investment that could only be recovered at a global scale’⁶.

Ultimately, this divergence of perceived interests amongst firms, combined with the schizophrenic attitude of most national administrations (*pro* European mutualisation, *anti* any loss of legal competence), produced a compromise where three layers of MA would co-exist:

- European MAs granted after assessment by the EMA (and final approval by the Commission);
- National MAs awarded 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 but, as we shall see in section 2, the first of these has since become increasingly predominant. The establishment of the EMA thus reflects a typical EU-scale mode of government: when faced with opposition, leave formal options open in full knowledge that one of them will quickly dominate in practice

1.3 Indirect government of the Finance IR: financialization and competition policy

As underlined earlier, change for the pharmaceutical industry during the 1990s and early 2000s was also driven by a process of ‘financialization’ and corporate concentration which refocused large pharmaceutical firms on blockbuster drugs (Montalban, 2008; Montalban and Sakinç, 2012). Financialization of this industry in Europe had three complementary causes. First, large US institutional investors began to seek ownership of European firms which caused the end of cross-shareholding in countries like France (Morin, 2000. Goyer, 2007) and Germany (Höpner, 2001). Indeed,

⁵ Interview, Brussels, June 2010.

⁶ Interview with representative of French Big Pharma companies (the LEEM), Paris, October 2010.

in the 1980s and early 1990s, large French companies had used cross-shareholding or direct participation from the State to avoid hostile takeovers. However, due to privatizations, the arrival of foreign institutional investors and the loss of power of France's two largest insurers (AXA and UAP), the cross-shareholding system was broken up. Second, financialization was also the consequence of changes in the training and career trajectories of senior managers who had become more finance orientated through increased emphasis being placed upon MBAs. If this has been a trans-industry phenomenon (Fligstein, 2001), research has shown it to have been particularly strong in the pharmaceutical industry (Vitols, 2002; Kätdler and Sperling, 2002; Froud et al., 2006; Montalban, 2007 ; Montalban and Sakinç, 2011).

The third overlapping cause of this change in pharmaceutical industry was growing competition on the product market and struggles for corporate control due to the precocious adoption of blockbuster business models by US and UK-based companies. For example, Höpner (2001) demonstrated that in Germany the more firms were exposed to foreign competition and struggles for corporate control, the more they adopted shareholder value management. Froud et al. (2006) showed that the blockbuster business model was more dependent on financial analysts' opinions and share prices, and this because of its supposedly greater 'transparency'. Similarly, in France Leaver and Montalban (2010) have shown that the Sanofi-Aventis merger, its adoption of a blockbuster business model and a more shareholder value-orientated model is the consequence of three developments. Firstly the decision by the main Sanofi-Synthélabo's shareholder (Total SA) to progressively sell its stake in the company and therefore increase the risks of a hostile takeover. Secondly, growing competition on the product market with generic drugs had begun to emerge. Finally, managers of this company came to believe that it needed to increase in size in order to penetrate the U. S. market. In short, all three of these developments amounted to considerable change not only in the structure and business models of corporations, but in the institutions of the whole industry's Commercial IR.

A major consequence of the above was that, like its U.S. equivalent, the European industry experienced a process of concentration through mergers and acquisitions (M&A) during the 1990s. Monsanto (US) and Pharmacia&Upjohn merged to form Pharmacia; Pfizer (US) acquired Warner Lambert (US) (2000) and later Pharmacia (2003); Glaxo Holding plc merged with Wellcome (1995) and later (2000) with Smithkline Beecham to create GlaxoSmithKline plc; Astra AB (Swedish) and Zeneca (UK) merged to create AstraZeneca plc (1999); Rhône Poulenc SA (French) and Hoechst AG (German) merged in 1999 to create Aventis and, subsequently, Sanofi-Synthélabo merged with Aventis to create Sanofi-Aventis; Ciba Geigy and Sandoz merged to create Novartis AG (1995). All of these European companies divested their non-pharmaceutical businesses (mainly chemicals and agro-chemicals) and now figure in the top 10 largest pharmaceutical companies, competing with the US-based Pfizer Inc, Merck & Co or Johnson&Johnson Inc.

All this transformation in the European industry would, however, have been impossible without two series of changes in trans-industry regulations. Firstly, capital markets were liberalized at the national and European scales (the 'Big Bang' of the City of London in 1986; liberalization in France during the same period) in alignment with The Single Market Act and the Maastricht Treaty. A second condition was the development of a

permissive EU mergers and acquisitions policy. As Chapter 5 explains more fully, the mergers mentioned above created massive and dominant pharmaceutical companies. In 2011, the top 10 pharmaceutical companies accounted for 59.40% of the total revenue of the top 50, whilst the top 20 accounted for 81.53% of this figure (source: Pharmaceutical Executives's website, May 2011; see also table 1). In all of these cases, the Commission did not oppose the mergers. Indeed, it raised no serious concerns about possible dominant positions due to what it called 'the weak global concentration of the industry'. Even when monopolies were forecast for some therapeutic indications (the categories which many argue are 'the relevant markets'), DG COMP simply made the companies concerned divest some of their assets⁷. Significantly, no merger was actually forbidden. In short, throughout the 1990s the financialization and concentration of Europe's pharmaceutical industry came to be seen by its dominant actors as a prime means of making it even more 'competitive'.

Table 1: The Top 25 pharmaceutical companies by sales revenue in 2011

S.No.	Company	2011 Revenue Sales (in \$ Billions)	Country	EU/nonEU
1	Pfizer	\$57.70	USA	non
2	Novartis	\$54.00	Switzerland	non
3	Merck	\$41.30	USA	non
4	Sanofi	\$37.00	France	EU
5	Roche	\$34.90	Switzerland	non
6	GlaxoSmithKline	\$34.40	UK	EU
7	AstraZeneca	\$33.60	UK	EU
8	Johnson & Johnson	\$24.40	USA	non
9	Abbott	\$22.40	USA	non
10	Eli Lilly	\$21.90	USA	non
11	Bristol-Myers Squibb	\$21.20	USA	non
12	Teva	\$16.70	Israel	non
13	Amgen	\$15.30	USA	non
14	Takeda	\$15.20	Japan	non
15	Boehringer Ingelheim	\$13.80	Germany	EU
16	Bayer	\$12.80	Germany	EU
17	Daiichi Sankyo	\$11.60	Japan	non
18	Novo Nordisk	\$11.50	Denmark	EU
19	Astellas	\$11.40	Japan	non
20	Gilead Sciences	\$8.10	USA	non
21	Otsuka	\$7.40	Japan	non
22	Merck KGaA	\$7.20	Germany	EU
23	Baxter International	\$6.10	USA	non
24	Mylan	\$5.50	USA	non
25	Servier	\$5.00	France	EU

Source : Authors' compilation using data from Pharmaceutical Executives's website, May 2011

⁷ E.g for the Sanofi-Aventis merger, in order to avoid dominant position on the injectable anticoagulants and cancer markets, Sanofi-Synthelabo were obliged to sell Arixtra, Fraxiparine and Campto to competitors. Ironically, Arixtra and Fraxiparine were sold to GlaxoSmithKline, the second largest pharmaceutical company in the world at that time, because it was absent from that particular market.

Overall then, to a considerable extent the pharmaceutical industry exemplifies linkages between corporate change since the late 1980s and the development of an EU scale of government. Indeed, these linkages largely explain why this government contained both major 'holes' and a significant bias towards the interests constructed and expressed by Big Pharma. The incompleteness of EU government encouraged convergence in national administrative practices and political choices, whilst leaving room for the commercial strategies of Europe's largest medicine producers.

2. Tentative EU Government Through Two Partial Reinstitutionalizations

Over the last ten to 15 years, a great deal of consolidation has taken place over the government of MAs, the liberalization of capital and mergers and acquisitions. Even more significantly, around MAs an institutionalization of the government of the Commercial IR at the scale of the EU has taken place, i.e. this government has intensified, densified and stabilized (Guigner, 2008). Contrary to much academic belief (Hancher, 2010: 672), however, this institutionalization has not flowed seamlessly from a 'political mandate' or 'strategies' developed in the mid-2000s either by the 'High level forum on the pharmaceutical industry'⁸ or via 'The Renewed Vision' for this industry published by the European Commission⁹. Instead, these isolated moments of publicization are the tip of an iceberg of more continuous and fundamental political work that has gone ahead without any such clearcut political mandate. Indeed, and more surprisingly still, the second part of this section will show that a growing number of actors have sought to even affect prices at this scale, and thus to infringe upon a competence that had previously been a national sanctuary. For the moment at least, defenders of the latter have resisted this challenge successfully. Nevertheless, our research reveals how quests for EU omnipresence in the government of this industry have begun to make significant inroads into the completeness of its national scale.

2.1 Densification and Intensification of EU-Scale Market Authorization

Notwithstanding the way the EMA was created and the formal role it received, since the end of the 1990s a considerable reinstitutionalization of this aspect of the EU's 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 Big Pharma companies. The key element here has been that despite 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.

The EMA's decision-making procedures provide an initial explanation of this displacement of authority and legitimacy. Through its Committee for Medicinal Products for Human Use, applications to be evaluated are divided up amongst national agencies (two for each drug) in accordance with their respective expertise. The results of these two opinions are then collated by the principal evaluator before being presented to the

⁸ From 2005 to 2008 this forum brought together on an annual basis senior representatives of pharmaceutical companies and relevant administrations from across Europe. It also structured a range of 'working groups' on technicized subjects such as pricing.

⁹ 'Safe, innovative and accessible medicines: A renewed vision for the pharmaceutical sector'. COM(2008) 666 final, adopted on the 10th of December, 2008.

committee as a whole. Most actors interviewed consider that a major effect of this process is a form of politically benign benchmarking designed to ‘improve the quality’ of all EMA’s evaluations. For example, according to the previously cited official from France’s MA agency:

‘This is quite something and provides the system with strength. One is challenged, and therefore this is a factor improving quality. It’s positive. It’s stimulating’¹⁰.

Importantly, however, the EMA itself possesses relatively few resources in terms of expertise. Instead, it takes support from national agencies, and the four most developed of these in particular (the French, the British, the German and the Swedish). This said, the EMA is nevertheless where nearly all MA applications for ‘innovatory’ products are made, whereas those for generics or ‘me too’ drugs continue to be made via a national agency. Moreover, in a number of cases the EMA has opposed decisions made by national agencies and required them to be changed¹¹.

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’, political work conducted by large firms and the Commission’s pharmaceuticals unit has ostensibly aimed to improve ‘the competitiveness’ of individual companies. From this angle, over the last decade the following series of directives and regulations to create new EU-scale policy instruments has been adopted, each of which in its way has contributed to consolidating the role of the EMA. More broadly, this political work has legitimized an EU-wide scale government of the pharmaceutical 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 nevertheless still on the EU’s agenda.

In nearly all of these examples of new policy instruments, EU legislation, and especially the initial proposal from the Commission, have been extremely close to positions taken by the EFPIA. Even if many of these legal instruments were ultimately adopted with some amendments due to the political work of actors such as the European Social Insurance Platform or the network *Europe et médicament*, such work 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 with the support of centre-right Members of the European Parliament (e.g. the French MEP Françoise Grossetête), have developed high levels of sustained influence. An interviewee working for a social insurance organization presented this situation as follows:

‘Big Pharma is extremely powerful (...) they have their own lobbyists, there are lobbyists from consultancy firms that can be mandated by the companies, by

¹⁰ Interview, Paris, October 2010.

¹¹ Interview *Précrire*, Paris, October 2011.

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... '12.

In addition, it is important to grasp that the reinstitutionalization of both the EMA and the government at the EU scale of issues linked to MAs is strongly linked to legislation from the late 1990s concerning 'orphan drugs'. Regulation 141/2000 codified an EU-wide category of medicines which, because they concern relatively small numbers of patients in each member state¹³, benefit from derogations from internal market law and its rules on intellectual property in particular. By 2009, no less than 57 orphan drugs had received an MA and 577 molecules had been given orphan status. This exclusive competence has therefore given the EMA itself the opportunity to develop expertise 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 as for other MAs. 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 assessor is here in the EMA and the *rapporteur* just comments 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'¹⁴.

This development takes on additional importance when one considers that, because of the challenges the blockbuster model has encountered, orphan drugs have shifted from being a minor issue for Big Pharma in the 1990s to a priority for nearly all the firms concerned. Indeed, considerable restructuring has taken place with some Big Pharma firms attempting to develop new business models based on personalized medicines and/or orphan drugs (e.g Roche Holding with Rituxan and Herceptin, Novartis with Glivec or Sanofi-Aventis when it recently acquired Genzyme).

Similarly, products generated by biotechnologies are generally classified as 'innovatory' and thus are assessed using the centralized procedure and the EMA. Indeed, all this intensification, densification and stabilization of the government of both orphan drugs and biotechnologies at the EU scale has reinforced the legitimacy of the EMA and made it a strategic arena, not only for the appraisal of drugs, but also for industrial policy. This is because orphan drugs and, more generally, 'personalized medicines' and biotechnologies, have all been problematized as opportunities for the global competitiveness and future development of pharmaceuticals in Europe.

In drawing this section to a close one finally needs to take into account the possible reinstitutionalizing effects of recent scandals over the safety of medicines. For example,

¹² Interview, Brussels, June 2010.

¹³ Since regulation 141/2000, an 'orphan drug' has been so defined whenever it is destined for less than 1 in 2000 EU patients.

¹⁴ Interview, London, December 2010.

in France the 2011 *Médiator* scandal sparked an intense politicization of drug approvals at the national scale, but little at the European one. As a former representative of the French MA agency (AFSSAPS) underlined during an interview conducted in French:

‘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 public space in this domain’. This has meant that 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. They do so in front of ours’¹⁵.

Following political work carried out by several whistleblowers, the drug *Médiator* was withdrawn from the market by AFSSAPS at the end of 2009. If a large part of this scandal can be explained by the unscrupulous behaviour of its manufacturer (Servier), it also revealed a number of problems within AFSSAPS which eventually led to a new French law concerning MAs. Moreover, this episode has also raised a number of questions concerning the government of the pharmaceutical industry at the European scale, and in particular conflicts between the EMA and national actors. For example, French critics of the status quo, in particular *La Mutualité Française* and *Prescrire*, have used the *Médiator* scandal to argue in favour of the EMA using evaluation methods that prove genuine therapeutic improvements compared to existing products, rather than using comparisons to placebos. However, the European Commission has opposed this move in the name of ‘letting the market decide’, a policy which in fact has meant that the EMA has often opposed decisions to withdraw drugs from the market made by agencies such as AFSSAPS (now ANSM). At least in France, the consequences of such confrontations have been the impossibility of including certain rules in new national ‘post-*Médiator*’ legislation. Indeed, representatives of the radical medical journal *Prescrire* now consider that the EMA is slowing what they see as ‘necessary’ regulatory change to enhance the safety of drugs (what *Prescrire* calls ‘the direction of History’)¹⁶.

Ultimately, however, this challenging of the EMA could and, we think should, be seen as proof of its capacity to withstand opposition and thus of its institutionalization. Despite isolated and sporadic protests over individual MAs, no actor involved in governing this industry now questions the existence of the EMA. Indeed, most even now see it as the legitimate representative of the EU in global forums that govern parts of the worldwide pharmaceutical industry (Katsikas, 2011).

2.2 National pricing challenged at the EU-scale: Parallel trade and Health Technology Assessment

If the EMA and systems of market authorization for pharmaceuticals thus appear to be relatively stable, the same cannot be said for the other key dimension of this industry’s Commercial IR: pricing and reimbursements. Despite commitments to ‘keep this national’ inscribed in legislation, and virtual silence on this point from academic health specialists, the pricing of drugs is currently experiencing considerable destabilization over the issues of ‘parallel trade’ and ‘medico-economic’ evaluations.

¹⁵ Interview, Paris, October 2010.

¹⁶ Interview, *Prescrire*, Paris, October 2011

From price differences to destabilized pricing systems

Prices for the same drug vary considerably throughout the EU because there is no genuine single market. If, as long ago as 1989, a minimalist ‘Transparency’ directive (89/105/EEC) was adopted to clarify the rules of pricing and reimbursement and certain obligations for national administrations (eg. regarding delays over allowing drugs onto their markets), it has not engendered many constraints. However, two relatively recent developments have led to calls for EU-scale intervention: increases in intra-EU trade of drugs and in the interdependence of national pricing systems.

Intra-EU imports of drugs known as ‘parallel trade’ have grown because of national price differences. Such trade is legal for drugs that have an MA but necessitates specific licencing. It has developed mainly in countries with high prices (e.g. the UK), which import from zones with lower ones (e.g. France, Spain or Greece) through parallel traders (companies specialized in import and export of drugs). Protests against parallel trade stem chiefly from the representatives of Big Pharma. Indeed, the EFPIA has contested this practice for many years, arguing firstly that it fosters trade in counterfeit drugs which could threaten safety and, secondly, that patients, pharmacists and payers do not benefit from decreases in price obtained in this way¹⁷. It claims that the only effect of parallel trade is to transfer profits from manufacturers to traders, a transfer that undermines investment in R&D.

In contrast to their position on parallel trade, Big Pharma have simultaneously sought to take advantage of medicine price differences within Europe in order to put pressure upon national pricing and reimbursement (P&R) systems. The latter have frequently benchmarked the prices of drugs made by their neighbours using a ‘basket’ of prices in order to set those of their own country at lower levels and thereby limit drug expenditure. The first result of this practice is that when one country changes the price of drugs, it has direct consequences on prices elsewhere. The second result of this benchmarking is that actors throughout the industry debate constantly about the existence, or not, of a ‘European price’ for drugs. For example, many Big Pharma companies have developed a strategy of selling their drugs first in ‘free pricing’ countries. A representative of the French national social insurance fund (the CNAM) underlined the effects of this practice on interview:

‘They want to obtain ‘the European price’ immediately. It’s intolerable. It’s a huge problem. They are dreaming here – no, but the European price! Today free pricing is the general rule. If an industrialist makes up their basket in a certain way by beginning the exercise in free pricing countries, they can have the price they want’¹⁸.

In summary, actor behaviour over intra-European differences in prices has proved destabilizing for both national administrations and pharmaceutical companies. The former because in the medium term this does not facilitate the equitable setting of

¹⁷ On this point it mobilizes an economist’s report conducted at the London School of Economics part-funded by Johnson & Johnson: Kanavacos J., Costa-i-Front J., Merkur S., Gemmin M., *The Economic Impact of Pharmaceutical Parallel Trade in European Union Member States: A Stakeholder Analysis*, LSE Special Research Paper, January 2004.

¹⁸ Interview, Paris, CNAM, November 2011.

prices and the control of health budgets. The latter because they would much rather avoid direct price competition that reduces their margins. Because of these conflicts over the pricing of drugs, the question of medico-economic evaluation has been raised by national authorities and the Commission as a technicized tool to redefine the value of drugs.

The promotion of medico-economic evaluation at the EU-scale

More broadly, all the above issues related to pricing within an interdependent but differentiated Europe are linked to dilemmas over how the value of each drug should be evaluated and recompensed. Here, and contrary to what most academic specialists conclude¹⁹, a great deal of activity has recently taken place at the EU scale on the problematization of 'medico-economic' evaluations which seek to go beyond assessment of therapeutic value in order to 'appraise' their social and economic worth. Indeed, since the mid 2000s, Health Technology Assessment (HTA) has become an object around which increasing collective and public activity has taken place within many European countries. HTA is now frequently invoked in consensual terms as being both a means of achieving the sustainability of health systems and a tool for pooling evaluation capacity throughout Europe. When one narrows the focus to the way HTA has recently been problematized and politicized within the government of this industry at the scale of the EU, one can see that considerable shifts have been taking place in the positions taken up by a range of actors throughout Europe. The explanation developed here is that political work undertaken at the EU-scale to enhance the role of HTA within this government has been fuelled largely by a new set of actors who's primary concerns are dominated as much by the funding of health systems as they are by concerns for the quality of care. This objective has certainly yet to be attained. Nevertheless, examining the causes and effects of the political work undertaken in this direction can generate important insights into the pharmaceutical industry's current Institutional Order and the role of the EU scale therein. This is because decisions on how much to price a drug, or whether to reimburse it, entail judgements about the value public authorities accord to human health, suffering and even life itself on one hand, and 'fair' rewards for innovation on the other.

Activity on HTA at the scale of the EU is often presented as beginning only in the mid-2000s. However, closer examination reveals that its origins need tracing to the early 1990s. Building upon inclusion of public health in the Maastricht Treaty signed in 1991, the Commission identified 'value for money in health care' as a priority (Banta, Kristensen, 2010). Subsequently, from 1994 to 1997, an initial research project was funded by the EU's framework programme: EUR-ASSESS. Around 100 experts were involved in research focused upon the harmonization of methodologies for the evaluation of health care. This project was followed by another ('HTA-Europe', 1997-2000), then yet another: the programme 'European collaboration in HTA' (ECHTA; 2000-2002). Not surprisingly, each of these three programmes concluded that more EU action was necessary on HTA. Indeed the Commission even published the findings of the HTA-Europe project as an unofficial policy document. Moreover, ECHTA's results lead to HTA being flagged as a priority issue to be dealt with in the EU's FP 7 research programme.

¹⁹ Within the 700 pages of the encyclopedic book recently published on *Health Systems Governance in Europe: The role of European Union Law and Policy* (Mossialos et al., 2010) no reference to medico-economic evaluation is made at all.

After a short hiatus, in 2005-8 collaboration was deepened by 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. The stated 'strategic objectives' of the EUnetHTA Project were to: 'reduce overlap and duplication of effort and hence promote more effective use of resources; increase HTA input to decision-making in Member States and the EU; strengthen the link between HTA and health care policy making in the EU and its Member States; and support countries with limited experience with HTA'²⁰. Now involving 300 experts, results of the project were presented at a major conference in Paris in November 2008.

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 was inscribed in EU law within the 'cross border care' directive adopted in March 2011 (2011/24, article 15). Concretely, the joint action operates through an annual conference²¹, work packages and the production of handbooks (eg. on 'core models' and on 'capacity building')²². In addition, since 2008 the EMA has been officially authorized to work with HTA bodies. Co-operation over HTA at the European scale has thus led to repositioning by a number of actors from different professions and disciplines (notably academics, employees of pharmaceutical and medical device companies, national agency staff). Indeed, the European Union as a political space and scale of government has clearly given strong impetus to this trend. However, the following three traits deeply mark what has, at least until recently, remained a largely depoliticized international field.

Firstly the field of HTA consistently features methodological discussions which avoid economic theory, or even quite simply issues of quantification and calculation. Despite the fact that a study has shown that HTA outcomes for the same drug are different in more than half the cases (Kanavos et al., 2010), very little recorded public debate has taken place over the 'medico-economic' dimension of evaluating medicines. Indeed, the indigenous literature is even vague about 'value for money' (see in particular the recent 'book' produced with support from the WHO and Pfizer called *Ensuring value for money in health care*: Sorenson, Drummond and Kanavos²³, 2010). More fundamentally still, one finds no discussion of which economic theories are being used, why and with what effects. We learn in general terms that notions of 'clinical efficacy' tend to dominate 'economic efficiency' in many national cases (in France for example). But, except in the case of the UK (Drummond, 2007; Drummond and Sorenson, 2009), and although a few economists have published some initial insights on this theme (Serre-Sastre & McGuire, 2009; Olivier & Sorenson, 2009), to our knowledge no analysis has been undertaken as to why this is so.

²⁰ www.eunetha.net/public/home.

²¹ For example, in Gdansk in December, 2011.

²² Backing for EU scale initiatives has also been given by the WHO, and this on two levels. First, its 'Europe' office set up a 'Health Evidence Network' (HEN) composed of 30 international agencies and organizations. Part-financed also by DG SANCO and the French Ministry of health, this network is not however limited to pharmaceutical issues. Second the WHO's European Ministerial Conference in June 2008 established 'the Tallinn charter' wherein HTA was framed as a means of creating resources for health systems; A certain congruence also exists with the OECD's 'Health project' and its document *Health Technologies and Decision-Making* published in 2005.

²³ Panos Kanavos is not only the 'Merck fellow in Pharmaceutical economics', he is also head of the LSE's Medical technology Research Group. In this capacity he has carried out work (undisclosed on his website) for the European Commission. He works within the LSE's 'Health and social care' department which produces a journal for practitioners, *Eurohealth*, four times a year. See in particular its issue 17(1) 2011 on 'pharmaceutical policy and the crisis'.

Secondly, in all the existing literature on HTA the role played by big pharmaceutical companies in the evaluation of medicines is virtually never referred to. Instead, one is left with the false impression that these are benign actors for whom the choice of evaluation methodology is best left to administrators and other ‘experts’. Once again the questions of social values and power are, perhaps deliberately, left out of analysis.

Of course, a third key question begged by all this mobilization around HTA at the EU scale concerns its impact upon national systems of P&R. At this scale a number of attempts to deinstitutionalize existing methods and reinstitutionalize alternatives have been made. In particular, since the mid 2000s, articulating MA and P & R systems has been increasingly problematized at national and EU-wide scales. Our research has focused upon the three examples synthesized below.

The first concerns the UK, and more precisely England and Wales. Here a National Institute for Clinical Excellence (NICE) was set up as long ago as 1999 to provide the NHS and the Ministry of Health with expertise and advice about the cost-effectiveness and social value of drugs and other health technologies. Ever since it has conducted a high quantity of studies which conclude that the drug should either be purchased or not and, indirectly, at what price. Although this system certainly has its critics (see Drummond, 2007), it has nevertheless ‘normalized’ and thus institutionalized an economics-driven form of HTA in this member state. Indeed, it has even influenced a sustained challenge to the PPRS system for pharmaceutical price setting which will be replaced in 2014 by ‘value-based pricing’²⁴. In short, in the UK over the last fifteen years HTA and medico-economic evaluation have become an integral part of the national scale government of the pharmaceutical industry.

Meanwhile, in France HTA has also developed considerably over the last decade but without NICE’s emphasis upon economics-informed calculations and advice on pricing and levels of reimbursement. Instead, a sustained debate has taken place about the role of both the arena within which prices are formally fixed (the *Comité économique des produits de santé*: CEPS) and the organisation responsible for evaluating all health practices and technologies: the *Haute Autorité de la Santé* (HAS). In the case of the former, many policy insiders, and in particular health insurance organizations, consider that the CEPS is currently incapable of undertaking genuine economic analysis:

Question: ‘So when fixing prices you compare with other products already on the market. But if you were to carry out extensive medico-economic evaluations, you would have to compare each drug with other therapies too...’

Response: ‘Yes of course, but we don’t do that at all, not at all. And that is where medico-economic evaluations would be precious – to allow us to create some space around all this. The studies we deal with are the ones done for the MA – there is nothing more than that’²⁵.

²⁴ Importantly, between September 2005 and 2007, the UK’s 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.

²⁵ Interview with Ministry of Health official, Paris, February, 2012.

As for the HAS, 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. Indeed, over 2008-11 this responsibility was strengthened to include a clear mandate over medico-economic evaluation. However, many actors deplore that the HAS still lacks adequate instruments and resources to accomplish this mission²⁶. Moreover, the very legitimacy of medico-economic analysis remains questioned by most actors in this industry who characterize their country as one in which it is impossible to put a price on health:

‘We are not in a country as utilitarian as England (...) we are in a country that is very egalitarian as regards access to healthcare’²⁷;

‘Culturally, this is not acceptable neither at a political level, nor for our fellow citizens’²⁸.

Finally, our research has examined the case of a smaller, newer member state: the Czech Republic. Contrary to the British case, but also that of its neighbours Slovakia, Poland and Hungary, HTA has yet to be introduced in this country and, according to national law, will only begin in 2014. Interviewees attribute the absence of this practice to a lack of native HTA experts (only two or three competent professors), governments that are only interested in cutting costs by giving drugs low prices and an administrative system that currently even has difficulties in processing MA applications. Indeed, the following quote from an interviewee who represents generic producers neatly synthesizes how all the Czech actors we encountered currently represent HTA:

‘What do we need HTA for? You first need to walk and then you can try to run! We have 8 systems to contain drug prices. Not one of these systems is working. So first get your ducks in a row. Make one of these systems work and then let’s start HTA. Before then, HTA is for me intellectually exciting. But what do we need it for? The government will make a pig’s ear out of it again’²⁹.

Ultimately, and notwithstanding the changes in national appraisal practices that have occurred partly as a result of EU-scale mobilizations, tensions over ‘sovereignty’ remain ever-present. 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 enthusiasm³⁰. Indeed, when the European commissioner for health, John Dali publicly set out the pooling of assessments as a goal for the EU³¹ no voices of opposition were raised. 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

²⁶ Interview, *La Mutualité française*, Paris, November 2010.

²⁷ Interview, HAS official, February 2012.

²⁸ Interview, Ministry of Health official, January 2012.

²⁹ Interview, Prague, May 2012.

³⁰ Interview, EFPIA, Brussels, June 2010.

³¹ See several of Dali’s speeches during autumn 2010.

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’³².

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. For example, this representative of a Big Pharma company stressed on interview that:

‘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’³³.

Just as emphatically, a representative of a social insurance organization underlined:

‘Each member state has developed its system over the years, depending on the culture of the country and there are a lot of practices that are just not transferable’³⁴.

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 many actors see as destined to lead towards more convergence between national practices, and perhaps even homogeneity. In summary, 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 EU and national scales. As yet it is impossible to know if HTA will ever become a tool for deep policy and institutional change. As one blogger has put it, is HTA a *deus ex machina* or a damp squib?³⁵ Our research relates the political work that a number of actors have currently undertaken in order to orient HTA in either of these directions, and this by problematizing the EU-scale as central to both.

³² Interview, CNAM, Paris, October 2010.

³³ Interview, LEEM, Paris, October 2010.

³⁴ Interview, ESIP, Brussels, June 2010.

³⁵ Blog.pharmexec.com, 29th August, 2012.

Conclusion

In seeking to characterize government of the pharmaceutical industry at the EU scale, this chapter tells a tale of both increased activity and complex, shared responsibilities with national arenas and actors. However, unlike many academics specialized in health, we consider it is insufficient and unhelpful to explain the development of this Institutional Order simply as a 'law and policy patchwork' (Hervey & Vanhercke, 2010). The overlaps demonstrated here between the EU and the national are anything but haphazard, owe nothing to chance and everything to the political work that has been carried out in this industry, both 'successfully' and 'unsuccessfully', over the past fifty years. Indeed, as we have shown, the EU scale is omnipresent within the government of this industry, deeply incomplete and driven by a particular problematization of the industry's interests and challenges.

To explain this state of affairs, our central hypothesis is that managers of Big Pharma, their interest group the EFPIA and officials from the Commission's pharmaceuticals unit have, each in their own way, pushed for the type of European governmentalization that has so far occurred in this industry – one in which both national and EU incompleteness appears to fit with their respective goals and priorities. Moreover, the advent of this form of government has been facilitated by the extremely supportive, and sometimes obsequious, approach towards Big Pharma adopted by nearly every European administration. Whilst expending vast amounts of energy in trying to protect 'national sovereignty' in the field of health, these administrations have frequently bent over backwards to assist Big Pharma through the establishment of the EMA, EU and national research funding, and the reproduction of pricing arrangements – and all this in the name of 'innovation'. The large pharmaceutical companies use this term constantly but it has rarely given rise to close examination except by their most radical critics. Indeed, 'innovation' lies at the heart of both a problematization of Europe's pharmaceutical industry which equates it with the interests constructed by these companies, and a legitimizing strategy which technicizes a whole series of issues that, in theory, could just as readily be framed and debated as highly political. These include patient safety, pricing rates, the medico-economic and value judgements used to set them and European citizens' medium to long-term access to healthcare. The incomplete character of the pharmaceutical industry's government at EU, national and global scales, allied to the massive resources of Big Pharma and its allies, bolsters the dominant problematization and strategy of legitimation currently deployed in this industry. Producing, as we have, knowledge about the causes and effects of this Institutional Order does not necessarily imply endorsing existing alternative problematizations and their politicization. However, it does strongly suggest that such framings merit more open and analytically informed public discussion.

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