Paper to be presented at the DRUID 2012

on

June 19 to June 21

at

CBS, Copenhagen, Denmark,

Big Pharma, Little Science? A bibliometric perspective on big pharma?s R&D decline

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Abstract

There is a widespread perception that pharmaceutical R&D is facing a productivity crisis characterised by stagnation in the numbers of new drug approvals in the face of increasing R&D costs. This study explores pharmaceutical R&D dynamics by examining the publication activities of all R&D laboratories of the major European and US pharmaceutical firms during the period 1995-2009. The empirical findings present an industry in transformation. In the first place, we observe a decline of the total number of publications by large firms. Second, we show a relative increase of their external collaborations suggesting a tendency to outsource, and a diversification of the disciplinary base, in particular towards computation, health services and more clinical approaches. Also evident is a more pronounced decline in publications by both R&D laboratories located in Europe and by firms with European headquarters. Finally, while publications by big pharma in emerging economies sharply increase, they remain extremely low compared with those in developed countries. In summary, the trend in this transformation is one of a gradual decrease in internal research efforts and increasing reliance on external research. These empirical insights support the view that large pharmaceutical

firms are increasingly becoming ?networks integrators? rather than the prime locus of drug discovery.

Jelcodes:L23,O32

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Keywords: Pharmaceuticals, bibliometrics, outsourcing, Europe, globalisation, research network, innovation, collaboration

1. Introduction

Studies from a variety of sources and perspectives suggest that the pharmaceutical industry is facing a productivity crisis and is undergoing a substantial transformation. A stagnant or declining number of new chemical entities (NCE) are approved each year in spite of major increases of R&D expenditures (Munos 2009; Pammolli, Magazzini, and Riccaboni 2011). As a response the pharmaceutical industry has engaged in a series of major mergers and waves of acquisitions, closed R&D sites, particularly in Europe and the US, sought cost savings through rationalisation (LaMattina 2011) and opened R&D laboratories in emerging countries with large markets such as India and China (Anon. 2010). The industry is increasingly outsourcing R&D to external research organisations, which is perceived to improve efficiency (Baum 2010). Governments are supporting these trends by increasingly focusing public sector funding on 'translational' research (Collins 2011).

In this paper we explore these shifts by studying changes in the publication activities of the world's 15 largest pharmaceutical firms in Europe and the US ('big pharma'). Historically, the role of big pharma in the production of scientific research has been important, with a collective R&D investment of $46bn on average over 2004-2007 (see Table 1) compared to an average annual spend of $28.5bn by the US National Institute of Health (NIH) over the same period.[1] As a result, the publication activity of the pharmaceutical firms is large (~10,000 document/year) and may be explored to trace changes in the industry. Publication data does not provide direct insight into the R&D processes because a variety of factors shape and mediate propensity to publish, but as discussed in the next section when handled with care and contrasted with other data sources, publication rate and patterns may shed some light on dynamics in the quantity, areas and modalities of R&D efforts, and thus provide glimpses of the underlying processes of change (Tijssen 2004, 713–715).

We will explore the shift in the industry from three perspectives: How has the knowledge base of pharma changed? How has its organisational structure evolved? How have pharmaceutical firms relocated their R&D activities? First, in the cognitive sphere, the shift since the 1970-80s with the advent of biotechnology from a random-screening regime, towards a guided-search regime could be expected to make pharma R&D more reliant on basic biological research (McKelvey, Orsenigo, and Pammolli 2004; Hopkins et al. 2007). However, the cumulative nature of competence acquisition by firms, means that this process would be expected to occur in a progressive manner (Nightingale and Martin 2004; Hopkins et al. 2007), rather than a disruptive one (Hwang and Christensen 2008). What do publications data tell us about the changes in the knowledge base?

Second, at the organisational level, the interaction between biotechnology firms and pharmaceutical industry has been presented as the prototypical example of the organisational network as the 'locus of innovation' (Powell, Koput, and Smith-Doerr 1996), with an estimate of 25% of R&D being outsourced in the UK (Howells, Gagliardi, and Malik 2008). Recent empirical research has also shown evidence for this shift in terms of drug discovery. (Munos 2009, 965) showed that the share of the drugs approved by large firms in the US has steadily decreased from ~80% in 1980 to about ~50% in 2008. Kneller (2010) reported that at least half the new drugs discovered in the USA between 1998 and 2007 originated from public laboratories or small firms (see also (Angell 2004, 52–73)).[2] If this is the case, can we see an increase in the dependence of big pharma on external collaborations? Is there evidence of pharmaceutical R&D becoming less 'R' (research) and more 'D' (development)?

[1] See NIH budget at http://www.nih.gov/about/director/budgetrequest/

[2] In the case of biotechnology-related patents the growth of small firms is even faster: from less than 15% in 1990-94 to more than 35% in 2000-04, with big pharma shrinking from ~42% to ~31% (Parimal Patel, Arundel, and Hopkins 2008).

Third, from a geographical perspective, the internationalisation of R&D either by off-shoring internal R&D or outsourcing it using external collaborations, has received significant policy and media attention. The perceived relocation of pharmaceutical activities is often accompanied by stories of European weakness in comparison to the US (Tijssen 2009). Given the relative importance of the pharmaceutical industry in various European economies, and its position as one of the (few) high-tech industries with a dominant European base, the potential decline of this sector has been a regular concern in the EU (e.g. see (Tijssen 2009; Pammolli, Magazzini, and Riccaboni 2011)). Do publications support the view of a European decline? Given the observation that interactions between publicly funded research and firms' R&D efforts often take place in close geographical proximity is this European decline also visible in big pharma's collaborative links?

Table 1. List of largest European and USA pharmaceutical firms mapped in this study.

Company	Publications 1995-2009	Employees (2008)	R&D spent/year (2004-2007 in M £)
GlaxoSmithKline	19,331	101,133	3,186
Novartis	15,477	96,717	3,604
Hoffmann–La Roche	14,351	80,080	4,195
AstraZeneca	11,378	66,100	2,740
Sanofi-Aventis	11,211	98,213	3,722
Bayer	8,125	107,299	2,270
Novo Nordisk	3,378	31,062	837
Boehringer Ingelheim	3,036	41,300	1,425
Aggregate EU	**84,863**	**621,904**	**21,979**
Pfizer	23,290	129,226	7,371
Merck	21,697	106,200	4,540
Eli Lilly	9,584	40,500	2,144
Johnson & Johnson	7,197	118,700	4,576
Abbott	6,482	69,000	1,440
Bristol-Myers Squibb	6,349	35,000	2,016
Amgen	5,070	16,900	1,908
Aggregate USA	**78,194**	**515,526**	**23,995**

Note: Publications include those of subsidiaries, acquisitions and parent firms of mergers. Source: 2009 UK R&D Scoreboard (BIS 2009)

There is a lack of agreement among scholar about what R&D off-shoring to developing countries precisely entails (Ujjual et al. 2011). Due to the relatively distinct activities pursued in the stage of drug discovery (lab based) and drug development (clinically based) it may well be the case that R&D off-shoring takes place in some activities and not in others. Some scholars argue in this respect that there is a shift towards a globalisation of innovation, for example via externalisation of clinical trials to Contract Research Organisations (CROs) (Archibugi and Iammarino 1999), whereas others suggest that local R&D centres are concerned with adaptation to local markets, for example with research on disease prevalent in tropical areas or among certain population groups (von Zedtwitz and Gassmann 2002). What do publications tell us?

To our knowledge, this is the first large scale study of pharmaceutical publication trends. The only published previous studies are by Robert Tijssen, who showed trends of collaborative modes (Tijssen 2004) or focused on the location of pharmaceutical R&D of European firms (Tijssen 2009). Our

analysis uses novel visualisation tools to intuitively convey to a non-expert audience the firms' knowledge base (Rafols, Porter, and Leydesdorff 2010) and collaboration networks (Perianes-Rodríguez, Olmeda-Gómez, and Moya-Anegón 2010). Data and bibliometric visualisations are made available in the Complementary Files listed in Appendix 1 and in a dedicated website.[3]

Our results suggest a gradual decrease in internal big pharma research efforts and increasing reliance on external research. These empirical insights support the prevalent view that large pharmaceutical firms are increasingly becoming 'networks integrators' rather than the prime locus of drug discovery (Hirschler and Kelland 2010, Hopkins et al. 2007).

2. The limitations of using publication data to track big pharma's R&D activity

Publications cannot be assumed to be a reliable proxy to describe the dynamics of research in a private firm, even in a science-based area such as pharmaceuticals. For example, the concerns raised over the scientific integrity of research conducted by pharmaceutical companies are likely to have affected publication strategies, especially in the clinical fields (e.g. (Angell 2004; Smith 2005)). As well as a decline in R&D we also observe that pharmaceutical companies may face decreased legitimacy in science which may be reflected in their publishing patterns (Sismondo 2009). Careful analysis is thus needed to make inferences from publication data.

To understand how big pharma's R&D activity differs from its publication activity, it is helpful to consider the concept of *Open Science*. Open Science is based on the pursuit of priority, for example to claim credit for discovery and to hasten diffusion of knowledge, and as such encourages the rapid disclosure of research findings in scientific journals (Merton 1973; Stephan 1996). In contrast, firms often rely on secrecy and protective mechanisms such as patents to limit knowledge spillover risks and ensure returns to their investments(Dasgupta and David 1994). This implies that the contributions of big pharma to Open Science cannot be simply considered unconditional accounts of their research efforts and their scientific discoveries. Rather, scientific publication activity in firms is incentivized by commercial interests and by pressures imposed on them by prescribers, healthcare payers and regulators to disclose data.

In the case of pharmaceutical research it is important to distinguish between the motivations firms have to publish during drug discovery and during drug development. With respect to the former, Hicks suggested that firms publish in order to 'participate in the barter-governed exchange of scientific and technical knowledge' and to send signals to investors (Hicks 1995, 421). Adopting an Open Science strategy is in this case is considered necessary in order to connect to the scientific community and access its resources in the form of knowledge, qualified labour and informal advice (Hicks 1995; Cockburn and Henderson 1998). Investments in R&D are in this context a means to create absorptive capacity which is necessary both to take advantage of (upstream) research conducted outside the organizational boundaries of pharmaceutical firms. The advent of biotechnology has in this context been associated with an increased of explicit interaction between industry and academic science (McKelvey, Orsenigo, and Pammolli 2004). Firm strategies have thus moved towards a more networked and 'open' model of innovation (Powell, Koput, and Smith-Doerr 1996; Chesbrough 2003), in which publishing is seen as positively associated with innovative success (Jong and Slavcheva 2012). However whether open innovation leads to more open science is an open question.

Concerning drug development, it can be argued that incentives to publish are higher than in other science-based industries, due to the highly regulated nature of drug development and the importance of clinical evidence for user uptake of innovations. Moreover, intellectual property will

[3] www.interdisciplinaryscience.net/pharma

already be in place on the underlying compound before drug development, which limits the risks of scooping. Scientific publications are therefore primarily written to diffuse information about the effectiveness and safety of pharmaceuticals to a wide range of stakeholders. This process is especially incentivized in an evidence-based medicine paradigm (Timmermans and Berg 2003; Montori and Guyatt 2008) which is an attempt to ground medical decisions directly in the available scientific evidence. It follows that pharmaceutical firms make use of publications as marketing tools that need to be carefully constructed and employed in order to win support in regulatory or policy arenas (e.g. in to gain approval of clinical trials) and in clinical settings (e.g. credibility among doctors) (Sismondo 2009; Smith 2005). In drug development scientific publications are also used as competitive devices to promote the superiority of a compound vis-a-vis potential substitutes introduced by competitors (Polidoro and Theeke 2011).

While publications are therefore important in drug discovery and drug development, their analysis needs to be undertaken carefully because publications serve a variety of purposes. As a result, changes in publication trends can reflect different underlying phenomena. For example, the propensity to publish may change when a company shifts towards more science-based areas and wants to engage with academics (Hicks 1995). Similarly, in drug development, publication may underestimate research in pharmaceutical firms if industrial scientists publish their own research using 'ghost writers', i.e. hidden behind the alleged authorship of academics (Sismondo 2007). This occurs because of the higher credibility of academic (perceived as 'disinterested') researchers' findings to investors and medical practitioners. Moreover, some portion of research may be expected to be held back from publication for reasons of commercial secrecy, as discussed above.

A final consideration is the extent to which tracking the publications of the 15 largest firms in an industry tells us about the industry as a whole. There are thousands of firms now engaged in pharmaceutical R&D. Most of these are small, but some are quite large, being either old but comparatively small pharma, or young (compared to large pharma), non-traditional firms, for example biotechs such as Biogen. While the sample here do not represent the industry as a whole, the firms tracked in this sample account for over 50% of the pharmaceuticals brought to market since 1950 (based on (Munos 2009)) and hence represent the core of the traditional pharmaceutical industry. Furthermore because the publications tracked include those of firms acquired by big pharma over the studied period, the publications also incorporate the attempts by these firms to renew their capabilities.

Given all these limitations, we conclude that the analysis of publications does not in itself reflect the dynamics of big pharma's R&D. However, at the high level of aggregation we conduct this study (based on about 10,000 publications per year in total, with around 150 to 1,500 publications per firm annually) it does raise interesting questions on R&D trends and firm strategies which then can be discussed a in comparison with complementary quantitative evidence to some trends revealed in other studies using a variety of other metrics such as patents and pharmaceutical projects (Kneller 2010; Pammolli, Magazzini, and Riccaboni 2011).

3. Materials and Methods

The papers authored by staff at 15 major European and USA pharmaceutical firms were downloaded from Thomson-Reuter's Web of Science (WoS). Complementary File 1 (URL embedded) lists the firm names used in retrieval, including subsidiaries, mergers and acquisitions. Information on each company's acquisitions, mergers and subsidiaries was collected from their annual reports and the Recombinant capital database (http://www.recap.com/). The document types chosen were "article", "letter", "note", "proceeding paper', and "review' for the period 1995-2009. A total of 160,841 records were obtained, standardised, processed and analysed with VantagePoint software

(http://thevantagepoint.com/). Publications were classified as European, when the affiliation contained at least one country in the European Union (EU) or in Switzerland, Norway, Lichtenstein and Iceland, the members of the European Free Trade Association (EFTA). The freeware programmes *Pajek* (http://pajek.imfm.si/) and *VOSviewer* (http://www.vosviewer.com/, (van Eck and Waltman 2010)) were used for visualisation.

To compare our dataset of the publications of the top 15 pharmaceutical firms to the field of sciences relevant to pharmaceutical R&D in general, we made two baseline datasets. First, to look into number of organisations and authors per paper, publications of the top 200 journals in which pharma published were downloaded from WoS. Two thousand publications were randomly selected from these journals for the years 1995, 1999, 2004 and 2009 and this data was used as a baseline for the Figure 5. Secondly, to investigate the relative change in the number of publications that list big pharma authors per journal and field, the total number of publications for the period 1995-2009 of the top 350 Journals in which big pharma published were downloaded from the Journal Citations Reports. This data was used as a baseline for Table 2.

4. Results: Shrinking knowledge production

Big pharma has published about 11,000 publications per year in 1995-2009. This is a substantial contribution in the biomedical area, about 4% of all the publications (estimated from the 350 journals where big pharma has the most publications).

The first insight from this study is that big pharma firms have reduced the number of publications they produce by around 0.8% per annum when taking into account additional boosts to publication counts from subsidiaries and acquisitions prior to them joining their current parent. This amounts to a 9% decrease over 15 years, as shown in Figure 1. The results are a conservative estimate for the decrease, given that we are using full counting (i.e. without assigning fractions to co-authoring organisations) and collaborations are increasing over time (as discussed in section 4.2).

This decrease is in stark contrast with R&D expenditure by large firms in the industry, which have increased in the order of 50% to 400% a decade (Arrowsmith 2012, 18) and the general inflationary tendency in publication volumes revealed in bibliometric studies of global scientific output (Persson, Glänzel, and Danell 2004; Leydesdorff and Wagner 2009). In the areas where big pharma is publishing the most, we have estimated an annual growth rate of 1.1%, amounting to a 16% growth over the period (estimated from the 350 journals where big pharma has the most publications). As a result, publications by big pharma show a relative decrease, from 5% of the total in the specialised pharma fields in 1995 to 4% in 2009 (again estimated from 350 top pharma journals). This slow decline is consistent with other studies apparently showing an absolute decline of patenting in pharmaceutical US patent classes 424 and 514 (Subramanian, Toney, and Jayachandran 2011, 68) and relative decline of patenting by big pharma in comparison to small firms in biotechnology (Parimal Patel, Arundel, and Hopkins 2008, 51).

However, if one looks at the publications by the core firms in our sample (defined as those with the name of the parent company or of mergers, see methods), one observes a modest increase of 0.6%, totalling an 8% growth over the period. The difference between growth in publications by core firms and a decrease in all big pharma publications can be attributed partly to R&D outsourcing, and partly to absorption and often rationalisation (i.e. closure) into the core firm of the R&D laboratories of the acquired firm. For example the former laboratories of firms such as Searle, Upjohn and Warner-Lambert were closed some time after their acquisition by Pfizer (LaMattina 2011). Merck is estimated to have reduced its workforce by 30% after its merger with Schering-Plough in 2009

(McBride). All the pharmaceutical industry (not just big pharma) is estimated to have reduced its workforce by 300,000 people since 2000 (Herper 2011).

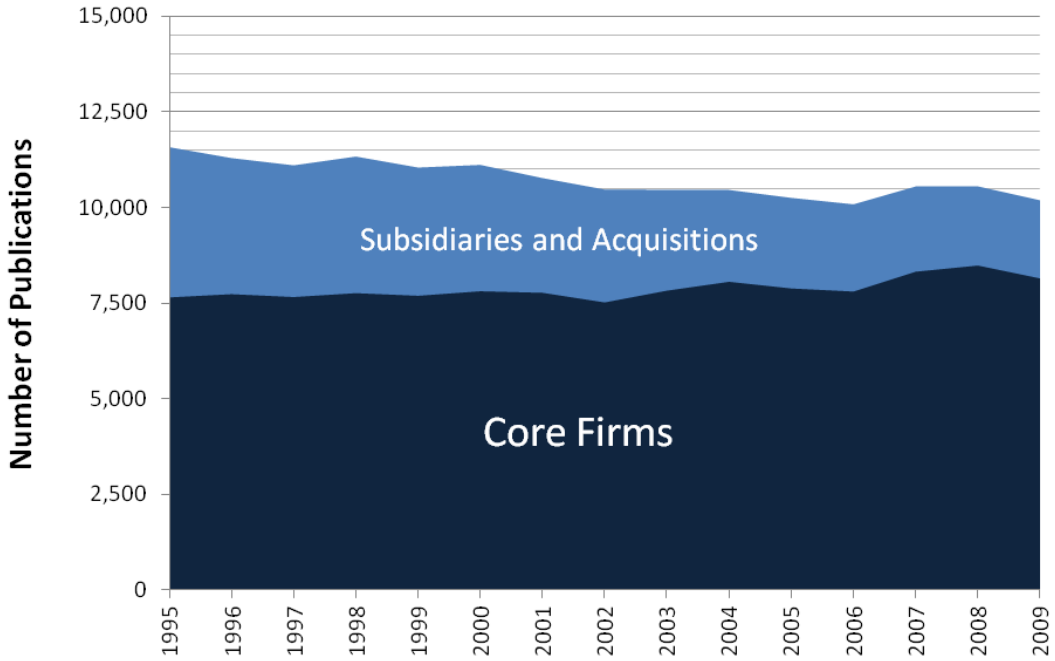

Figure 1. Total number of publications per year of top 15 pharmaceutical firms.
'Core firms' includes only publications by R&D labs of the main firm or (or antecedent's names) before a merger. 'Subsidiaries and Acquisitions' includes the outputs published under the name of the acquired firms before and after the transaction.

Figure 2 illustrates the wider dynamics of apparent core firm enlargement with overall R&D shrinkage in the case of the GlaxoSmithKline, which saw a sharp decrease in its aggregate number of publications in the aftermath of the merger of Glaxo-Wellcome and SmithKline Beecham in 2000. In the cases of Pfizer, Novartis and Bayer, a similar dynamic is observed for acquisitions. The only firm that shows significant growth in publications over the period is Johnson & Johnson. Data for each firm is available at Complementary File 2.

One can assume that the firms showing lower number of publications in relation to their R&D investment are also those with the highest degree of R&D outsourcing. For example, Sanofi-Aventis, who has reduced its publications per year from ~1200 to ~400, report that 'in Feb 2011, 64% of our development portfolio consisted of projects originated by external R&D' (Sanofi-Aventis 2010, 17). It appears that outsourcing is very actively pursued. AstraZeneca states that 'We intends to increase our externalisation efforts to access the best, most cutting edge science, whatever its origin, with a target of 40% of our pipeline sources from outside our laboratories by 2014' (AstraZeneca 2010, 29).

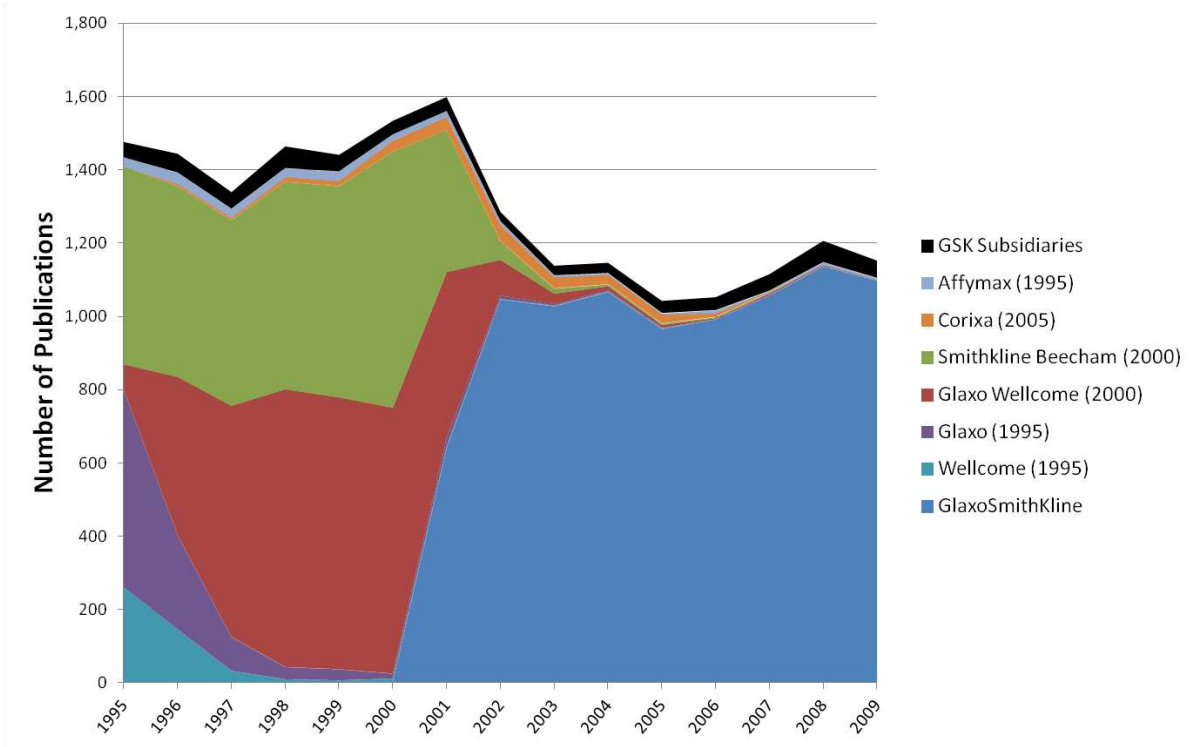

Figure 2. Number of publications per year of GlaxoSmithKline, its subsidiaries, and the parent firms before merger. See other firms in Complementary File 2.

4.1 Cognitive shifts: Diversification of the knowledge base

Next we examine the areas of research where large pharma is most active and how they changed over time. Figure 3[4] shows the distribution of the publications by big pharma over the global map of science (Rafols, Porter, and Leydesdorff 2010). Each node represents a research field as defined by Web of Science Categories. The position and colours of the nodes is given by their relative similarity (strong similarity is shown with links). The size (area) of nodes shows the percentage of publications in that area. Figure 3 illustrates that the knowledge base of pharmaceuticals is centred on biomedical sciences (green nodes: Pharmacology and Pharmacy, Biochemistry and Molecular Biology), with some important contributions in Chemistry (in blue: Organic Chemistry and Medicinal Chemistry), Immunology and Infectious Diseases, and then a few smaller areas of Clinical Medicine (in red). Data is available at Complementary File 3, for the aggregate and for each firm.

Figure 4 shows the areas with positive (top) and negative (bottom) growth in publication numbers. The visualisation reveals a broad pattern of diversification, with a decrease in the traditional yet still dominant biomedical and chemical disciplines and an increase in peripheral areas related to new techniques (e.g. computational biology and related), and disciplines more oriented to clinical applications of therapeutics or health services.[5] The latter observation is consistent with the observation that 'industry has shifted resources away from drug discovery to late clinical developments' (Munos and Chin 2011, 1). For example, the proportion of pharma-biotech alliances in the pre-clinical stage decreased from 46% to 38% in 2007-2011, while those in marketed stage increased from 24% to 28% of total (Ratner 2012, 119).

[4] For a webpage visualisation see http://www.scimago.es/perianes/spru/Interaction_Categories.html.
[5] This diversification is captured by an increase in the Shannon-Wiener diversity (from 3.87 to 3.95).

In the cognitive sciences, one also observes a move away from basic science (e.g. Neuroscience) and towards more applied fields (Psychiatry and Clinical Neurology). The decrease in publications related to plants and environment is possibly due to the externalisation of the agrochemical divisions from pharmaceutical firms. For example, Syngenta was created in 2000 by the spinning out and merger of Zeneca Agrochemicals and Novartis Agribusiness.

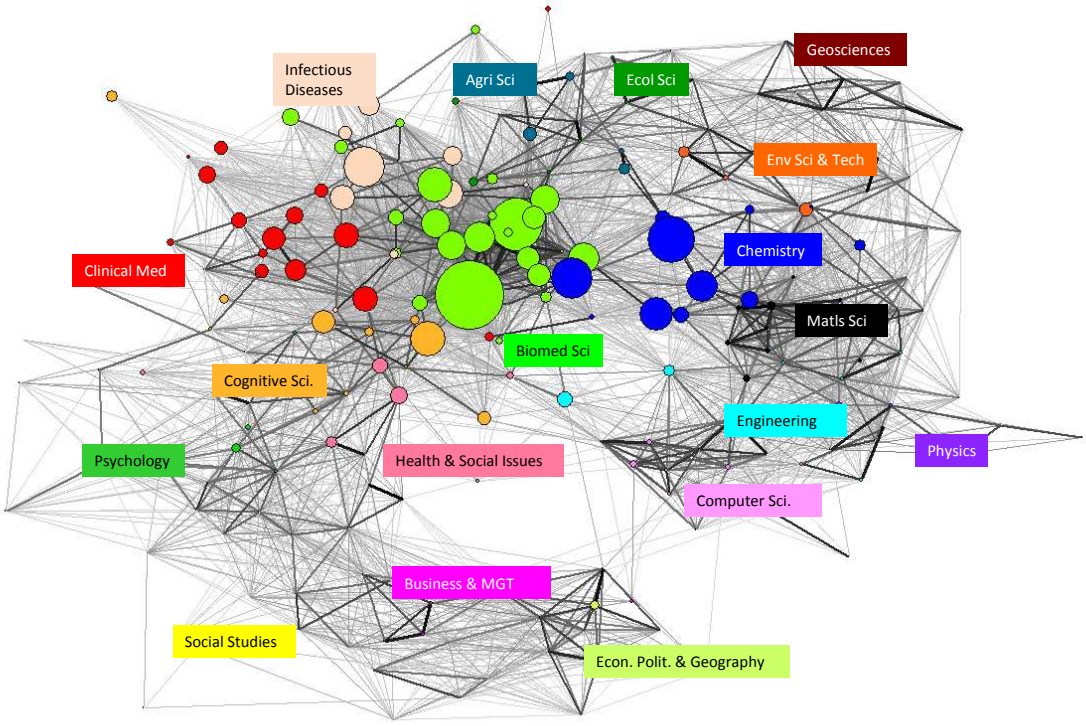

Figure 3. Distribution of publications by the top 15 pharmaceutical firms over the global map of science. Nodes represent subject categories, with the area proportional to number of publications. The position of nodes is determined by similarity in citation patterns between the subject categories they represent.

The growth of clinical areas such as oncology or rheumatology are consistent with data from pharmaceutical project data (Pammolli, Magazzini, and Riccaboni 2011, 431). However, for other areas, such as cardiovascular, research output in terms of publications is slowly increasing (2.5% over 10 years) in spite of a substantial (-5%) decrease in the number of projects (Pammolli, Magazzini, and Riccaboni 2011). Such apparent inconsistencies, though not surprising given variations in field definition and unit of analysis, warn against hasty interpretations of data.

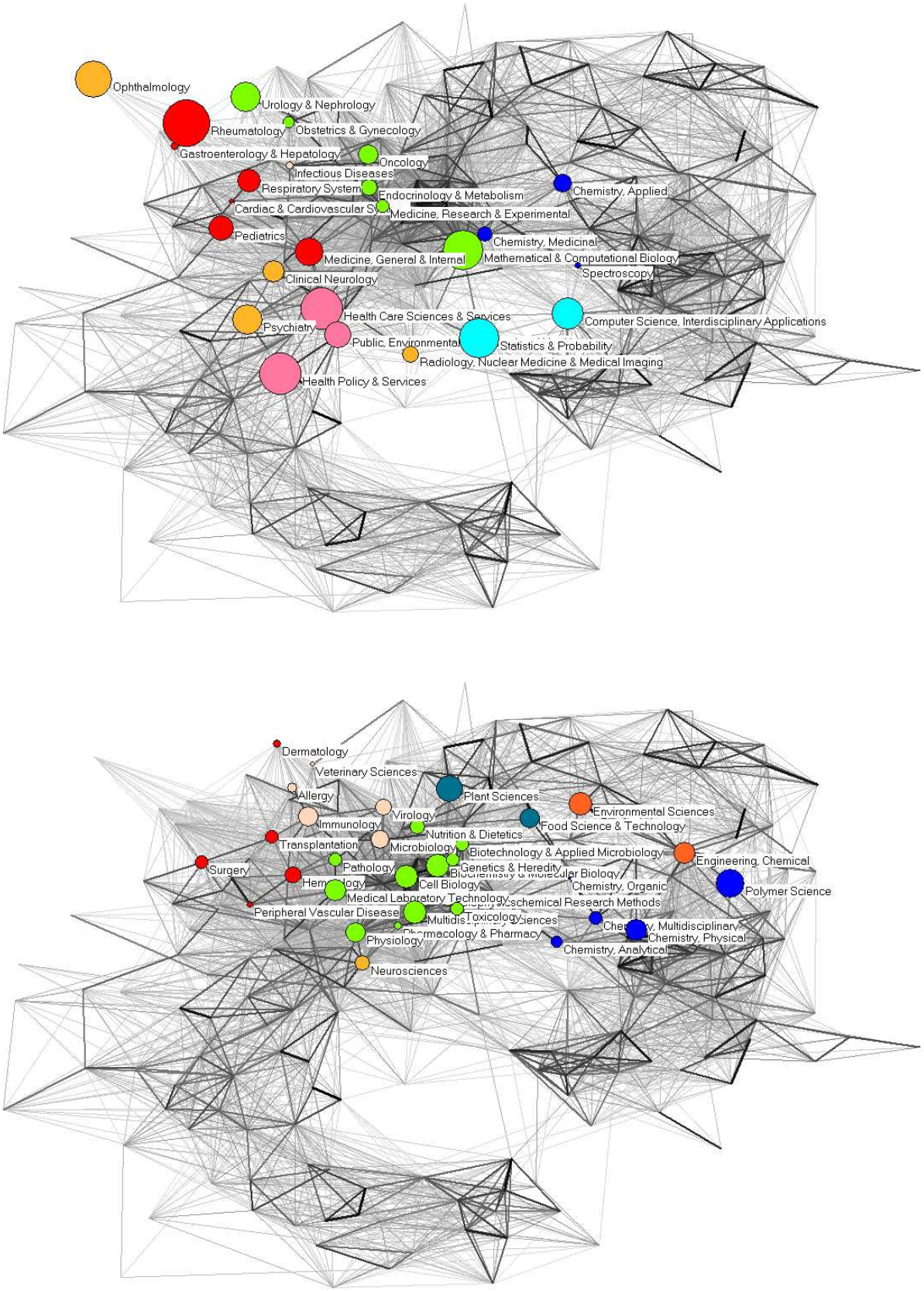

Figure 4. Growth rate (top) and decrease rate (bottom) of publications by pharmaceutical firm in different scientific subject categories. Area of nodes is proportional to the growth (decrease) in publications. Only subject categories with more than 0.5% of the total publications are shown.

We also tried to visualise the specialisations of each firm using Web of Science publication data, but found big pharma had quite similar profiles at this coarse level of aggregation.[6] In order to improve the granularity of description, we created a map based on the 191 journals that where big pharma publishes most frequently, available in Complementary File 4. See also interactive website: http://www.scimago.es/perianes/spru/Interaction_Companies.html.

The results of the visualisation were mixed. These more granular maps (not shown in printed version) capture some of the specialisation patterns: for example, Eli Lilly's focus on mental illness, or Novo Nordisk's effort in endocrinology. However, the maps were less successful at eliciting the differences in focus between larger firms such as Pfizer, Novartis or Merck. This may suggest isomorphic pressures in the industry as leading firms are joined by fast followers into new therapeutic areas (quite likely given the industry's reputation for producing 'me-too' drugs (Angell 2004, 74–93)), but we believe that this might also signal the need for new analyses requiring more sophisticated approaches, for example using keywords such as the Medical Subject Heading (MeSH) provided by PubMed (Leydesdorff, Rotolo, and Rafols 2012).

The overall picture is that big pharma's is reducing research in areas of traditional core expertise, namely in biomedical and chemistry areas, while at the same time diversifying into areas such as computational biology and fields that are closer to the patient (or perhaps market) such as health services and clinical research. However, as big pharma moves into new fields it relies more on external collaborations, as discussed in the next section.

4.2 Organisational shifts: Increasing collaborations and out-sourcing

The number of collaboration in science has been steadily increasing for decades (Hicks and Katz 1996; Wuchty, Jones, and Uzzi 2007). This trends towards 'team science' has been particularly pronounced in the biological sciences, medicine and neuroscience (Porter and Rafols 2009, 730). Our data shows that such trends are even stronger in big pharma, but there is a twist: besides collaborating more, big pharma also allows their partners to take the lead in a greater proportion of publications produced from the collaborations.

Figure 5 illustrates the increase of the number of authors and the number of organisations per article for pharmaceuticals in comparison with a sample of papers (baseline) in related fields (2,000 publications per year of analysis randomly extracted from the 200 top journals of pharma publication). Not only are pharmaceutical papers more collaborative, but their co-authorships are growing faster than average in the fields in which they publish.

A crucial observation from studying co-authorship is that in big pharma collaborations, the external partners increasingly play the leading intellectual role. This is shown in Table 2, by the significant decrease in the percentage of big pharma-based first authors in collaborative publications (from 43% to 35%), and of big pharma-based corresponding authors (from 41% to 34%) over the period studied.

This trend is more prominent in the fields and journals into which big pharma has more recently entered (arguably those where new competences are more likely to be demanded), in contrast to the fields and journals where big pharma is shrinking its publication output (which are those of traditional core expertise). In the fields with increasing output, the share of big pharma corresponding authors decreased from 44%- to 36% in 1998-2009 (and from 47% to 39% in the ten fastest growing). In the case of areas with declining output, the share of pharma's corresponding authorship remained quite stable, declining only from 52% to 49% (from 52% to 48% in those

[6] A previous study had shown no effect of these small field differences between firms on innovation performance (D'Este 2005, 37).

declining fastest). Likewise, the percentage of corresponding authors in growing journals decreased from 52% to 47% (from 70% to 60% in ten fastest growing), whereas the percentage in shrinking journals only declined marginally from 51% to 49% (from 51.2% to 50.5% in ten fastest shrinking). The inertia in the maintenance of the core expertise and the difficulty in catching up with new fields, is a general characteristic of firm dynamics given the cumulative nature of firms technological competences (Hopkins et al. 2007; P. Patel and Pavitt 1997).

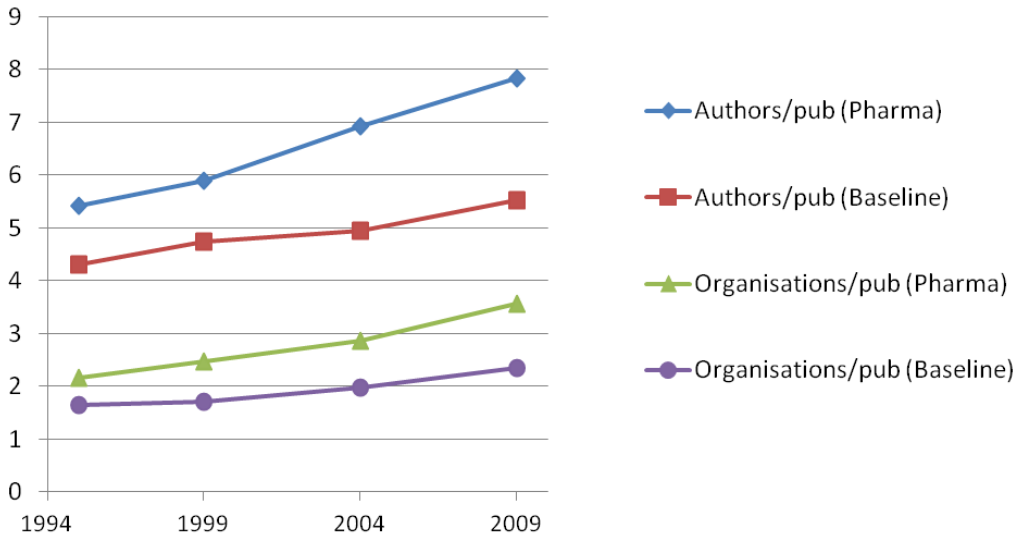

Figure 5. Trends in collaborative practices in pharma R&D publications, compared to control publications in the same scientific fields (baseline).

The overall picture is consistent with a trend towards R&D outsourcing, driven by pressures to seek cost efficiencies (Baum, 2010). Outsourcing entails a reduction of internal R&D laboratory capacity and the parallel expansion of alliance networks with small firms and academic laboratories (Powell, Koput, and Smith-Doerr 1996), in which big pharma is intellectual follower rather than the leader. This does not necessarily imply that big pharma's ability to capture value from these alliances is reduced and this may be a topic for further study.

Table 2. Trends in scientific leadership in co-authored publications

Year	1998[(1)]	2002	2006	2009
% publications with external collaboration	62.1%	67.6%	69.1%	71.7%
% organisations collab. baseline (estimate)	55.0%	59.0%	63.2%	66.4%
Pharma-based first author	43.1%	38.4%	36.2%	35.0%
Pharma-based corresponding author	40.7%	36.6%	35.0%	33.6%
In expanding fields[2)]	43.9%	38.9%	35.9%	35.6%
In shrinking fields[(2)]	52.3%	50.1%	50.5%	48.8%
Pharma corresp. author (top 350 journals)	50.8%	46.5%	47.3%	47.0%
In expanding journals	52.4%	48.0%	48.1%	46.6%
In shrinking journals	50.9%	46.4%	47.6%	48.8%

Notes: (1) Data starts in 1998 due to partial missing data on corresponding and first authors in 1995-1997. (2) Since some journals are assigned to various fields (Web of Science Categories), this figure is a slight overestimate.

4.2 Geographical shifts

4.3.1 The decline of big pharma's European R&D

It has been suggested that European pharmaceuticals firms have weakened over recent decades (McKelvey, Orsenigo, and Pammolli 2004). The trends confirm such decline both in terms of the publications of all European R&D laboratories (shown in Figure 6, left, including labs of American firms, such as Pfizer's site a Sandwich, UK), and of all laboratories of firms with European headquarters (shown in Figure 6, right, including USA labs of European firms). Besides the decline in number of publications, European-headquartered firms have also decreased the proportion of publications that they lead, as shown by number of corresponding authors, from 45% to 35% (Figure 6, right), whereas US-based firms have undergone a less marked decline (from 52% to 47%). Geographical data discussed in this section is available in Complementary File 5.
Figure 7 shows that the decline of big pharma's European publications has been concentrated in the UK, Switzerland and France. In contrast, big pharma have maintained their German publication output and increased their output in smaller European countries such as Sweden, Belgium and Denmark.

Part of the European decline may be attributed to the fact that whereas Europe-based firms have located an important share of their R&D activities in USA laboratories (producing about 35%), USA-based firms on the other hand have a smaller presence in Europe (producing only 22% of their publications). This is illustrated in Figure 8 (left).

Such imbalances in the USA versus European presence of big pharma has been previously well documented, e.g. by publications (Tijssen 2009) and patent inventors (Friedman 2010; Pammolli, Magazzini, and Riccaboni 2011). In the latter case, patent concentration in the home continent of the firm is even more acute, as shown in Table 3. These data should be taken as conservatives estimates of home country because publication data counts the publications of acquired firms with the parent company –which means that acquisitions explain a very important proportion of the non-home publications of firms. For example, Roche's large percentage of USA publications is partly explained by its acquisition of Genentech; or Johnson and Johnson's large European presence is largely due to its Belgian subsidiary Janssen.

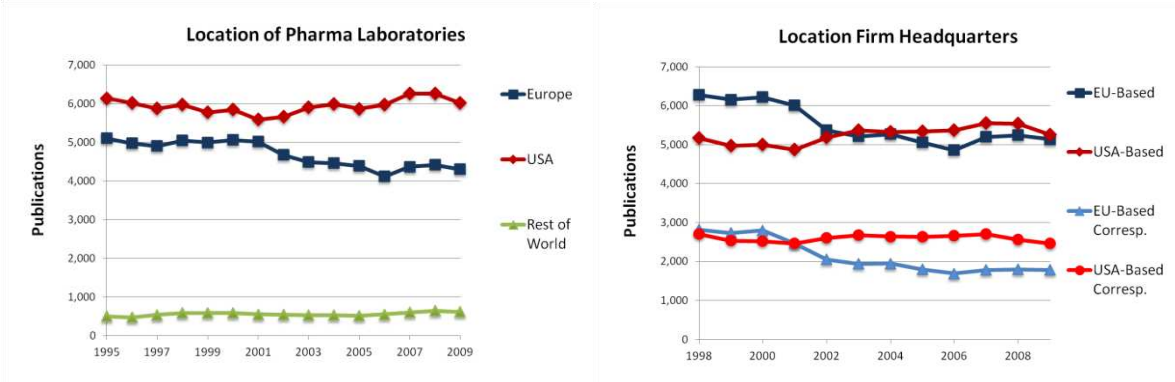

Figure 6. Publications by location of pharmaceutical R&D laboratories (left). Publications by locations of firm headquarters (right), for all publications (top) and for those with big pharma affiliations for the corresponding author (bottom).

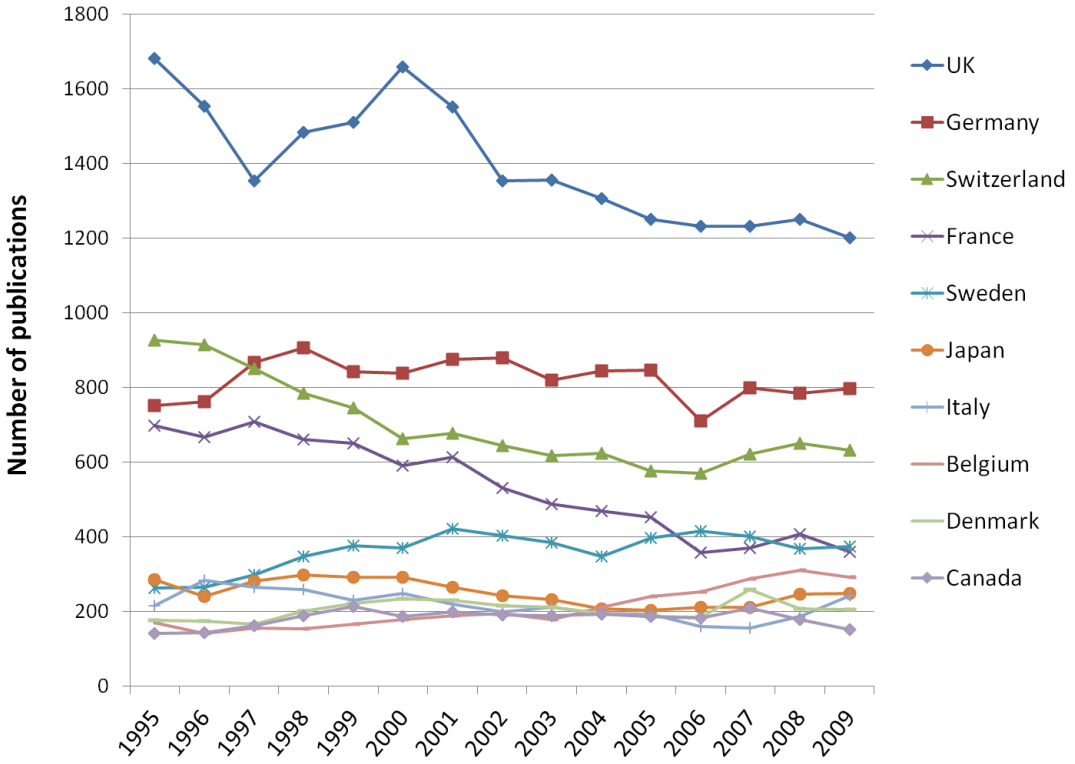

Figure 7. Location of pharmaceutical R&D laboratories authoring papers

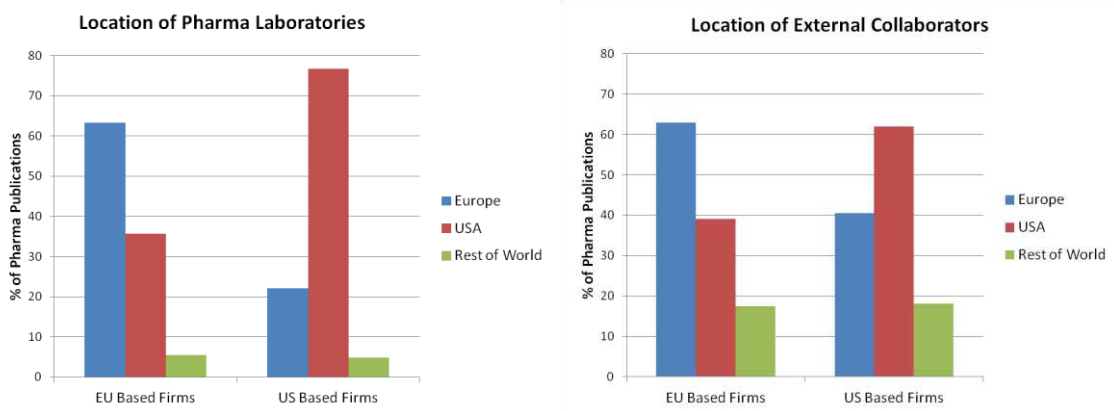

Figure 8. Location of pharmaceutical R&D laboratories (left) and external collaborators (right) on headquarters base (Europe vs. US).

Although in most of this analysis we adopt a Europe versus USA perspective, a more careful analysis of the data reveals that European pharmaceutical companies are still remarkably national (or bi-national as a results of mergers in the case of AstraZeneca and Sanofi-Aventis) (see Table 3). Outside their home countries, European firms have more publications from US-based labs than all their non-domestic European labs (i.e. Europe excluding the 'home country' of the firm). Such is the extent of the national base for collaborations that when co-authorships are mapped into organisational networks there are striking similarities to the natural geographic distribution of countries, as shown

in Figure 9, with big pharma playing a notable role spanning the bibliometric equivalent of the 'Atlantic'.[7]

One recurrent argument of why European (or Japanese) pharmaceutical firms locate R&D centres in the US is that American basic biomedical research is of higher quality than European research (e.g. see (McKelvey, Orsenigo, and Pammolli 2004) – indeed there is a parallel discussion on this in relation to other industries (Dosi, Llerena, and Labini 2006). Given this argument, it seems paradoxical that although USA-based firms have much less R&D in Europe than their EU-based counterparts, both USA and European-based firms have a very similar percentage of their total publications with external collaborators from across the Atlantic (about 40%). Given that the vast majority of these external collaborators are public research organisations, one can argue that in pharmaceutical research European public research is probably not so bad after all. Alternatively it may reflect that the strategic interest of USA-based firms in the European pharmaceutical market is equal to the interest of European-based firms in the USA pharmaceutical market, as local collaborations are needed to prepare drugs launches in those markets. Given this interest, scientific activities may well be employed across the Atlantic for marketing reasons, patient availability and proximity to regulators and medical practitioner. The rapid increase in clinical trial activities in Central and Eastern European countries may also be a reason for this.

Table 3. Comparison between 'Home country' and regional location of research in 1995-2009.

		% of Publications				% Patents[(2)]
Company	**Home Country**	**Home Country**	**Europe[(1)]**	**USA**	**Rest of World**	**by US inventors**
USA Firms						
Pfizer	USA	See USA	24.2	75.6	3.4	81
Merck	USA	See USA	24.3	71.0	8.3	88
Eli Lilly	USA	See USA	19.9	81.7	3.9	n.a.
Johnson & Johnson	USA	See USA	33.9	65.7	4.7	86
Abbott	USA	See USA	22.7	77.0	1.8	90
Bristol-Myers Squibb	USA	See USA	7.2	93.0	2.0	90
Amgen	USA	See USA	3.2	94.4	3.8	n.a.
Aggregate USA		**76.8**	**22.0**	**76.8**	**4.8**	
European Firms						
GlaxoSmithKline	UK	44.5	15.8	43.9	2.4	47
Novartis	Switzerland	41.1	21.6	40.2	4.4	26
Hoffmann–La Roche	Switzerland	24.4	17.6	50.8	10.7	46
AstraZeneca	UK & Sweden	77.7	3.7	19.4	3.4	19
Sanofi-Aventis	Fran. & Germ.[(3)]	63.5	11.5	23.9	5.3	20
Bayer	Germany	62.2	6.8	29.2	5.7	n.a.
Novo Nordisk	Denmark	87.5	4.3	9.1	2.3	n.a.
Boehringer Ingelheim	Germany	40.8	17.2	34.9	14.7	n.a.
Aggregate EU[(4)]		**51.5**	**14.0**	**35.7**	**5.4**	**n.a.**
Aggregate EU			**63.3**	**35.7**	**5.4**	**n.a.**

Notes: (1) In this table, 'Europe' excludes the home country in the case of European firms. (2) Source: Pammolli et al. (2011, p.434). Based on location of pharmaceutical firms' inventors on patents from 1980-2004.

[7] See interactive map at http://www.scimago.es/perianes/spru/Interaction_Colaborations.html

(3) The headquarters of Sanofi-Aventis are in France, but during the period under study one of its antecedent companies, Hoechst, had its headquarters in Germany. (4) This European aggregate is based on the sum of European firms. It includes double counting (estimated at 2.5%) due to collaboration between firms.

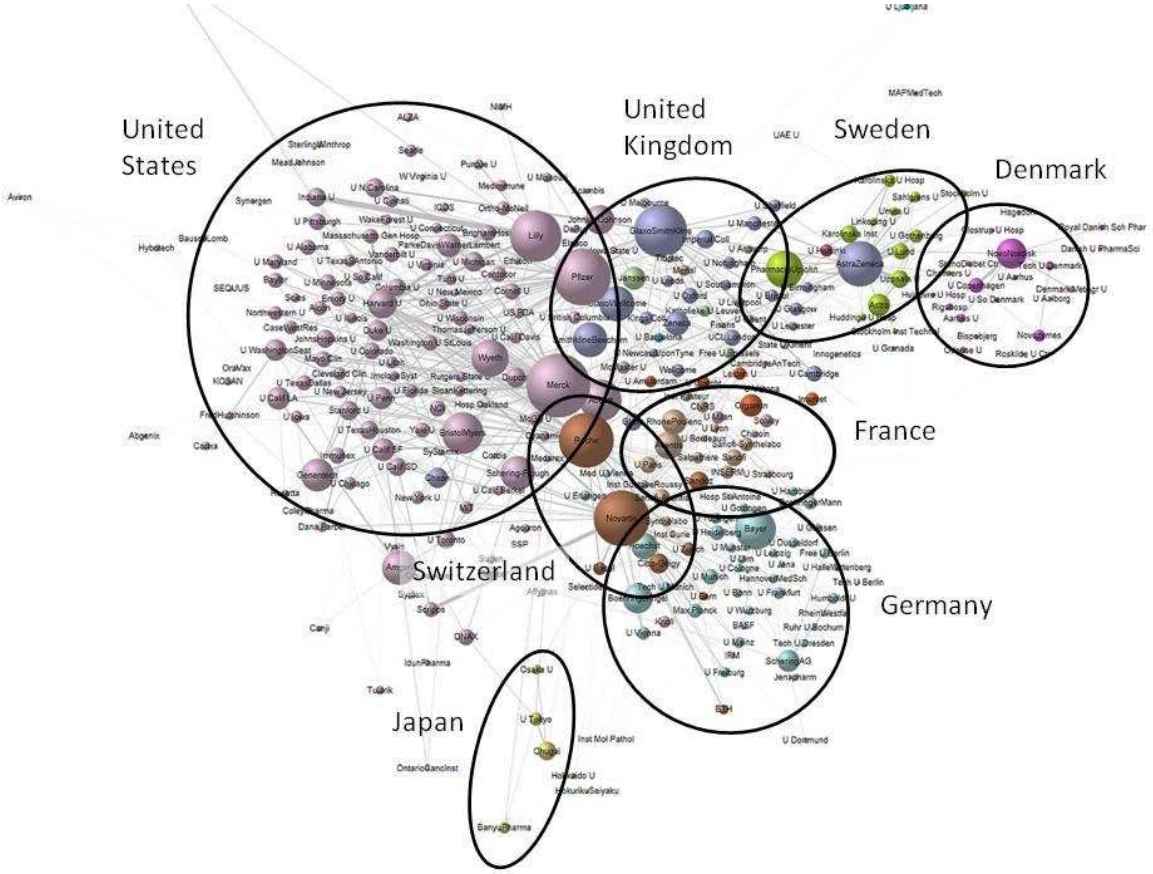

Figure 9. Collaboration network of pharmaceutical firms.

4.3.2 Limited globalisation – so far.

If there is a decline of European R&D associated with off-shoring and outsourcing of R&D, is there evidence of an increase in publications of R&D in emerging countries associated with this? The answer, for now, is negative. The percentage of big pharma publications outside of USA and Europe has remained stably low, increasing only from about 500 to about 650 publications per year over the period 1995-2009, although in relative terms these publications have increased from 4% to 6% of big pharma's total. Most of these publications (~60-70%) have originated in advanced economies such as Japan and Canada. Following investments in R&D centres (Anon. 2010) countries such as Singapore, India and China show rapid growth in publications starting from a very low base. However, the absolute number of publications emerging from big pharma's new eastern R&D laboratories is still very low, and with only the exception of Singapore less than 20 publications/year on average as shown in Figure 10 (compared with ~200 in Italy or ~600 in Switzerland).[8]

Emerging countries are a comparatively much more important contributor of publications from external pharma collaborations. Whereas in 1998, only 10% of big pharma collaborators were from outside of Europe or the USA, this figure increased to 15% by 2009. This growth is partly due to the

[8] The numbers are so low that one wonders if research carried out in R&D laboratories in emerging countries is published with affiliations of the headquarter laboratories. Such practice has been observed in patents.

growing importance of universities in developed economies such as Canada and Australia (35% and 17% of 'rest of the world' collaborative publications in 2009, respectively). However, part of the increase was also due to rapid increase in the collaborations between big pharma and public research organisations in countries such as China (157 publications in 2009), Brazil (98), South Korea (75), India (57) and Singapore (55). These collaborations are mainly between local public research organisations and R&D labs of big pharma in other countries. As shown in Table 4, co-location of local research organisations and local big pharma R&D labs does not appear to be the driver behind the increase of big pharma's collaborative publications by emerging countries.

A more plausible explanation for the increasing collaboration of pharma with emerging economies is the rapid globalization of clinical research activities (Thiers, Sinskey, and Berndt 2008; Petryna 2009). The conduct of clinical trials requires the involvement of many individuals which often necessitates a division of labour between those researchers that are appointed in the scientific management teams that design the study and analyze the data, and (clinical) investigators that merely enrol patients for data analysis. It is the latter's activity that is increasingly conducted in emerging economies and in this case relations between pharmaceutical companies and researchers from these countries are often mediated by a third party such as a Contract Research Organizations (CROs). The increase in external collaborators in emerging economies may be a reflection of this and it is likely that the observed scientific activities of these countries is in this case an underestimation as authorship for publication mainly accrues to researchers with scientific leadership and less often to the researchers that are actually engaged with patients on the ground in this type of clinical work (Hoekman et al. 2012).

In summary, publication data raises questions about the extent to which the opening of R&D centres in emerging economies such as India or China constitute a globalisation of pharmaceutical R&D –in the sense of making these new centres 'competitors' to those in the developed countries. The small number of publications from big pharma labs in these countries is consistent with relatively small units of 70 to 300 researchers in most cases (Ujjual et al. 2011), but also suggests these R&D labs are so far fulfilling other purposes, in particular an adaptation of their products to the emerging markets. These include: (i) research on issues specific to human and physical geographies such as tropical diseases or genetic susceptibilities; (ii) development of low cost drugs to cater for the medical needs in terms of cost and dosage of developing country populations; (iii) establishment of links with CROs conduction clinical trials, as well as broadening the genetic make-up of clinical trial populations (iv) presence in large markets with growing wealth and its associated medical needs, e.g. diabetes, cardiovascular complications (Anon. 2010; Ujjual et al. 2011, 22).

Since the globalisation of pharmaceutical R&D centres is a recent phenomenon and publication takes times, there is the possibility that publication counts do not capture the most up-to-date trends. Singapore, the emerging country with most publications, saw the investment in new pharma labs (Lilly, Novartis, Pfizer) in the early 2000s, whereas most centres in China have only opened since the mid 2000s (Roche in 2004; Pfizer and Sanofi-Aventis in 2005; GSK and AstraZeneca in 2007; Novartis, 2008; Lilly and Johnson and Johnson in 2009; source: (Anon. 2010)).

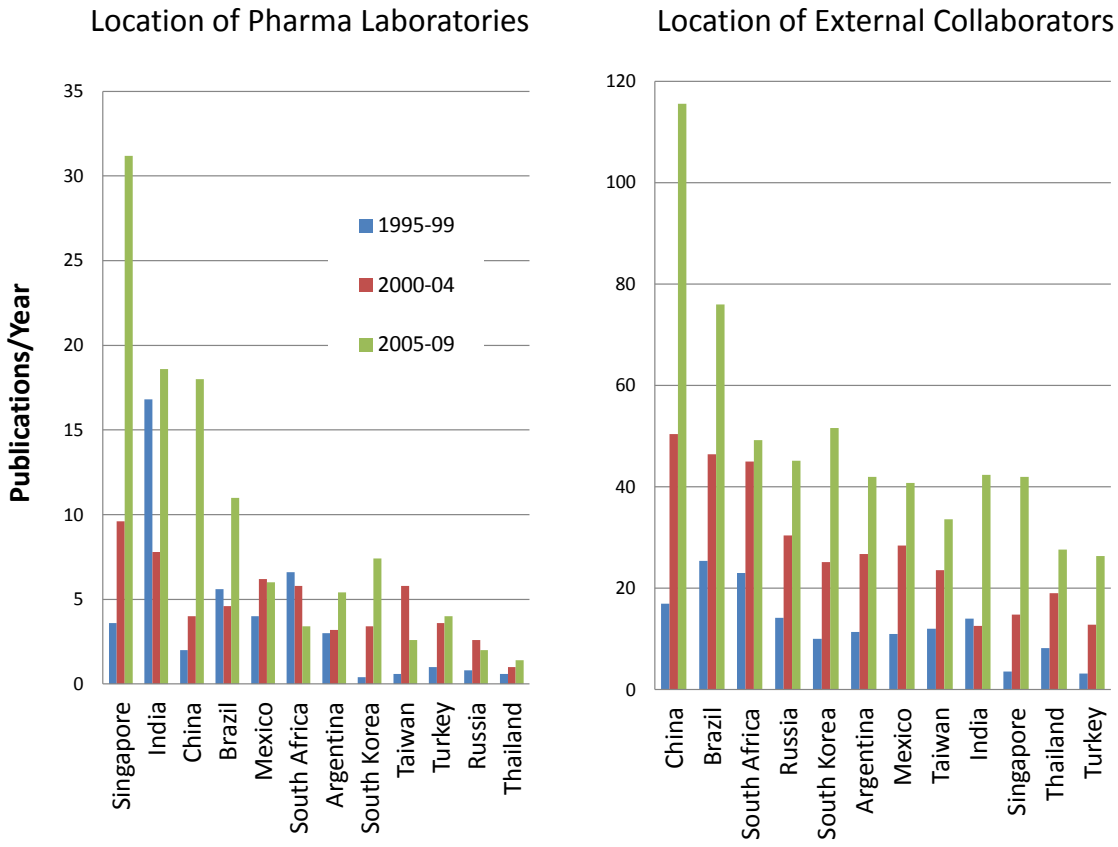

Figure 10. Location of pharmaceutical R&D laboratories by emergent countries.

Table 4. Collaborations between local research organisations and local R&D labs of big pharma in emerging countries.

Country of External Collaboration	% in collaboration with big pharma's local R&D labs		
	1995-99	2000-04	2005-09
India	19%	36%	26%
Singapore	11%	18%	19%
China	6%	4%	13%
South Korea	4%	13%	13%
Brazil	17%	9%	13%
South Africa	15%	9%	4%

5. Discussion: Causes and consequences of pharma's retreat from open science

This paper has analysed the publication output of the 15 major pharmaceutical firms in Europe and the US, including publications by all acquisitions made by these firms in the period 1995-2009, that represents the core of the traditional pharmaceutical industry – big pharma. The analysis suggests that these firms are undergoing a shift away from the open science activities associated with drug discovery and towards a systems integrator role (Munos 2009; Paul et al. 2010; Pammolli, Magazzini, and Riccaboni 2011; Hopkins et al. 2007).

Our empirical data provides some evidence of this shift from three perspectives. In the first place, a diversification of the knowledge base away from the tradition expertise in chemistry and biology towards computation, health services and more clinical fields. This diversification may be characterised crudely as a shift from basic towards clinical research, from research to development, or from bench towards bedside. Such a shift might be resulting from technological opportunities created by information technologies (Nightingale 2000; Bonaccorsi 2008), as the outcome of socio-economic pressures in medicine towards practices that are more sensitive to the patient's context or individual needs (Amir-Aslani and Mangematin 2010) and/or of management strategies to reduce the financial risk associated with drug discovery (Munos and Chin 2011)[9].

Second, to access these new areas of knowledge we observe an increase in external collaborations and of external leadership of co-authored papers, suggesting a tendency to outsource, in agreement with industry reports of increasing externalisation of R&D efforts (Baum 2010; Hirschler and Kelland 2010). Such trends are consistent with the view that the locus of innovation is shifting from in-house R&D to small firms and public organisations (Munos 2009; Kneller 2010) or to the organisational network (Powell, Koput, and Smith-Doerr 1996). However these expanding collaborations are increasingly intellectually led by the collaborators rather than big pharma. Whether this has any implications for big pharma's ability to capture values from these relationships remains to be explored.

Third, from the geographic perspective, we find a more pronounced decline in publications by Europe-based big pharma (including their US labs) as well as total output of big pharma's European labs (including those owned by US firms), in comparison to all big pharma labs located in the US or all labs owned by USA firms. The relative decline in European laboratories is not uniform, with Germany resisting the trend, while the UK, France and Switzerland succumb most, and Sweden, Denmark and Belgium buck the trend entirely. The shift away from undertaking internal R&D in Europe does not detract from the importance of European collaborators for big pharma – with European collaborators apparently as important to US-based big pharma as US collaborators are to EU-based big pharma.

Finally, while publications by 'big pharma' in emergent countries have sharply increased, from a low base, over the period studied, these remain extremely low compared with those in developed countries. Publishing activity in these R&D centres in developing countries have so far a small 'research' component and a larger 'development' component, possibly associated with adaptation to local growing markets and coordination of the research outsourcing to local CROs or public centres (Hoekman et al. 2012).

Finally, we observe a slow decline of the total number of publications by big pharma, in stark contrast with the inflationary tendencies of most bibliometric indicators in the period (Persson, Glänzel, and Danell 2004). This confirms earlier suggestions of a publication decline from corporate laboratories, inferred from a shorter period (1996-2001) and only for certain collaborative modes (Tijssen 2004). Based on our empirical data we can merely argue that there seems to be a shift away from an 'open science' strategy in pharma, which might be due to either a decrease of R&D performed in-house by pharma (possibly due to increased R&D outsourcing), or a decrease in the propensity to publish. As carefully argued by Tijssen (Tijssen 2004, 726–727), one cannot rule out the possibility that big pharma is conducting the same or greater amount of R&D, but just publishing less –for example, because academic collaborators refrain from mentioning industrial involvement or because of fears of knowledge leaking out before patenting. Or it could be also be that the retreat from publishing activities is due to a combination of increasing costs in the business of medical

[9] See (Pammolli, Magazzini, and Riccaboni 2011) for an oppositve view on risk taking.

writing, heightened awareness by medical journals of the 'marketing' function of pharma articles and/or in the wake of scandals following ethically dubious practices such ghost writing (Sismondo 2009; Smith 2005).

However, industry analysts report of R&D laboratories closures (LaMattina 2011), decrease of R&D expenditure in comparison to sales (from the traditional 15-20% to ~10% according to (Petsko 2011, 3)), outsourcing of R&D (Hirschler and Kelland 2010; Baum 2010), relative reduction of research in comparison to development (Jensen 2010) and a drop by half in number of new pharma-biotech alliances (Ratner 2012). This strongly suggests that pharma's in-house R&D efforts are decreasing significantly. In fact, the decline in publication trends shown in Figure 1 might be a gross underestimate of the degree of in-house R&D reduction, because of increasing co-authorship trends observed during the period.

In any case, either of these (perhaps complementary) interpretations tells of a decline in the importance of open science consistent with the idea that pharmaceutical companies are increasingly 'network integrators' instead of the prime locus of drug discovery (Subramanian, Toney, and Jayachandran 2011). As the chief executive of GlaxoSmithKline explains:

> 'Big Pharma players can no longer hope to generate the absolutely best science in all areas on their own. Therefore, rebuilding the R&D Engine in Big Pharma standard operating procedure should be to decide on a scientific bet (for example, kinases in oncology), shop around among all the external players that are pursuing such research, and establish a contractual relationship with the best.' (Garnier 2008, 75–76)

In doing so, they are following other high-tech sectors, such as various firms in semiconductors and information technologies in the retreat from corporate R&D (Tijssen 2004; The Economist 2007). Instead of being the R&D engine, big pharma, as network integrator, is possibly taking on the role of financier, regulatory liaison, and lobbyists for publicly funded medical research, and salesman. Whether this is a desirable development depends on the belief in the capacities of big pharma to coordinate and integrate these activities for the public good.

At this stage, one can only speculate on the causes and consequences of big pharma's retreat from open science. In a linear view on innovation where high-quality scientific activity results in new compounds, big pharma's lack of investment in in-house science (or at least in genuine high risk research) can be seen as the cause of its R&D productivity crisis (Munos and Chin 2011). Another view is that R&D cuts are just the consequence of the crisis: higher R&D costs and expiring patents lead to lack of investment which results in a shortage of capital to keep R&D.[10]

Any discussion of the causality chains in big pharma's apparent structural transition will be complex and is beyond the scope of this study. An understanding of the industry evolution would require an analysis not only of corporate R&D activities, but of its interplay of financial markets, emerging economies, increased regulatory stringency, demography changes resulting in new types of disease addressed, technologies used in drug discovery, and changes in health provision triggered by welfare cuts. We nevertheless speculatively advance two debates where the retreat of big pharma from open science will figure centrally.

The first debate is about the big pharma's capabilities of carrying out the role system integrator while reducing its role as contributor to the scientific base. If science-based knowledge is becoming more important in drug discovery, and firms need to develop *absorptive capacity* by interacting with academia and small biotechs in order to acquire this knowledge (Cockburn and Henderson 1998),

[10] We thank Ed Steinmueller for this point.

how will they be able to select which areas to invest in the absence of a substantial in-house research? The apparent answer appears to be for academia to step in by doing 'translational research' and setting up private-public centres that facilitate 'open innovation' (Collins 2011; West and Nightingale 2009). The viability of this model is unproven.

The second debate concerns how the redistribution of research efforts will or should affect the redistribution of the social benefits and economic returns derived from drugs. Some observers have seriously questioned the economic returns enjoyed by big pharma in the last 20 years (Angell 2004; Mazzucato 2011, 96), in particular given the crucial contributions already made by public research (McMillan, Narin, and Deeds 2000) and the forthcoming increases (Collins 2011). Reuters' analysts have put it eloquently (Hirschler and Kelland 2010, 9):

> 'Drug companies have long promoted the idea that they pursue new drugs for the good of humanity; it's an argument Big Pharma regularly uses to justify the huge profits it makes. High returns, the industry argues, can be ploughed back into research on the next medical breakthrough. If Big Pharma is not doing the research itself, will the big margins be harder to defend?'

In summary, the analysis of publications over the last 15 years has provided us with a window on an apparently major transition in the pharmaceutical industry. Multidimensional studies weaving trends in the knowledge base results with financial, regulatory and social trends will be needed to better understand and steer future scenarios of health provision (Crommelin et al, 2009).

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Appendix 1: List of complementary files

Available at: www.interdisciplinaryscience.net/pharma

- Complementary File 1: List of firm’s subsidiaries, acquisitions and mergers
- Complementary File 2: Publication trends by firm
- Complementary File 3: Web of Science Categories (WCs) of publication
- Complementary File 4: Specialisation science maps: aggregate and by firm
- Complementary File 5: Publication and collaboration trends by region and country

The authors are willing to share further materials upon request.