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Adapting the Innovation Landscape

UK Biopharma R&D Sourcebook 2015

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Preface

Evidence. It has always been the fuel for progress, but it has never been more prominent in public debate than it is now. At a recent Sense About Science event, we attendees were welcomed by staff wearing badges encouraging us to "Ask for Evidence". The Academy of Medical Sciences is exploring the evidence around medicines and how society uses that evolving evidence to judge the risks and benefits. Evidence-based policy making is likewise expected, although it is not always clear if we have the data to support it.

Data alone is certainly not evidence, but it is a critical component. The Association of the British Pharmaceutical Industry (ABPI) would like to help build the data, not only about our medicines, but about the work we do, our role in the UK and how this fits in to a changing global landscape for drug discovery, development, manufacture and use of medicines for the benefit of patients in the UK and worldwide. It is with this aim that we launch our first annual **R&D Sourcebook.**

The **R&D Sourcebook** aims to provide a snapshot of some of the key measures by which our industry develops medicines and the context in which this takes place. We have these data grouped in four sections: **Global health and the role of biopharma, Investing in innovation, Driving clinical research to deliver medicines and Collaborating for Innovation.** We plan to refine and extend this analysis over the coming years, and so we would welcome feedback on the data shared and the format for the report.

Each year the **R&D Sourcebook** will explore a different theme through essays from our ABPI Innovation Board Chair and from industry experts. This year's theme for the inaugural **R&D Sourcebook** is **Adapting the Innovation Landscape**. We want to understand not only how our industry is adapting to the changing innovation landscape but also how and why our members may be changing that landscape through the strategies they take. This year's invited essays come from academic and industry expert, Jack Scannell (Casmi and INNOGEN), and Adrian Towse and Jorge Mestre-Ferrandiz (Office of Health Economics). Both are thought-provoking and will stir up as much debate and discussion in your community as they have at the ABPI.

We hope you find the **R&D Sourcebook** valuable to your engagement with the biopharmaceutical industry and that it will enrich the evidence we bring to bear on the discovery and development of medicines.

Dr Virginia Acha
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Association of the British Pharmaceutical Industry.

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Adapting the Innovation Landscape

Dr Neil Weir
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Seven years since the publication of Jean-Paul Garnier's call for change to improve R&D productivity in the Harvard Business Review ("Rebuilding the R&D Engine in Big Pharma"[1]), how much has really changed?

The call then was for more 'entrepreneurial' R&D teams, and indeed, many biopharmaceutical companies have reorganised their R&D organisation to allow for more independence amongst research teams and the potential for longer term extramural collaborations. We are seeing companies now organise their R&D teams to compete with external opportunities for development and commercialisation within the business, to keep the competitive drive high. Beyond organisational structure, companies have also refocused their R&D portfolio and adapted new technologies and strategy to concentrate resources on the most novel research. Although the value of these changes will only be demonstrated over time, the increase in the number of new medicines approved in recent years suggests that companies have 'refreshed the R&D model'[2]. R&D productivity concerns were raised not only about the number of medicines, but also the innovative value of these medicines. As of 2014, the FDA reported that of the 41 approved medicines, forty-one percent (17 medicines) were first-in-class, and the same number of medicines were dedicated to rare disease[3]. Companies are clearly responding to the signals for novel therapeutics in areas of unmet need.

Beyond companies, other stakeholders have taken up the challenge to improve innovation and productivity in drug discovery and development. Notably, the regulatory authorities have progressed the concept of adaptive pathways[4] to achieve what Garnier referred to in 2008 as "the progressive blockbuster"[1]. Although medicines developed through adaptive pathways may not be 'blockbusters', the approach to regulatory review and the continual process for establishing the evidence of a medicine have changed our approach to drug development in line with scientific possibility. Targeted therapies are likewise adapting our paradigm for drug development and clinical practice in such a way as to introduce new disciplines for innovation (e.g. bioinformatics). Of course, our anticipation of these developments often outstrips the time it takes to realise the opportunity. In 2008, Garnier lamented that "one of the biggest disappointments of the past decade is that the sequencing of the human genome and the industrialization of techniques employed in the early discovery process have not become miracle cures for sliding R&D productivity."[1] Arguably, we are beginning to see the fruition of this innovation now. Adapting the innovation landscape takes time.

The frontier for innovation in medicines is vibrant, and biopharmaceutical companies are leading the way, working together with academics and other partners (IT, consumers, industry) to realise these aims. The leading biopharmaceutical companies have changed their own R&D models and adapted the innovation landscape in which they work by the way they invest in R&D, clinical research and collaborate with others. These collaborations have taken us beyond focusing only on the medicine, to consider broader possibilities in health services and information. To help us better understand this process, we need to consider the evidence of what has changed and how companies are innovating in new medicines and solutions for patients. Many of the changes companies have undertaken and the roles that they are playing in new technology development and advances in medicines remain unreported and unnoticed.

By publishing this first **R&D Sourcebook**, we hope to share some evidence of how industry is continuing to innovate and to adapt the landscape in which we work to best serve the progress of science for the benefit of patients. As you will find in the Sourcebook, the biopharmaceutical industry is continuing to make the largest investment in R&D for medicines, with over £88.5 billion ($137 billion) invested in 2014 worldwide, and £4.1 billion in the UK alone. We are focusing investments in a wider range of technologies than ever before, and the skills and collaborations we are seeking follow this trend. The UK has played a critical role in the evolution of life sciences, but as the biopharmaceutical innovation landscape is changing, the question remains: will the UK continue to adapt and advance with us?

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Pharmaceutical Evolution:
Clinical Selection versus Intelligent Design

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Charles Darwin's opponents sometimes advance an alternative theory, known as "Intelligent Design". They argue that the human eye, a favourite example, is so exquisite that it cannot be the mere consequence of natural selection acting on random heritable variation. Instead, there must be an Intelligent Designer. Most biological scientists view Intelligent Design as a fallacy. The argument also irritates squid, whose magnificent eyes avoid some bad design features of the human model [1].

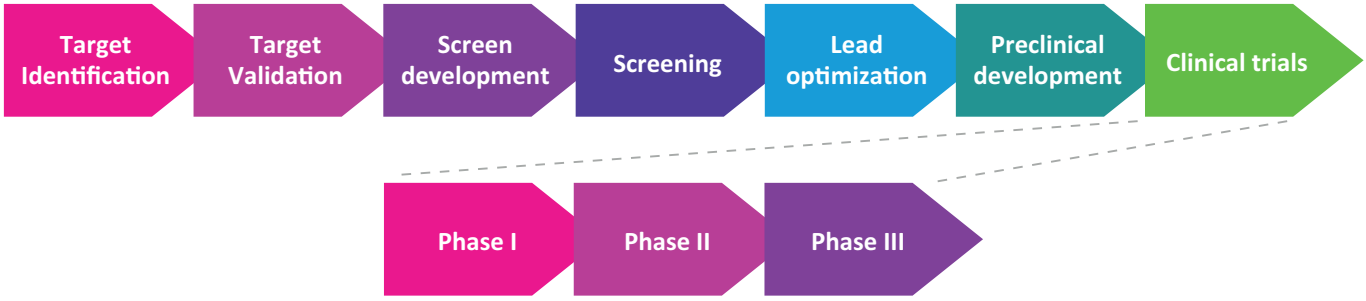
There is an analogous divergence when it comes to pharmaceutical innovation. On one hand, many successful drugs appear to have been Intelligently Designed for a specific therapeutic use [2] [3]. Their designers exist, and the few I have met seem ferociously intelligent. Here, Gleevec/imatinib plays the role that the human eye does for creationists. On the other hand, luck is often important and drugs' natural environment, the clinic, can select in a way that the Intelligent Designers would not have anticipated [3] [4].

I think there is a problematic tendency to over-estimate the importance of Intelligent Design versus Clinical Selection in pharmaceutical innovation. Intelligent Design is the public face of commercial R&D. It dominates academic biomedical science. It influences drug regulators and doctors. It aligns with the most valuable kinds of intellectual property, and so influences pricing and reimbursement. In contrast, things are made difficult for late-stage serendipity, for the real-word experiences of patients and doctors, and for creative users, who, in my view, already do much of the innovative heavy lifting. The skew is reflected in relative over-investment in "molecular reductionism" [5], which often lacks predictive validity, and in relative under-investment in optimizing the use of drugs in their natural environment. The skew can also squeeze the pharmacological variation on which Clinical Selection acts, slowing the rate of therapeutic evolution.

From mechanistic story to creation myth

Nearly all drugs are sold to regulators and prescribers with a mechanistic story: "Disease phenotype y is caused by the (mis)behaviour of molecular component x which can be drugged with drug d. Therefore drug d alleviates disease phenotype y." Sometimes these stories are both precise and true (e.g., when y = staphylococcal infection, x = DD-transpeptidase, and d = penicillin). Sometimes they are not (e.g., when y = ADHD, x = "something to do with dopamine?", and y = dextroamphetamine) [6].

Mechanistic stories transform into creation myths, around which society organizes both academic and commercial drug discovery. Nearly all drugs enter clinical development with a plausible mechanistic story. Around 10% succeed and emerge with their stories either intact or retrospectively adjusted for commercial consumption [1]. The other 90% fail for reasons on which their stories were silent. People outside of R&D rarely hear the stories of these 90%. It is survivor bias that makes both drugs and human eyes appear more Intelligently Designed than they actually are.



The drug industry generally describes R&D to outsiders in terms of Intelligent Design via "target-based drug discovery version 1.0" (Figure 1). This is an academic/industrial process built on a set of assumptions that mirror stories of drug action:

1. Molecular component x, the target, (mis)behaves in such a way that it causes disease phenotype y (hence the Target Identification and Target Validation chevrons in Figure 1).
2. Molecular component x can be drugged with drug d in a way that causes an improvement in y without an unacceptable decline in other phenotypic traits (hence the Screen Development, Screening, Lead Optimization, and Preclinical Development chevrons in Figure 1).
3. There exists a sufficient number of identifiable and exploitable instances of x, d, and y (hence taxes and philanthropy pay for basic academic biomedical science, and taxes and health insurance premiums incentivize commercial drug discovery).
4. Therefore, the academic/industrial process set out in the grey chevrons of Figure 1 will deliver, with high efficiency, a large number of good drug candidates into clinical trials (black chevrons).

But we have known for years that the academic/industrial process in Figure 1 **has not worked very well** [2]. The cost efficiency and quality of the scientific and technological tools available at each chevron have improved spectacularly. DNA sequencing has become over a billion times cheaper since the 1970s, for better Target Identification; transgenic mice have been invented, for Target Validation; the cost of high throughput screening tests has declined around 10 fold per decade; etc., etc. In contrast, there is a reproducibility crisis in academic biomedical science [7] [8] [9], drug industry R&D spending per approved drug has increased, in inflation adjusted terms, nearly two orders of magnitude since 1950 [10] and the drugs that the chevrons deliver into clinical development are more likely to fail now than in the 1970s. This shows that one or more of assumptions (1) to (4) must have been wrong. Yet Figure 1 remains the standard way of impressing the public and policy makers with the process of drug discovery.

The struggle for existence

While the story of drug discovery is framed in terms of Intelligent Design, the way money is spent points to a reality that Darwin would recognize; the production of variation followed by selection: "… as more individuals are produced than can possibly survive, there must in every case be a struggle for existence..." [11] The struggle is shown in R&D attrition statistics (e.g., 24 targets to hit projects, 15 lead optimization projects, 12 preclinical projects, etc., per approved drug) [12] and in the clinical development of successful drugs.

Avastin/bevacizumab, for example, is a monoclonal antibody that scavenges VEGF-A, an endogenous signaling molecule that stimulates the growth of new blood vessels. The drug has 7 FDA approved indications in oncology [3]. The FDA prescribing information cites 10 clinical trials on which these approved indications are based. The drug is used off-label in several other cancers, in eye diseases including age-related macular degeneration (AMD), and in a handful of other conditions.

I guess that a perfectly efficient, cost-conscious, Intelligent Designer could have got 7 indications approved by the FDA with 20 clinical trials or fewer (the 10 "pivotal" trials plus associated Phase I and Phase II efforts). If I go to the standard clinical trials database, clinicaltrials.gov, I can search for trials involving Avastin/bevacizumab. Limiting my search to interventional studies, I find not 20 trials, but 1,662. Now, many of them used Avastin/bevacizumab almost incidentally (e.g., as the standard of care on top of which to add a new treatment). Others were testing off-label uses that Roche/Genentech might not welcome (e.g., AMD where Avastin/bevacizumab competes with another drug, sold by Roche/Genentech, that is both more lucrative and FDA approved). However, Roche/Genentech had a hand in 506 trials, sponsoring 153 and collaborating on another 353.

If one skims through these 506 trials, and compares them with the 7 approved indications, one gets the strong impression of a selection process, albeit one that was highly directed and commercially astute. Roche/Genentech had no good way of predicting what Avastin/bevacizumab would do in patients, particularly in drug combinations – critical in oncology – where synergistic or cumulative efficacy and toxicity can both occur. The intellectual property clock was ticking. Other drugs were competing to capture valuable markets. Therefore, it made sense to run multiple trials in parallel, many of which could never inform the other development streams, and many of which led nowhere. Only now do we know that Avastin/bevacizumab was a relative success in some areas (e.g., metastatic colorectal cancer) but a relative or total failure in others (e.g., breast cancer, adjuvant colorectal cancer). At the same time, of course, the huge development program raised Avastin/bevacizumab's profile among oncologists. The drug was ubiquitous at cancer conventions for the best part of a decade.

Interestingly, while Avastin/bevacizumab struggled for existence, indication by indication, its mechanistic story

[1] For example, the drug Xalkori/crizotinib is now sold as an ultra-targeted ALK-inhibitor; an archetypical "personalized medicine" for patients with ALK-mutated lung cancers. Crizotinib does inhibit ALK, but it was produced during a campaign to inhibit a different protein, MEK [45]. For similar comments on Avastin/bevacizumab and Gleevec/imatinib, see later.

[2] Although there is evidence that enough experience has accumulated that it has started working a little better. See, for example, reference: [46].

[3] Two indications in metastatic colorectal cancer, and a single indication in each of non-squamous cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer, and ovarian cancer.

has been up for debate. The drug was Intelligently Designed to starve the growing tumours of their blood supply [13]. It may, in fact, work in an entirely different way, by normalizing tumour blood supply [14] [15].

Similar comments apply to Gleevec/imatinib, although here there is the impression of a more narrowly focused selection process. There are 10 FDA approved indications; four in leukaemia that depend primarily on inhibition of bcr-abl, the target for which the drug was Intelligently Designed, and 6 others. The other indications depend on proteins that happen to be similar to bcr-abl, and which Gleevec/imatinib fortuitously inhibits. Clinicaltrials.gov shows 517 interventional trials involving Gleevec/imatinib. As with Avastin/bevacizumab, the drug is a control or background treatment in many of these trials. However, Novartis sponsored 86 and collaborated on another 84. The drug has seen development failures (e.g., glioblastoma) and results that may yet lead to unexpected successes (e.g., pulmonary arterial hypertension). As with Avastin/bevacizumab, the mechanistic story has shifted over time. In 2002, fresh from its first FDA approval, Gleevec/imatinib was "a **selective** inhibitor of the BCR-ABL tyrosine kinase causative of chronic myeloid leukemia." [16] Now that the drug works in diseases that have nothing to do with bcr-abl, it has conveniently transmuted into "a **broad-spectrum** tyrosine kinase inhibitor." [17] [my emphasis]

User-led innovation

Clinical trial sponsors pick which battles to fight and how to fight them, and – importantly – which battles to avoid. Trials are "a messy mixture of science, regulation, public relations and marketing" [10] which often lack what might be called ecological validity. This leads to another important Clinical Selection step that happens when drugs are released into their natural environment. They often do better or worse than expected when they meet real patients in the real world, with their comorbidities, concurrent medications, variable adherence, and given the fact that the things that patients find important are often not measured in trials. This real world step is not merely passive. Users, patients and doctors, are themselves important innovators.

User-innovators have been studied in a variety of technical fields, from mountain biking to scientific instruments. To quote from DeMonaco et al. [18], one of the few studies of user-led innovation in pharmaceuticals:

- *"Traditionally, it has been assumed by innovation process scholars, that product manufacturers would be the developers of all or most new products … However, empirical research during the past two decades has now shown that product users rather than manufacturers are the actual developers of many of the commercially important new products in fields studied to date… Users, it has been found, tend to develop products and applications involving functional novelty. In contrast, manufacturers tend to develop products and applications that address well-understood needs."*

This makes sense. It is hard for most manufacturers to invest to satisfy uses that are not obvious at the point at which the investment is made. Pharmaceutical R&D decisions often require "target product profiles" against which to judge drug candidates. How can one produce a target product profile for medical needs that one does not understand?

DeMonaco et al. go on to argue that one should expect high rates of innovation among the users of pharmaceuticals [18]:

- *"Clinical practitioners carry out a much higher volume of formal and informal experiments than do manufacturers and universities. In the case of laboratories and formal clinical trials, the total volume of experiments going on in humans per new molecular entity probably only numbers in the hundreds or thousands of subject exposures for each new indication or use. In the case of clinical practice, the total volume of formal and informal experiments going on is equivalent to the number of prescriptions generated for the product… "*
- *"Information asymmetries exist in the case of discovery of new applications for existing drugs. As a consequence, many of the potential applications of an approved drug* ***cannot be predicted on the basis of data available to laboratory researchers.*** *Instead, it seems reasonable that many will only be discovered via "learning by doing" during widespread testing and use in the field." [my emphasis]*

This prediction seems to be born out. DeMonaco et al. [18] examined the cohort of 29 new molecular entities (NMEs) approved by the FDA in 1998. Over the next 5 years, 144 new and effective off-label uses were found for drugs in the cohort. 85 of the 144, nearly 60%, were field discoveries by practicing physicians, made independently of researchers at Universities and of the drug industry .

DeMonaco et al.'s work resonates with my reading of history. R&D seemed remarkably efficient and productive, though ethically problematic, during the "golden age" of drug discovery (~1945 to ~1975) when something akin to user-led innovation often blended seamlessly into a very different discovery processes, in which clinical practitioners were more heavily involved than they are now [3] [19] [20] [21] [22] [10].

It also strikes me that discovery by clinical observation tends to have high predictive validity versus the scientific push of Intelligent Design [23] [24]. The screening model of the human patient is another human patient, not an isolated protein. Furthermore, the sample sizes on which field discoveries are based are generally small, often a single serendipitous observation. Small, noisy, therapeutic

signals are not detectable when n = 1, so the effects that can be discovered in the field will tend to be large. I find it ironic that there is such little overt support for a discovery model that, a priori, will detect therapeutic effects that are likely to be both large and valid, yet so much support for the model that is shown in Figure 1.

"I know he is a good general, but is he lucky?"

Clinical Selection means that the real-world adoption of drugs, indeed their therapeutic significance, is very hard for Intelligent Designers to anticipate. Important drugs change medical practice. The Chief Executives of drug companies don't seem to know which of their products will win and which will lose [25]. Wall Street analysts' pre-launch forecasts are notoriously unreliable, though often better than the forecasts of the companies themselves [4] [26].

There is a wonderful paper by Kesselheim and Avorn from 2013 [27], which hints at this point. The paper identifies drugs that have had huge clinical significance, those that physicians believe have been most "transformative" over the last 25 years. I would love to know the detailed discovery and development history of all the drugs in the paper. Fortunately, Kesselheim and colleagues are working on this [2] [28]. However, in the meantime, I think I know a little of the history of several of them (many readers will certainly know much more).

The anti-TNF biologics were first developed for septic shock but failed in Phase II trials before finding uses in rheumatoid arthritis and other auto-immune diseases. Roche licensed its anti-TNF, Enbrel/etanercept to Amgen, presumably because it saw minimal commercial opportunities itself. Enbrel now generates sales of around $5 billion per year and the anti-TNFs have become the World's most lucrative drug class. SmithKlineBeecham patented a class of Viagra/sildenafil-type drugs but stopped work on them, seeing no real medical need and fearing the reputational risk from treating a "lifestyle" condition [29]. This was several years before Pfizer's allegedly serendipitous discovery of Viagra/sildenafil's priapic effects during a Phase I trial. The precarious development of Gleevec/imatinib is well known [2], with the project nearly expiring in the merger between Ciba-Geigy and Sandoz which created Novartis. Mevacor/lovastatin had a bumpy ride [30]. Merck halted clinical development in 1980, after Sankyo stopped trials of a similar drug, probably spotting an animal toxicity signal. Mevavor/lovastatin was resurrected in a physician-led study in high risk patients in 1982, after which Merck revived its own program. The drug was approved on the basis of surrogate endpoints in 1987. Whether lowering cholesterol was beneficial or not remained controversial until 1994, when another statin (simvastatin/Zocor) was shown to improve overall mortality. Diprivan/propofol is an anaesthetic. It appears to have been transformative because its launch coincided with the introduction of the endotracheal mask and complemented the development of day case surgery [28]; not something that could have been anticipated by its Intelligent Designers. Diprivan/propofol has also found a use at sub-anaesthetic doses as an antipruritic; the serendipitous discovery of an anaesthetist [18]. Ceredase/alglucerase may be important, in part at least, because it led to the discovery of far more Gaucher Disease patients than anyone believed possible, and a market of far lower price sensitivity than anyone believed possible. This transformed the industry's investment in ultra-orphan diseases. I understand that GlaxoWellcome started with modest expectations for its flucitasone/salmeterol combination (Advair or Seretide), but ended up with annual sales 10 times higher than forecast. Botulinum toxin was approved in 1989 as an orphan drug for use in strabismus, hemifacial spasms, and blepharospasm. Its widespread cosmetic application followed from clinical observations made during on-label use [18]. Etc., etc.

Getting more from Clinical Selection

Since pharmacological innovation involves more Clinical Selection and perhaps less Intelligent Design than most people believe, things should be organized differently [26]. Rapid and cost-effective progress requires more drugs brought into the real world more cheaply. The role of R&D should be to provide the maximum quantity of acceptably safe chemical diversity on which real-world Clinical Selection then acts. As Mao Tse Tung said: "Letting a Hundred Flowers Blossom and a Hundred Schools of Thought Contend is the Policy for Promoting Progress." Regulation, intellectual property rights, and pricing should incentivize the creation of acceptably safe diversity, its unbiased real-world selection by patients and doctors, and diffusion of users' discoveries. Furthermore, it is a mistake to insist on too much "evidence" on drugs' efficacy prior to real-world use, as such evidence evidently fails to support accurate predictions of drugs' ultimate utility. In particular, Phase III trials of low ecological validity inflate R&D costs and reduce pharmacological variation.

There are, no doubt, practical problems with this Maoist vision. It may be unacceptably dangerous for patients. It does not sit well with current drug regulation, nor intellectual property laws, nor reimbursement practices, nor the questionable dogmas of "evidence-based" medicine. However, absent a revolution which I do not expect, there are some small steps being made in the right direction, and other steps that could be taken rather easily.

One step is the European Medicines Agency's Adaptive Licensing (AL) pilot [31] [32] [33] [34] [35] [36] [35] [37]. As I have written elsewhere [37], "AL structures clinical development around

[4] Of course, there are regulatory constraints that may discourage the industry from being too interested in off-label uses

the graded introduction of a new drug as evidence on its risk-benefit profile accumulates by a variety of means [31] [34] [35]. Perhaps, for example, commercial sales in a high-need subset of patients can be permitted on the basis of the results of Phase II trials, while further evidence is collected that allows a broader label and wider use in a larger patient population. The emphasis shifts away from large pre-approval trials and towards more diverse and

perhaps more ecologically valid evidence of real-world utility (e.g., patient registries for safety data)." The initial implementation of AL will probably replicate some of the problems that exist in the current system. Its emphasis on prospectively planned evidence generation has the whiff of Intelligent Design. If things are too inflexible, AL will discard drugs that do something useful, but not the precise thing that the Intelligent Designer hoped. The commercial incentives for trial sponsors don't change. Sponsors still pick which battles to fight and which to avoid. Nor is it clear that AL will appear attractive to trial sponsors, except under a narrow set of circumstances [37].

However, I am hopeful because the experience and infrastructure that AL generates may provide an environment under which more acceptably safe chemical diversity can be released into the real world. AL may also provide evidential tools that, in the long run, make it easier for doctors and patients to decide which of the diversity is useful and which is useless.

Looking well beyond of the pharmaceutical mainstream, user-led innovation has seen an internet-enabled resurgence. At the "ultra" end of the ultra-orphan diseases, I know of one group, representing few tens of children worldwide with NGLY1-deficiency, which appears to be making progress via self-experimentation (or sometimes parent-experimentation) [38] [39]. Their approach reminds me of more mainstream R&D in the 1940s and 1950s [19] [3]. I know another group that systematically collates and shares patients' experiences of prescribed medicines, including negative side effects and unexpected benefits [40]. They are second only to the FDA in terms of the number of adverse event reports they collect. I am sure there are other similar initiatives that I have missed [41] [42].

I am going to finish by suggesting two further steps. The first is to mitigate what innovation economists call "market failure in the peer-to-peer diffusion of user-innovations." [43].

There is a huge infrastructure that provides financial incentives for drug producers to innovate and then to spread their innovations far and wide [44] [43]. Incentives include intellectual property rights, R&D subsidies and tax breaks, and a relative, if not absolute, tolerance for high drug prices. We would not have 1,662 Avastin/bevacizumab trials listed on clinicaltrials.gov if it were a cheap generic. Governments put these incentives in place because they believe the benefits of innovation and its efficient diffusion outweigh the incentives' cost. In contrast, there are small-to-zero financial incentives for user-innovators to spread good therapeutic news. Most of the time, it is too much effort for a busy physician or patient to rigorously test and then "market" their discovery, even when they believe it is important [43].

I propose that health systems promote the "diffusion" of user-led innovation to a greater degree. The National Health Service in the UK, the Centers for Medicare and Medicaid Services in the US, and other major payers should each award two annual prizes; big enough to hit the headlines. One prize is for the user-led innovation with the greatest health benefit over the previous 5 years. The other is for the most effective proselytization of an important user-led innovation.

My second proposal is an assault on survivor bias in stories of R&D. This will help shrink Intelligent Design to its rightful – still large – size in public and policy consciousness. From now on, any eminent discoverer of any drug should be allowed to talk about his or her great discovery only on the condition that she or he dedicates an equal amount of time to a case-control project. The case-control must have involved the discoverer. It should have appeared prospectively similar to the great success, but must have been an abject failure. There should then be time for impertinent questions on whether anything other than luck distinguished the two.

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Maximising R&D Productivity: new initiatives and gaps in the analysis

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Introduction

Last year's ABPI Annual Conference saw the launch of "Securing a future for innovative medicines: a discussion paper" (ABPI, 2014). We both contributed extensively to this report which highlighted five global challenges that have a direct effect on the topic of this year's ABPI R&D conference theme: how can we maximise R&D productivity? **These five challenges include:**

1. The increasing importance of specialised and stratified medicines
2. Rising medicine development costs
3. Closer benefit risk monitoring by regulators over a medicines' life cycle
4. Increasing demand for real world evidence (RWE) by health technology assessment (HTA) bodies acting on behalf of payers and regulators, resulting from a growing interest in relative effectiveness
5. The potential disconnect between the evidence needs of regulators and payers/HTA bodies.

All of these challenge efforts to improve the productivity – the ratio of the effort that goes into R&D to the number and value of the products that come out.

Since then several developments on early access and adaptive pathways have taken place, designed to address some of these challenges. This essay focuses on them. It has three sections. First, we provide some context on the rationale for early access schemes and adaptive pathways, highlighting what we think is a key trade-off. Second, we discuss some recent key initiatives in the US and Europe – emphasising where relevant the information gaps on the impact of such initiatives. Third, we outline on-going research OHE is undertaking to address such gaps.

Context

Across the globe there is a strong call for regulatory agencies to develop new models of marketing authorisation for medicines in development that could address high unmet medical need. In order for changes in the regulatory pathway for licensing drugs to be successful, key stakeholders – patients, payers and the HTA bodies who act on their behalf, the pharmaceutical industry, and regulators – must all realise or understand the value of those changes.

Mechanisms to allow the earlier introduction of new medicines must all confront the trade-off between evidence development and timely access (Woodcock, 2012). At early stages of development when relatively little is understood of the overall properties and effects of a medicine, the risks associated with its introduction are relatively higher. However a consequence of delaying licensing until the evidence base is beyond doubt is the mortality and morbidity cost imposed on patients who could have benefited from earlier treatment; patients with urgent unmet medical need are likely to great emphasis on getting the opportunity to access a treatment. For this reason, there have been a range of regulatory responses to expedite the development and licensing of medicines that have the potential to address serious or life-threatening conditions where there are currently few alternative treatment options.

A key issue in making a trade-off between evidence and access is managing uncertainty. On the one hand, decision uncertainty would intuitively be greater if that decision is taken earlier in the lifetime of a medicine, based on less data. For payers this means a higher chance that the assessment of relative and/or cost-effectiveness of a medicine that comes out of this assessment is wrong. Like-wise, regulators and patients may have to accept a more uncertain risk/benefit ratio. On the other hand, decisions to be made at earlier time points will typically be made for a narrower subset of patients, for whom we may be reasonably certain of outcomes, particularly if companies' R&D and trial designs adapted to a model of progressive expansion of patient indications (generating data first, and more quickly, for those in whom it is believed the medicine will work best).

Recent initiatives: Adaptive pathways, Breakthrough Therapy Designation and PRIME

Evidence is generated not as a one-off pre-licensing exercise, but iteratively over the course of a drug's life cycle as we understand more and more about a product through randomised and pragmatic clinical trials and then, beyond the point of licensing, through observational studies as well as randomised and pragmatic clinical trials. A regulatory pathway that could reflect this iterative understanding may involve an early licensing decision for a narrow population base for which evidence of efficacy exists, which would be revisited periodically with the licensing indication expanded or restricted based on new efficacy and safety data (Eichler et al., 2012). This is captured in the concept of Adaptive Licencing, an approach which is being piloted (since March 2014) by the European Medicines Agency (EMA); re-named 'Medicine's Adaptive Pathways to Patients' (MAPPs) (or 'Adaptive Pathways') to reflect the broader environment for medicine approval and adoption, which must incorporate HTA bodies and payers. According to the EMA, "the main aim of the pilot is to help develop an understanding of how future adaptive pathways might be designed for different types of products and indications. It provides a framework for open and informal dialogue between stakeholders". The adaptive pathways approach builds on regulatory processes already in place.

The EMA published a report in December 2014 on the initial experience with the pilot project and the next steps (EMA, 2014a). It reported that six out of 10 products initially identified as fulfilling the criteria to be eligible for the pilot have been selected to undergo detailed (so called stage II) discussions (one or more) with the participation of all stakeholders. As stated by the EMA, these adaptive licensing pilot discussions do not replace the formal scientific advice and protocol assistance procedures – they should be deemed as "an opportunity for enhanced and prospective brainstorming interactions in a confidential environment with regulators and other downstream stakeholders (HTA, patients) prior to a formal regulatory interaction steps" (EMA, 2014b). The first of these stage II meetings took place in December 2014 with others already planned during 2015.

As a result of the experience, the EMA will:

1. Concentrate efforts, from February 2015, on the remaining selected proposals for discussion in stage II, which will include in-depth, face-to-face meetings with the selected applicants
2. Consider new applications after February 2015 for stage II if they are well-developed.

Three criteria are listed by the EMA that identify a good candidate product for adaptive pathways:

1. an iterative development plan, either by gradual expansion of the target population (e.g. starting from a population with a high medical need) or by progressive reduction of uncertainty after initial authorisation, based on surrogate endpoints
2. an ability to engage HTAs and other downstream stakeholders, with proposals for how their requirements can be met
3. proposals for the monitoring, collection and use of real-world post-authorisation data as a complement to randomised clinical trial data.

In September 2015, the ADAPT SMART (Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes), a European public-private collaboration bringing together 32 international participants, was launched. This project focuses on laying the foundations for MAPPs to be put into practice in Europe (ADAPT SMART, 2015), and will support Innovative Medicines Initiative 2 (IMI2) projects investigating MAPPs tools and methodologies. It has received funding from Innovative Medicines Initiative 2 (IMI2).

In the UK, the Accelerated Access Review interim report (AAR, 2015) recommends that the UK builds on the experience of this pilot to ensure "optimal use, on a product by product basis, of current and future flexibilities in the regulatory processes for the licensing and conditional approval of new products".

On the other end of the scale, schemes developed to promote early access to medicines could be as simple as finding ways to expedite the current process of marketing authorisation; the U.S. Food and Drug Administration (FDA)'s Breakthrough Therapy Designation (BTD) could be regarded as this sort of scheme.

Before the introduction of the BTD, there were three FDA programmes that aim to *'facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition'* (FDA, 2014): fast track designation, accelerated approval, and priority review designation.

BTD is considered based on the following criteria:

- The medicine is intended to treat a serious or life-threatening disease / condition
- Preliminary clinical evidence demonstrates substantial improvement over existing therapies on one or more clinically significant endpoints.

Preliminary clinical data required to support a BTD application is generally from Phase 1 or 2 clinical trials (FDA, 2014).

The FDA describes four key features of the BTD scheme:

1. *Intensive guidance on efficient drug development.* Sponsors are encouraged and supported by the FDA to design efficient clinical trials, which minimise the number of patients exposed to a clearly less efficacious treatment. Given the selection requirement of BTD that medicines show early promise of substantial improvements, it is thought this will result in smaller or more efficient (shorter) clinical trials. FDA supply timely advice and communications to support sponsors in the design and conduct of an efficient drug development programme that will meet subsequent FDA approval
2. *Organisational commitment involving senior managers.* Senior and experienced review and regulatory health project management staff are assigned to the projects to facilitate pro-active and multi-disciplinary review
3. *Rolling review.* Manufacturers are permitted to submit portions of an FDA marketing application as they become available, in order to expedite the final review process
4. *Other actions to expedite review. A medicine with BTD may also be eligible for priority review.*

By providing early and intensive guidance from the FDA, a BTD may speed up the process of development and review, thereby providing earlier access for patients by facilitating an earlier marketing authorisation.

The BTD programme has had positive traction with industry, as evidenced by the high volume of applications (258 up to March 2014, since the programme's inception in 2012), around 30% of which have been granted. It has been argued that the main reason for rejection has been failure of the preliminary clinical data to suggest "substantial" benefit over existing therapies (Woodcock, 2014).

Given the fact that the BTD programme is still young, it is difficult to assess the impact of BTD on drug development times. Based on analysis from March 2014, for the 3 (out of 41) BTD products that had so far gone on to receive marketing authorisation, the average development time (measured between initiation dates of Phase I trials and approval) was around five years (Aggarwal, 2014). This compares with previous research that has shown development times (Phases I-III) to be between six and seven years (Mestre-Ferrandiz et al. (2012); Di Masi (2015)). Since this analysis from March 2014 at least a further 21 breakthrough designated medicines have gone on to be granted marketing authorisation; analysis of development times with this larger sample size has not been reported.

The EMA launched on 26 October 2015 a consultation on a similar scheme to BTD – PRIME (PRIority MEdicines). PRIME aims to "strengthen support to medicines that have the potential to benefit patients who presently have no treatment options, or that may offer a major therapeutic advantage over existing treatments. These are considered priority medicines by EMA, hence the name of the scheme" (EMA, 2015). PRIME builds on existing regulatory tools, particularly the use of scientific advice and accelerated assessment.

The eligibility criteria foreseen for PRIME are those of the accelerated assessment procedure. This means that to be eligible to enter the scheme, a medicine would have preliminary clinical evidence indicating that it has the potential to bring significant benefits to patients with unmet medical needs and hence be of major interest from a public health and therapeutic innovation perspective. PRIME offers regulatory and scientific support to these products through advice at key milestones with potential involvement of multiple stakeholders (e.g. health technology assessment bodies and patients), when relevant. As with BTD, EMA has stated clearly that it will use the same evaluation standards for medicines receiving PRIME support when assessing their marketing authorisation. The launch of PRIME is planned for the first quarter of 2016.

Knowledge gap: What is in for payers?

One of us presented at ISPOR Europe in May 2015 some work in progress that explores how early access schemes and adaptive approaches impact payers. We believe this is a critical issue where little work has been done to date. Payers and reimbursement bodies (including many HTA agencies acting on their behalf) have major concerns about funding new medicines on the basis of early data. Without payer "buy in" and hence medicine listing and reimbursement, companies do not have a viable commercial model for early access and patients will not get earlier access to licensed medicines unless they can pay for them out-of-pocket.

We see payers' concerns as follows:

- They are struggling to pay for fully licensed medicines with a "full" evidence base;
- Lowering evidence standards sends the wrong signals;
- Increased uncertainty about outcomes has a cost in that it increases the likelihood of making mistakes;
- Monitoring outcomes (to ensure the medicine does deliver) as a form of Coverage with Evidence Development (CED) is difficult;
- There is a greater likelihood of problems at re-review, i.e. a need to change the decision. There may be a need to agree a managed entry agreement at the outset.

These remarks highlight again the tension around managing uncertainty. Both industry and EMA strongly refute claims that MAPPs necessarily implies a lowering of evidence standards. This is because with better targeting and stratification, smaller and shorter trials might still deliver the same statistical reliability of evidence.

Our modelling work built on Baird et al. (2013) – focussing, however, on modelling how different scenarios (such as the BTD and adaptive approaches) might influence the benefits and costs to payers, issues not addressed in the Baird et al. (2013) analysis.

What next for us?
On-going research to explore possibilities to reduce R&D costs

We have also started a new project, commissioned by the ABPI, to evaluate options to improve the productivity of drug development. We will create a model of R&D costs that can be used to estimate the impacts of different (combinations of) changes to the R&D process. A key element, is to model early access and adaptive pathways, building on our work modelling the benefits and costs to payers. In addition, we will model a number of other "what if" options (which are not mutually exclusive):

1 Reducing failure rates:

   a Changing the trend in the attrition rates by mean of generating better evidence at earlier stages;

   b Promoting alliances among companies and between companies and regulators/payers/HTA bodies to streamline the Clinical Trial [CT] phase to get better (more relevant) evidence earlier and speed up the development process;

   c The development of biomarkers and companion diagnostics that give better evidence of efficacy and safety by mean of a better selection of patients for CTs with greater prospects of success.

2 Pre-competitive collaboration, open innovation and economies of scale to bring:

   a More efficient use of the drug discovery resources to the benefit of society including industry and its academic collaborators;

   b Pooling trials and knowledge through a more efficient CT phase and drug development process.

This work focuses on the 'input' variable measuring R&D productivity i.e. R&D costs. It will not attempt to address how to measure the value of the products that come out i.e. the 'output' variable. We have already argued before (Mestre-Ferrandiz et al, 2012) that measuring R&D productivity is not straight forward. For instance, if we measure the 'output' as the 'count' of new products launched, redirecting the R&D efforts from the more difficult, but higher value projects to the 'easier' projects will show an increase in R&D productivity; on the contrary, if R&D is directed towards more difficult and riskier therapeutic areas, with high unmet need (which is what Pammolli et al. (2011) suggest is happening), this will show a decline in R&D productivity as fewer new products might be launched. This means that we must be cautious on how we use the concept of 'R&D productivity' when discussing the economics of R&D in the life sciences sector.

We look forward to report back next year on our key findings.

Adrian Towse and Jorge Mestre-Ferrandiz.

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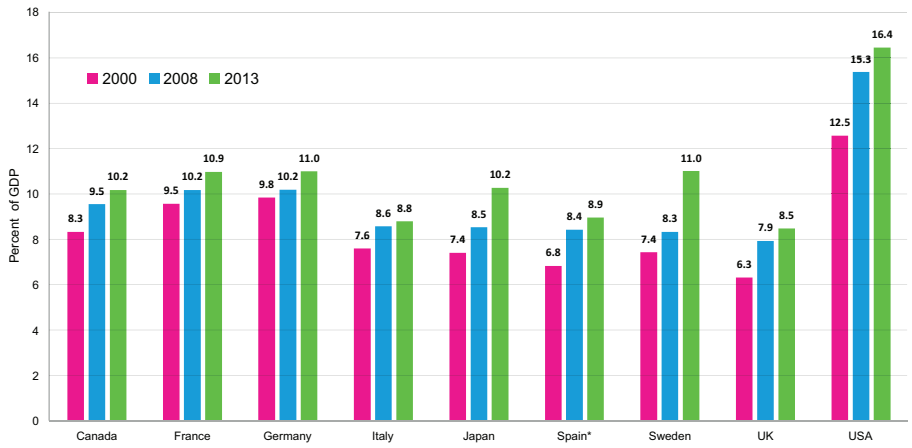
Global Health and the Role of Biopharma

The burden of healthcare expenditure and the impact of demographic change are rarely out of public discourse. However, although our investment in healthcare has been rising over decades (mirrored accordingly in the improvement in health outcomes and life expectancy), the economic crisis in 2008 initiated a curb on the growth of the share of investment in healthcare that continues into the present.

In this section, we review some key measures of how the UK aligns with global trends in healthcare investment and pharmaceutical markets, and in that context, how the UK biopharma industry is contributing to UK economic growth and prosperity.

3.1 **The growth of total expenditure on health** as a share of gross domestic product (GDP) **has slowed since 2008** across many countries, although not for all (c.f. Sweden and Japan), according to the OECD. For this peer group, the expenditure on healthcare as a share of GDP is highest in the US and **lowest in the UK**.

Health Expenditure as per cent of GDP

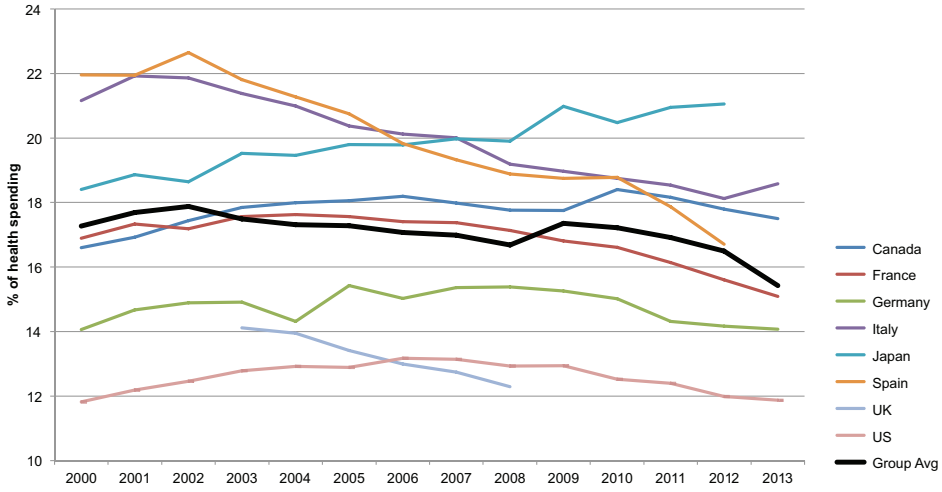


SOURCE: OECD Health Database (accessed October 2015).

NOTES: The data for 2013 for Spain relates to 2012.

3.2 **Pharmaceutical expenditure as a share of health expenditure has declined** for many of the leading OECD economies and most particularly since 2008, according to the OECD Health Expenditure indicators. Although this data series is incomplete for the UK, the trend until 2008 also demonstrated a significant decline in pharmaceutical expenditure as a share of total health expenditure.

Pharmaceutical spending as a % of health spending, 2000 – 2013

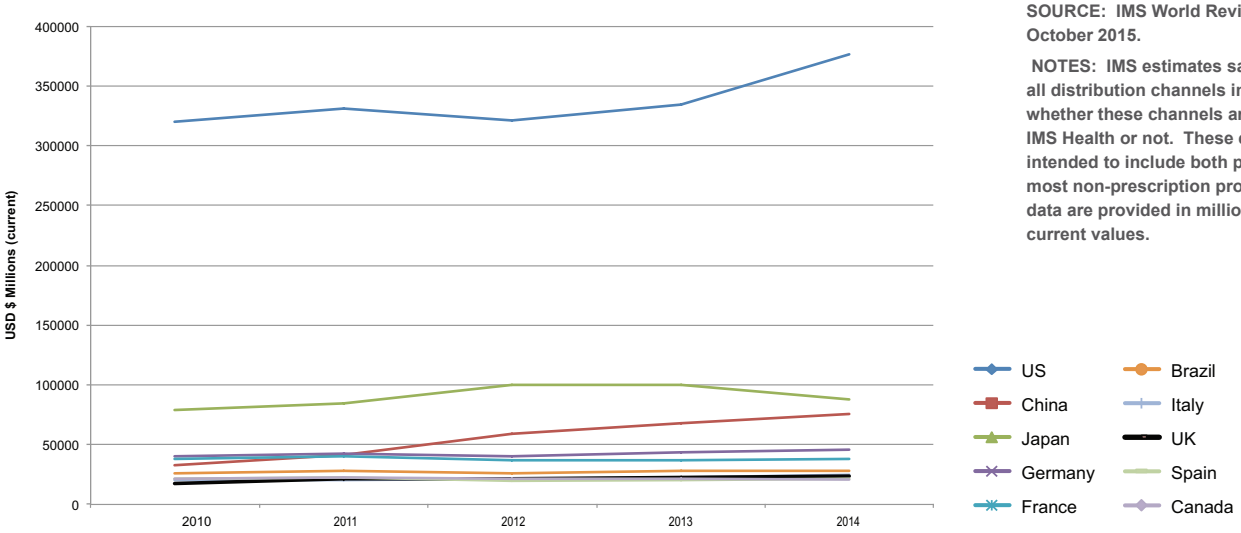


SOURCE: OECD (2015), Pharmaceutical spending (indicator). doi: 10.1787/998febf6-en; accessed October 19, 2015.

NOTES: The OECD Health expenditure and financing: Health expenditure indicators; The OECD defines pharmaceutical spending as expenditures on prescriptions medicines and over-the-counter products. In some countries, the data also include other medical non-durable goods (adding approximately 5% to the expenditure). The spending also includes pharmacists' remuneration when the latter is separate from the price of medicines. Pharmaceuticals consumed in hospitals are excluded. Final expenditure on pharmaceuticals includes wholesale and retail margins and value-added tax. This indicator is measured in percentage of total expenditure on health, in USD per capita (using PPP) and in percentage of GDP. https://data.oecd.org/healthres/pharmaceutical-spending.htm

3.3 Of the top 10 largest markets for pharmaceuticals worldwide, **the United States continues to lead by a widening margin.** However, important growth is also seen in **China,** which is now nearly tied with **Japan** as the second largest market. Over this period, Japan has reversed its growth in total sales. The other leading markets are much more closely grouped with less change in overall sales.

Worldwide pharmaceutical markets Top 10 Countries



SOURCE: IMS World Review, accessed October 2015.

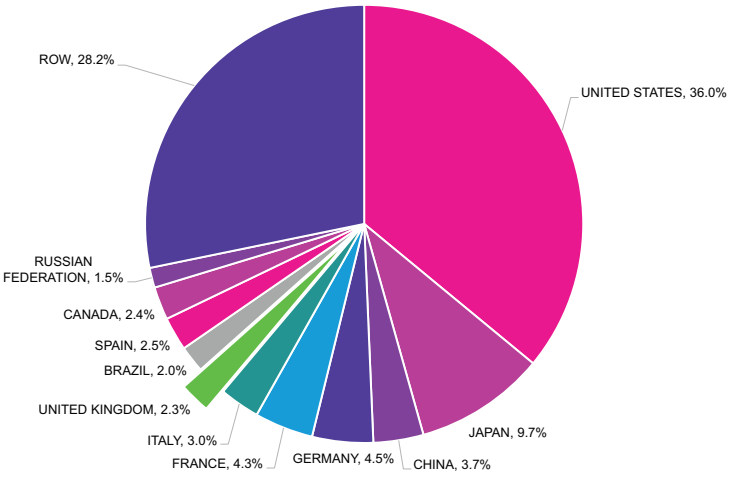
NOTES: IMS estimates sales through all distribution channels in all countries, whether these channels are audited by IMS Health or not. These estimates are intended to include both prescription and most non-prescription products. These data are provided in millions of US dollars, current values.

3.4 Considering the top 10 markets as a share of the total worldwide pharmaceutical market gives an easier view of the dynamics, particularly if we contrast the figures from 2010 with those of 2014. Again, we note the continued dominance of the US market as part of the world total, and even more notably the growth in share of **China's pharmaceutical market.** The **UK has also grown in relative size, although the growth is modest.**

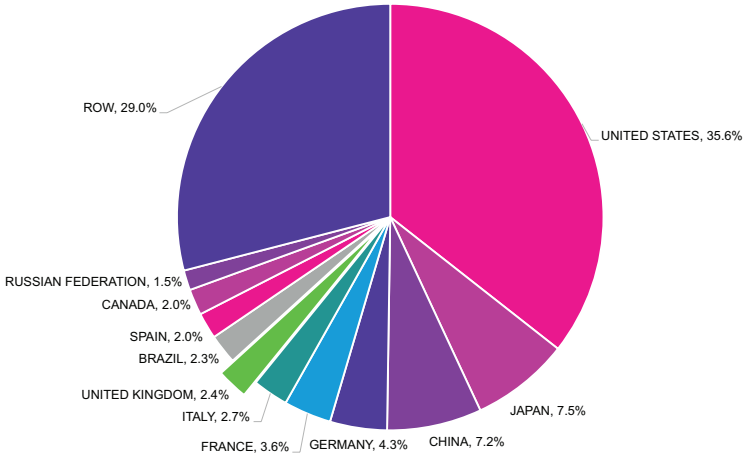
SOURCE: IMS World Review, accessed October 2015.

NOTES: IMS estimates sales through all distribution channels in all countries, whether these channels are audited by IMS Health or not. These estimates are intended to include both prescription and most non-prescription products. These data are provided in millions of US dollars, current values.

Share of world pharmaceutical market 2010 for leading pharmaceutical markets



Share of world pharmaceutical market 2014 for leading pharmaceutical markets



Share of the Global Medicines Market

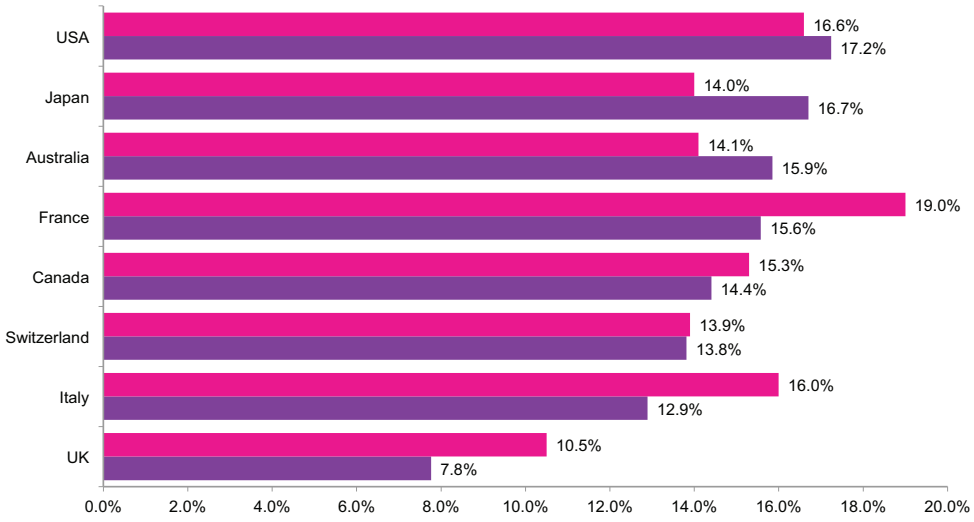
	2010	2011	2012	2013	2014
UNITED STATES	35.98%	34.40%	33.23%	33.66%	35.59%
JAPAN	9.65%	10.38%	10.39%	8.49%	7.46%
CHINA	3.70%	4.27%	6.06%	6.81%	7.18%
GERMANY	4.50%	4.39%	4.13%	4.38%	4.32%
FRANCE	4.34%	4.15%	3.82%	3.78%	3.61%
ITALY	2.97%	2.94%	2.69%	2.79%	2.70%
UNITED KINGDOM	**2.29%**	**2.16%**	**2.19%**	**2.22%**	**2.38%**
BRAZIL	1.97%	2.27%	2.24%	2.30%	2.25%
SPAIN	2.48%	2.33%	2.04%	2.07%	1.99%
CANADA	2.44%	2.32%	2.27%	2.16%	1.97%
RUSSIAN FEDERATION	1.47%	1.60%	1.68%	1.70%	1.51%

SOURCE: IMS World Review, Accessed October 27, 2015.

NOTES: IMS estimates sales through all distribution channels in all countries, whether these channels are audited by IMS Health or not. These estimates are intended to include both prescription and most non-prescription products. These data are provided in millions of US dollars, current values.

3.5 Considering **only recently launched medicines** (within the previous 5 years), the relative shares of different countries show differences both within the peer group and across the years 2009 and 2013. Between 2009 and 2013, the US, Japan and Australia increased their relative share for newly launched medicines, whilst the shares of European countries (with the exception of Switzerland, which had relatively little change) declined. The **UK**, already with the **relatively lowest share of newly launched medicines** in this peer group in 2009, **declined further by 2013.**

Market shares for medicines launched in the previous 5 years

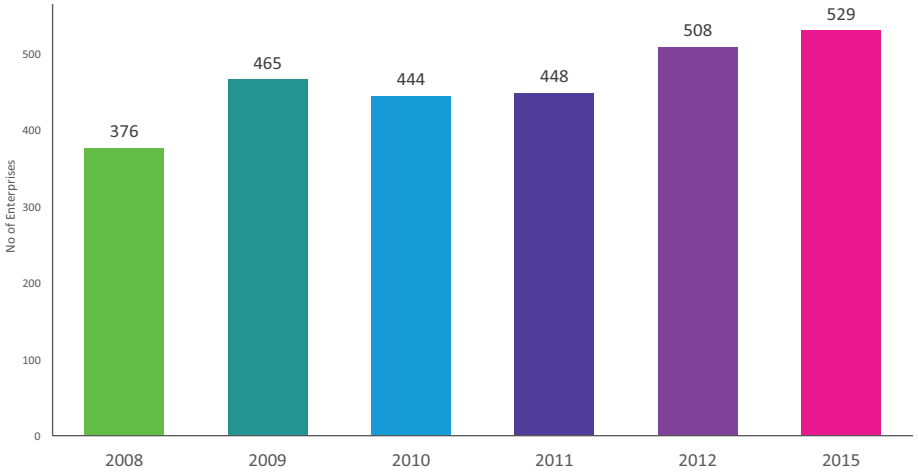


SOURCE: IMS World Review Analyst 2014.

NOTES: The analysis above uses IMS Midas definition for new products, which is broader than new molecular entities (NMEs) and, for example, will include branded generics. Where possible new branded generics have been excluded (these will be formulations with significant sales).

3.6 In the UK, the **biopharmaceutical industry represents an important sector** for economic growth. The **number of pharmaceutical enterprises has been increasing** since 2008. According to the Office for National Statistics, by 2013 the number of enterprises operating in the UK was 529.

Number of pharmaceutical enterprises operating in the UK

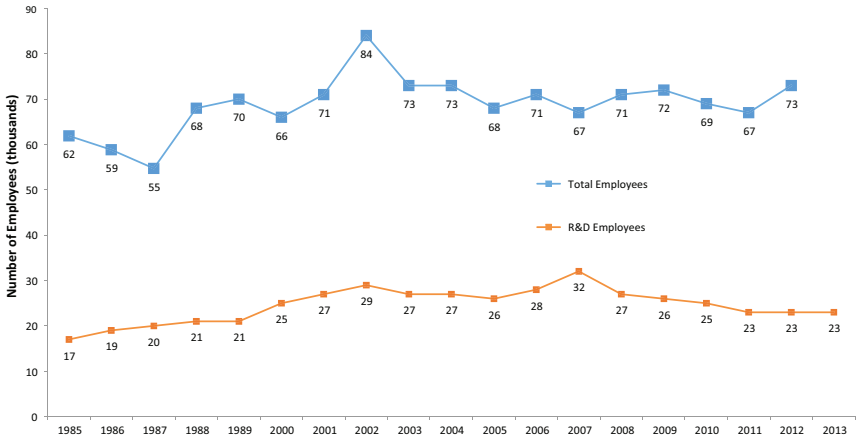


SOURCE: Office for National Statistics. Annual Business Survey 2013.

NOTES: The data relates to the manufacture of basic pharmaceutical products and pharmaceutical preparations, SIC (2007) 21. Enterprises here defined as VAT registered organisations self-referring as a manufacturer of basic pharmaceutical products and pharmaceutical preparations.

3.7 In the UK, the **biopharmaceutical industry represents an important employer** for high value jobs. According to the Office for National Statistics, the number of jobs reached **73,000 in 2013, with 23,000 of those jobs dedicated to R&D.**

UK pharmaceutical industry employees, 1995 - 2013 (thousands)

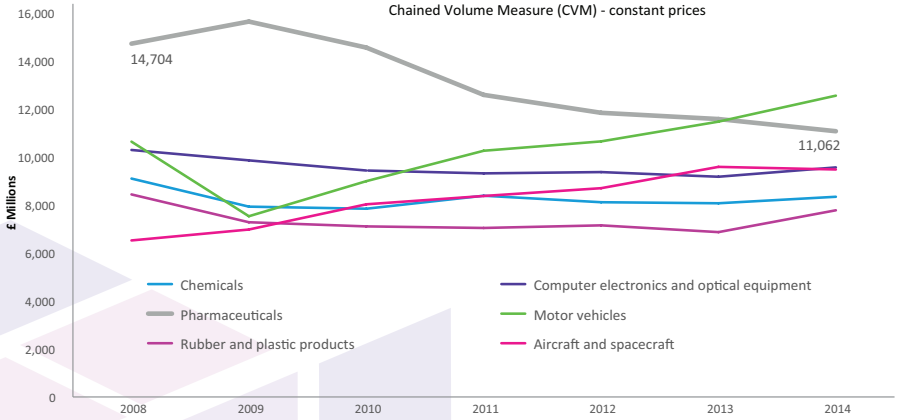


SOURCE: Office for National Statistics. Annual Business Survey 2013 (provisional), Section C, Manufacturing, Release date 13 November 2014; Office for National Statistics Business Enterprise Research and Development, 2013.

NOTES: Total employment figures for the Pharmaceutical industry for 2013 have been suppressed by the Office for National Statistics because the information is suppressed to avoid disclosure, according to the notes in the Annual Business Survey. The ONS reported employment statistics use UK Standard Industrial Classification of Economic Activities 2007 (UK SIC 2007). Inquires suggest that research and development enterprises have been excluded since 2008. Therefore, since 2008 manufacturing employment statistics from the Annual Business Survey have been added to BERD employment statistics. This is not a perfect solution and there may be some overlap.

3.8 In terms of Gross Value Added (GVA) to the UK economy, the pharmaceuticals industry **remains a leading sector contributing to wealth.** However, this contribution has been in **decline since 2009**, reflecting the loss of operations and manufacturing activity from the UK.

Gross Value Added (GVA)

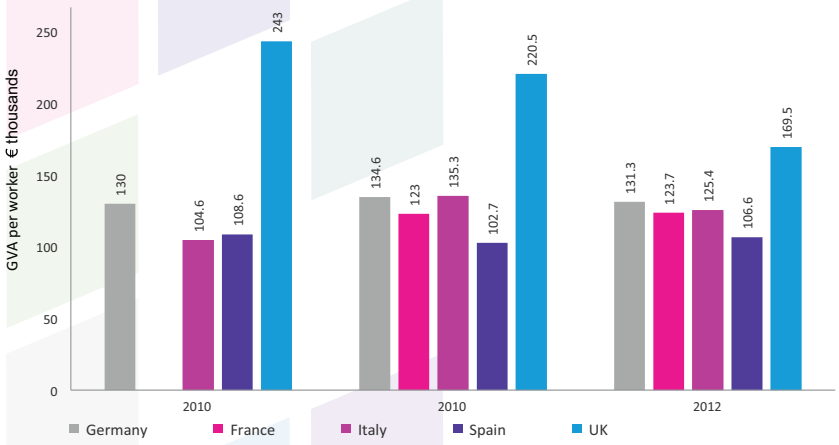


SOURCE: Office for National Statistics

NOTES: Gross Value Added (GVA) figures are calculated in pounds millions using the Chained Volume Measure (CVM)-constant prices method. GVA measures the contribution to the economy of each individual producer, industry or sector in the United Kingdom. For the Annual Business Survey the "production" approach for measuring GVA is used. The 'production' approach to estimating GDP looks at the contribution of each economic unit by estimating the value of an output (goods or services) less the value of inputs used in that output's production process.

3.9 Comparing Gross Value Added (GVA) per worker in the pharmaceutical industry across the European "Big 5" countries (UK, France, Germany, Italy, Spain), the **UK retains the highest GVA per worker;** however this value is in decline, whereas the other countries values' are relatively stable. Each euro of a pharmaceutical sector worker's pay generated an **average of €3.45 of product** over the period 2008 to 2012. The other sectors generated comparable average returns of €1.62 to €2.21 for each euro of workers' pay.

Gross Value Added (GVA)



SOURCE: Eurostat

NOTES: The data for France were not available for 2008. 2009 and 2011 have been omitted because of data availability issues. GVA measures the contribution to the economy of each individual producer, industry or sector in the United Kingdom. For the Annual Business Survey the "production" approach for measuring GVA is used. The 'production' approach to estimating GDP looks at the contribution of each economic unit by estimating the value of an output (goods or services) less the value of inputs used in that output's production process.

Investing in Innovation

The drive for innovation in medicines is clear – there are many diseases which remain untreated and opportunities to improve healthcare for patients.The challenge is how to keep up with the rapid pace of scientific advances and incorporate these breakthroughs into treatments. Our members commit substantial investment in Research & Development to make this possible.

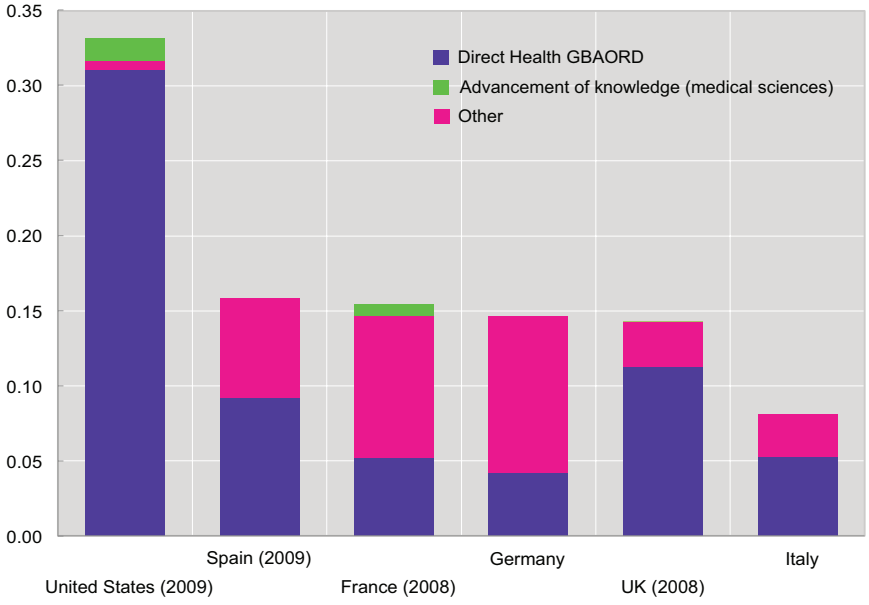
Any candidate medicine begins with the research and investment in discovery research to understand the disease biology, target identification and validation, proof of principle and proof of concept efforts for a lead compound, followed by refinements of the lead compound and pre-clinical safety testing. These candidate treatments are then explored in clinical settings and beyond to establish how best to further develop and then use these valued treatments. However, the journey from idea to implementation of a treatment for care is fraught with considerable scientific uncertainty and risk, and most ideas never make it through to a patient, although they do play a role in the progress of science.

It takes a long time to make this journey, on average 10 to 12 years, with clinical trials alone taking six to seven years on average[1]. Some industry analysts have calculated average costs for developing and licensing a new medicine at well over £1 billion. A recent Tufts Center for the Study of Drug Development (CSDD) estimated costs could reach $2.6 billion[2]. Overall, in 2014, the estimate was that the research-based pharmaceutical industry collectively spent over $137 billion on R&D annually[3].

In this section, we will review the investment made into R&D for health and specifically medicines and what role the UK plays in this broader global activity.

4.1 Medicines are only one part of investment in research in healthcare. Global investment in healthcare research is an important component, but a difficult metric to obtain because of the variation in funding types and organisations supporting this work globally. Such a measure includes government, the private sector and the academic / non-profit sectors. It is easiest to identify government funding for R&D related to public health, as defined by the OECD Frascati Manual. The United States is the largest funder for GDP spent on health R&D, but the data below also show the difference in channels for funding, with non-oriented R&D funding and academic funding ("Advancement of knowledge") playing a greater role in European countries.

Public funding of health-related R&D, 2010



SOURCE: OECD STI Scoreboard 2011, "Health Innovation". OECD estimates based on Research and Development Database, May 2011 and national sources.

NOTES: Government budget appropriations or outlays for R&D (GBAORD) measures the funds committed by the federal/central government for R&D. It can be broken down by various socioeconomic objectives, including health care. Advancement of knowledge comprises non-oriented R&D and general university funds (the estimated R&D content of government block grants to universities). Other includes other relevant national and international categories such as general support for R&D in hospitals4.

1 A drug target is a molecular structure in the body that, when it interacts with a potential drug compound, produces a clinical effect, such as treatment or prevention of disease.1 Pharmaceutical Research and Manufacturers of America (PhRMA). Biopharmaceutical Research & Development: the Process Behind New Medicines. 20 (Washington, DC, 2015).

The United States leads by far the amount of **government expenditure on health R&D** expenditure, followed by the United Kingdom. The **UK has increased the investment by government in health R&D steadily since 2000.**

Government funding in Health R&D, selected countries

	Canada	France	Germany	Italy	Japan	Spain	Sweden	United Kingdom	United States
	US Dollar, millions	US Dollar, millions	US Dollar, millions	US Dollar, millions	US Dollar, millions	US Dollar, millions	US Dollar, millions	US Dollar, millions	US Dollar, millions
2000	517	785	602	624	823	292	23	1500	18766
2001	706	918	708	733	902	132	15	1623	21741
2002	856	993	731	..	964	492	15	1688	24754
2003	943	920	793	..	1032	575	24	1818	27335
2004	966	938	817	..	1040	751	24	1941	29346
2005	1084	1060	859	1093	1076	763	24	1977	29871
2006	1141	964	946	1122	1133	1303	31	2226	29702
2007	1336	1049	1062	1664	1178	1529	18	2280	31080
2008	1336	1090	1056	1554	1250	1380	18	2507	31054
2009	1426	1284	1237	1296	1246	1373	30	2778	43926
2010	1470	1353	1252	1273	1466	1562	60	2747	34206
2011	1355	1353	1394	1254	1480	1500	45	2756	33536
2012	1406	1318	1612	1190	1658	952	44	2714	33924
2013	..	1332	1603	1069	1651	1296	62	2901	32454
2014	..	1282	1672	..	1642	..	63	..	33993

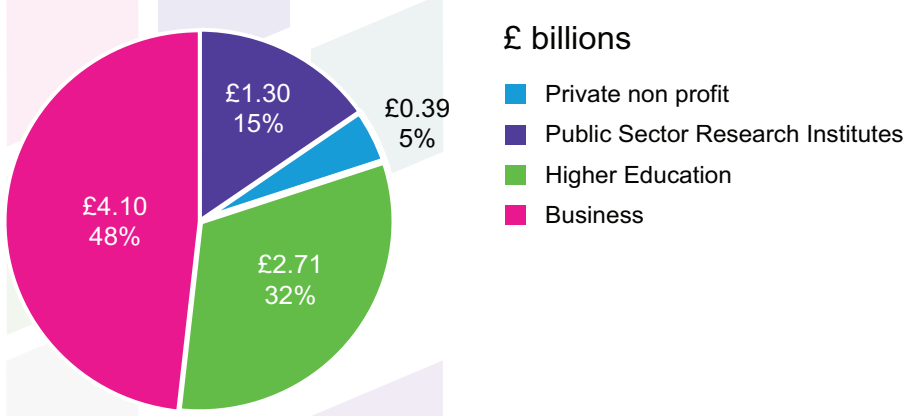
Legend:	
a:	Break in series with previous year for which data is available
b:	Secretariat estimate or projection based on national sources
c:	National estimate or projection
h:	Federal or central government only
p:	Provisional
s:	Unrevised breakdown not adding to the revised total
v:	The sum of the breakdown does not add to the total

SOURCE: OECD STAN database (Science, Technology and Patents) accessed 27 October, 2015.

NOTES: The OECD Structural Analysis (STAN) database defines total expenditure on health as the sum of expenditure on activities that – through application of medical, paramedical and nursing knowledge and technology – has goals of: promoting health and preventing disease, curing illness and reducing premature mortality, caring for persons affected by chronic illness who require nursing care, caring for persons with health-related impairments, disability and handicaps who require nursing care, assisting patients to die with dignity, providing and administering public health, providing and administering health programmes, health insurance and other funding arrangements. Legend provides notes for the different data series, as provided by the OECD.

4.2 In the UK, **the total national expenditure on all R&D** (the Gross Domestic Expenditure on R&D, or GERD) reached £28.9 billion in 2013, according to the Office for National Statistics. This represented an increase by 7.3% over the past 5 years, and 13.3% over the past 10. The UK Clinical Research Collaboration has calculated the total UK health-related R&D figures, now published in the UK Health Research Analysis 2014 together with funding flows (link below)[5]. According to this analysis, national expenditure has declined since 2009/2010 (£9.28 billion, price adjusted) to an estimate of £8.5 billion in 2014. Much of that difference reflects a reduction in business expenditure on R&D.

UK health research expenditure by performing sector, 2014

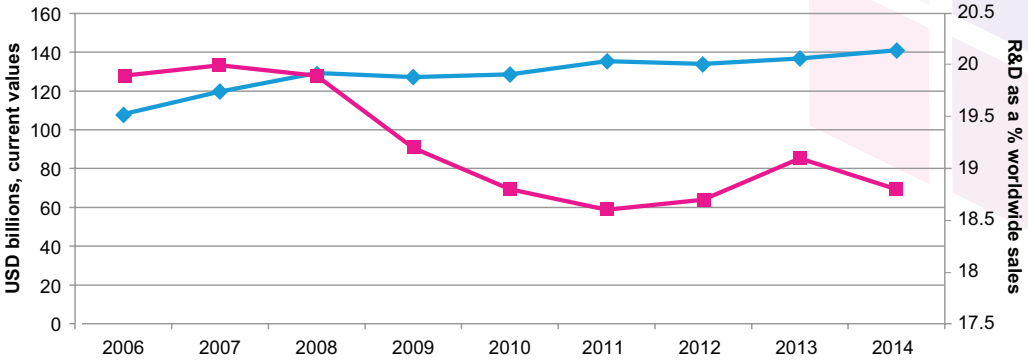


SOURCE: UK Clinical Research Collaboration (CRC). 2015. "UK Health Research Analysis, 2014", pp 21-22. http://www.ukcrc.org/research-coordination/health-research-analysis/uk-health-research-analysis/

NOTES: For this analysis, the UK CRC team followed a "top down" approach, using information on total research and development activity across the research performing sectors. This is the second estimation of these figures, following the previous analysis in the 2009/10 report. The estimation is modelled on the Gross Expenditure in Research and Development (GERD), and is detailed in Appendix 4 of the report.

4.3 According to EvaluatePharma[6], the **worldwide pharmaceutical industry invested over $1.2 trillion in R&D** in the decade from 2004 to 2014 and they forecast an annual investment of $162 billion by 2020. The figures below demonstrate that this **investment is growing moderately**, with only a recent decline in 2012 followed by a return to growth in worldwide R&D expenditure. The R&D intensity (R&D expenditure as a share of sales) however has declined, although at 18.8% in 2014, still one of the highest of any sector globally. **The US retains the highest share of R&D expenditure. In Europe, the UK has the highest share** if we exclude exchange rate effects.

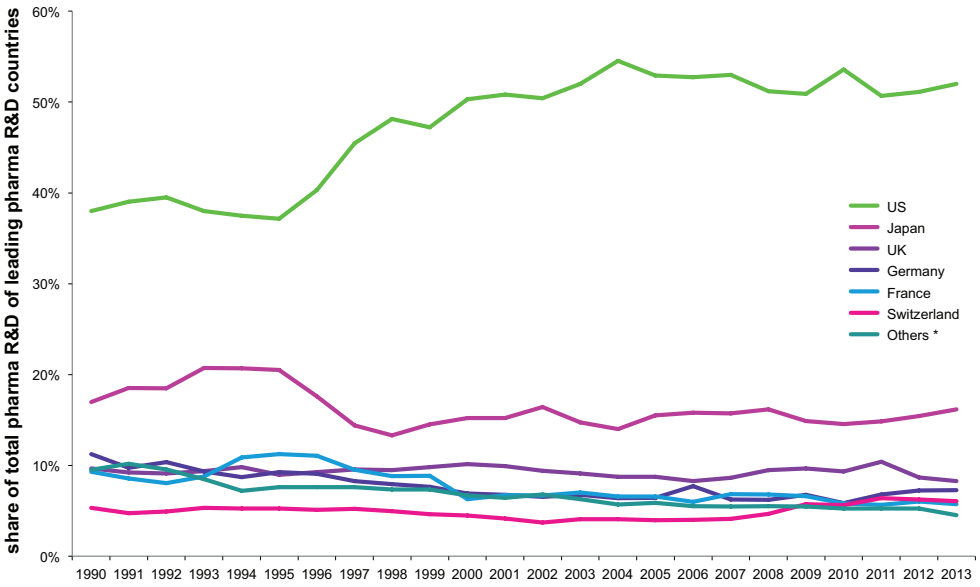
Worldwide Pharmaceutical R&D expenditure



SOURCE: EvaluatePharma, WORLD PREVIEW 2014: OUTLOOK TO 20206, p. 15.

NOTES: EvaluatePharma date this analysis to 1st June 2014. Industry sales are based on the top 500 pharmaceutical and biotech companies.

Share of Total Pharmaceutical R&D of Leading Pharma R&D Countries - 2000 Fixed Exchange Rates



SOURCE: ABPI/Office of Health Economics calculations based on National Trade Association reported expenditure figures.

NOTES: The chart figures are based upon national trade association reported expenditure levels and may not reflect official statistics. "Others" countries include Australia, Ireland, Italy, Netherlands, Spain and Sweden. The chart uses exchange rates fixed at 2000 levels. If actual exchange rates are used, the relative shares of European countries change, with the UK declining in relative value.

4.4 The Pharmaceutical Research and Manufacturers of America (PhRMA) association surveys its members annually and it explores the trend in **PhRMA Members total expenditure on R&D**. The figure below describes an earlier decline in expenditure (2011 and 2012) and a return to growth in 2013. The R&D intensity is also increasing, rather than decreasing over that period, suggesting that the amount of sales for these companies has declined relative to the relatively small growth in R&D expenditure.

The survey also explores the R&D expenditure of members spent in the US (PhRMA US R&D), generally leading global multinational biopharmaceutical companies. For this group of companies, the US retains the great majority of R&D expenditure.

R&D Expenditure for PhRMA Member Companies

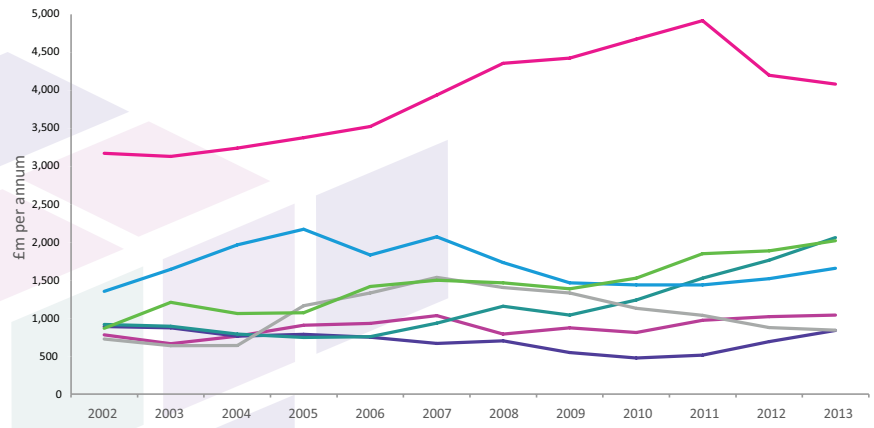
SOURCE: PhRMA 2015 Profile, Appendix, Tables 1 and 2; accessed October 17, 2015. http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf

NOTES: PhRMA collects this information through its Annual Membership Survey. All figures include company-financed R&D only. US R&D (referred in the Profile as Domestic R&D) includes all R&D expenditures within the US by all PhRMA member companies. A list of PhRMA member companies is available in the 2015 Profile (pp 61-2) and online (http://www.phrma.org/about/member-companies).

4.5 **In the UK, biopharmaceuticals remain the highest R&D spending sector**, although the level of investment has declined in recent years. The sector reached a peak in its share of overall UK business expenditure on R&D in 2010, with a share of 29% of the total. According to the 2013 survey, the biopharmaceutical industry spent **£4.1 billion** in the UK on R&D[7]. The significant decline coincides with some important closures of R&D activities and sites amongst biopharmaceutical companies. The next largest spending sectors are motor vehicles and parts and computer programming & information services. Aerospace has also seen a return to growth in R&D after a decline.

The UK is a relatively R&D intensive country for pharmaceuticals, with an intensity (that is, UK R&D expenditure as a share of UK sales) of **34%** in 2013. The R&D intensity for pharmaceuticals in the UK has been considerably higher than other sectors, until recently with the sharp increase in the R&D intensity share of computer programming & information systems since 2010.

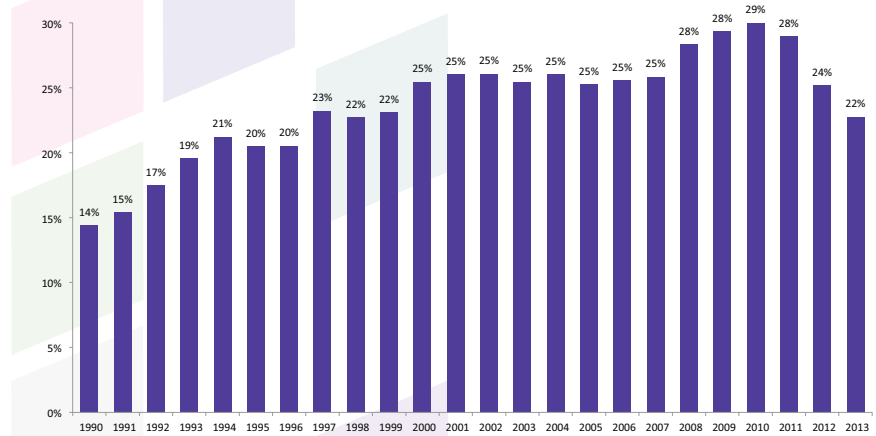
Leading industries for UK R&D expenditure



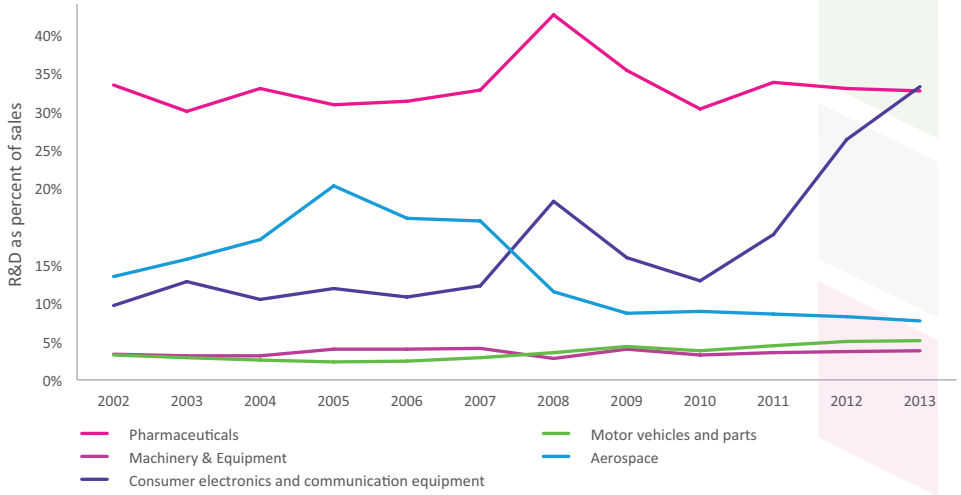
SOURCE: UK Office for National Statistics (ONS), Business Enterprise Research and Development (BERD) survey 2013

NOTES: The BERD survey is conducted annually by ONS. As part of the 2013 survey, approximately 5,400 questionnaires were sent to businesses known to perform R&D. This included around 400 of the largest R&D spenders, which accounted for approximately 77% of the 2013 total R&D expenditure estimate. Smaller R&D performers and others believed to be performing R&D were selected using various sampling fractions. Industry product group and business employment size were the stratification variables. Completed questionnaire were returned by 5,112 businesses, representing a response rate of 95%. The data are reported irrespective of the residence of the ultimate owner, but overseas activities of affiliates of UK businesses are not included.

Pharmaceutical R&D as a percent of all industry R&D



Pharmaceutical R&D as a percent of all industry R&D

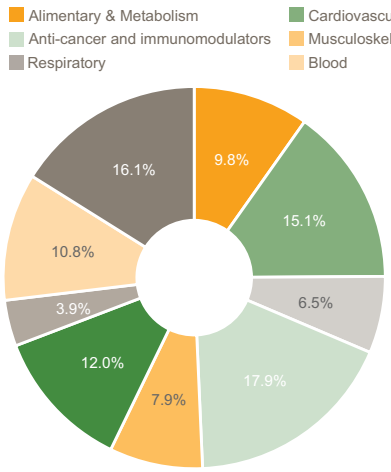


SOURCE: UK Office for National Statistics (ONS), Business Enterprise Research and Development (BERD) survey 2013

NOTES: The BERD survey is conducted annually by ONS. As part of the 2013 survey, approximately 5,400 questionnaires were sent to businesses known to perform R&D. This included around 400 of the largest R&D spenders, which accounted for approximately 77% of the 2013 total R&D expenditure estimate. Smaller R&D performers and others believed to be performing R&D were selected using various sampling fractions. Industry product group and business employment size were the stratification variables. Completed questionnaire were returned by 5,112 businesses, representing a response rate of 95%. The data are reported irrespective of the residence of the ultimate owner, but overseas activities of affiliates of UK businesses are not included.

4.6 A **comparison of R&D expenditure by therapeutic area in 2009 and 2014**, drawn from the Thomson Reuters CMR International Pharmaceutical R&D Factbook, highlights the substantial growth of anticancer and immunomodulators in the share of investment. In 2014, this share was nearly one third of all R&D expenditure, compared to 17.9% in 2009. Other areas have also seen an increase (alimentary and metabolism, respiratory and musculoskeletal research), whilst others have seen a decline (anti-infectives, nervous system and cardiovascular research programmes).

Total R&D expenditure in 2009 by Therapeutic area



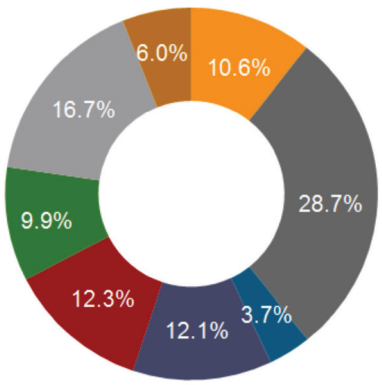
'OTHER' CATEGORY BREAKDOWN	%
Unknown	7
Genitourinary & sex hormones	3.7
Hormones (ex sex hormones & insulin)	1.8
Sensory	1.7
Various	1.6
Dermatologicals	0.3

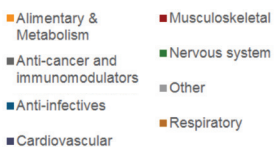
The proportion of total R&D expenditure by therapeutic area presented in this figure is based on data from 20 companies (7 Major, 13 Mid and Other) Total R&D expenditure represented = US$32.82bn

SOURCE: Thomson Reuters CMR International Pharmaceutical R&D Factbook 2010 and 2014; Drawn from the Industry R&D Investment Programme and reproduced with permission.

NOTES: Thomson Reuters CMR International undertakes a comprehensive benchmarking of international performance metrics, and some of this evidence is reproduced in its annual Pharmaceutical R&D Factbook. For details, please refer to http://cmr.thomsonreuters.com/. Presented is the distribution of total R&D expenditure in 2009 and 2014 by therapeutic area calculated from data provided by 20 companies in 2009 (7 Major, 13 Mid and other) within a total R&D expenditure of US $ 32.8 billion, and 9 companies in 2014 (6 Major and 3 Mid and other) within a total R&D expenditure of US $28.1 billion. Major companies are defined as those spending ≥US$ 2 billion in 2014 on ethical pharmaceutical R&D. Mid companies are defined as those spending ≥US$ 0.7 billion and <US$ 2 billion in 2014 on ethical pharmaceutical R&D. Other companies are defined as those spending <US$ 0.7 billion in 2014 on ethical pharmaceutical R&D.

Total R&D expenditure in 2014 by Therapeutic area

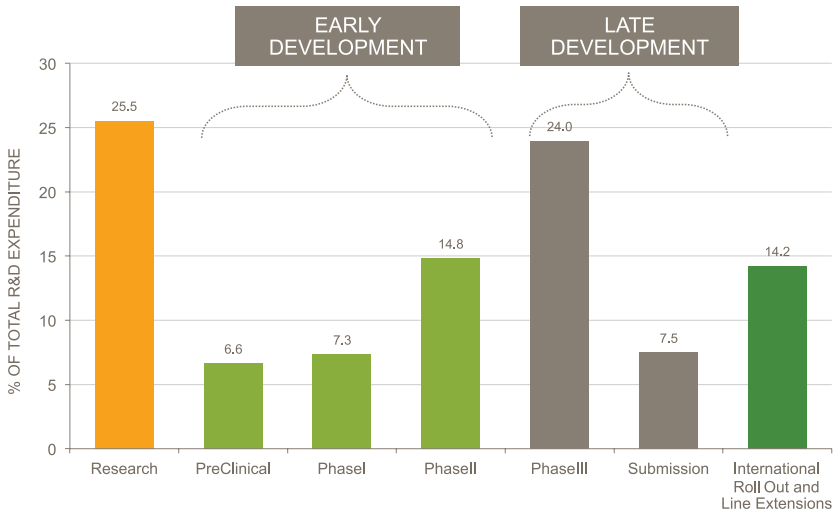




'OTHER' CATEGORY BREAKDOWN	%
Blood	3.5
Genitourinary & sex hormones	2.6
Hormones (exc sex hormones & insulin)	1.7
Dermatologicals	1.1
Sensory	0.4
Various	7.4

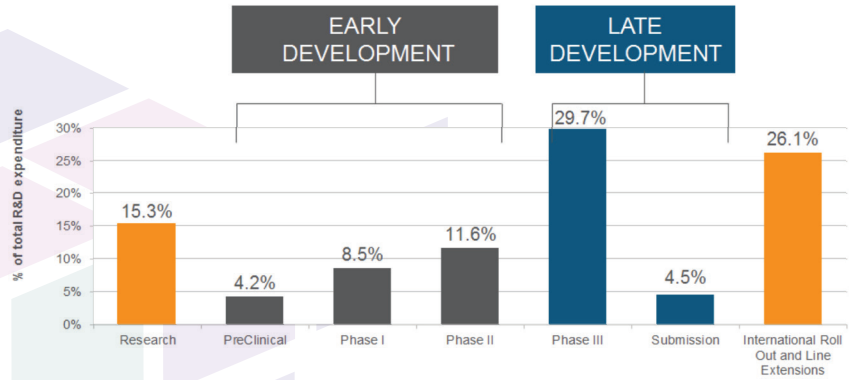
4.7 According to the Thomson Reuters CMR International Pharmaceutical R&D Factbook, the **structure of R&D expenditure by phase of development** by biopharmaceutical companies has changed between 2009 and 2014. **Expenditure on both Phase I and Phase III research has increased** as a share, whilst expenditure on research has declined. Both years are snapshots of expenditure and will reflect the state of the industry pipeline at that point, which will have an impact on the nature of investment required. However, there is a clear increase in roll-out and line extensions in the R&D investment programme, as companies seek to extend the value of the medicine beyond the original indication(s).

Total R&D expenditure in 2009 by each stage of R&D



This graph is based on data from 14 companies (5 Major, 9 Mid and Other)
Major companies are defined as those spending ≥US$ 2 billion in 2009 on ethical pharmaceutical R&D.
Mid and Other companies are defined as those spending <US$ 2 billion in 2009 on ethical pharmaceutical R&D.

Proportion of total R&D Expenditure in 2014 by phase of R&D



SOURCE: Thomson Reuters CMR International Pharmaceutical R&D Factbook 2010 and 2014; Drawn from the Industry R&D Investment Programme and reproduced with permission.

NOTES: Thomson Reuters CMR International undertakes a comprehensive benchmarking of international performance metrics, and some of this evidence is reproduced in its annual Pharmaceutical R&D Factbook. For details, please refer to http://cmr.thomsonreuters.com/. Presented is the proportion of R&D expenditure by stage of R&D calculated as an aggregate of the data supplied by 14 companies (5 Major, 9 Mid and Other) in 2009 and for 10 companies (8 Major, 2 Mid and Other) in 2014. Major companies are defined as those spending ≥US$ 2 billion in 2014 on ethical pharmaceutical R&D. Mid companies are defined as those spending ≥US$ 0.7 billion and <US$ 2 billion in 2014 on ethical pharmaceutical R&D. Other companies are defined as those spending <US$ 0.7 billion in 2014 on ethical pharmaceutical R&D.

Other definitions:

International roll out (including Line Extensions): Stage of R&D from 'First launch in first core market' onwards (e.g. Phase IV expenditure, regulatory fees, etc for further work to support the launch for the same indication in other markets).

Phase I: Stage of R&D from 'First human dose' to 'First patient dose'

Phase II: Stage of R&D from 'First patient dose' to 'First pivotal dose'

Phase III: Stage of R&D from 'First pivotal dose' to 'First submission'

Preclinical: Stage of R&D from 'First toxicity dose for the active substance' to 'First human dose'

Research: Stage of R&D up to the 'First toxicity dose for the active substance'.

Submission: Stage of R&D from 'First submission' to 'First launch'

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Driving Clinical Research to Deliver Medicines

Any candidate medicine has to undertake extensive studies in humans to demonstrate that it is safe and effective before it can be licensed for use in the UK. There have been **three key phases** of clinical research which collectively provide the evidence to support a decision on the relative benefits of a medicine for clinical use in comparison with its risks. The European Medicines Agency, the regulatory authority for Europe and comprised of Member State authorities such as the UK's Medicines and Healthcare products Regulatory Authority (MHRA), has launched pilots to explore **an adaptive pathway for clinical research** that may supersede the now familiar three-phase approach. Nevertheless, most medicines under development today follow this familiar development lifecycle.

Under this current paradigm, industry-sponsored clinical research represents an important share of clinical research. Companies will work with physician researchers to conduct the research with them, conducting the research to a specific plan (the study protocol). Often these studies will be held in several countries around the world simultaneously to collectively provide an evidence base for the medicine. From start to finish, the clinical development phase takes an average of 6 to 7 years, and **ultimately less than 12% of candidate medicines that enter clinical testing make it to approval**[1].

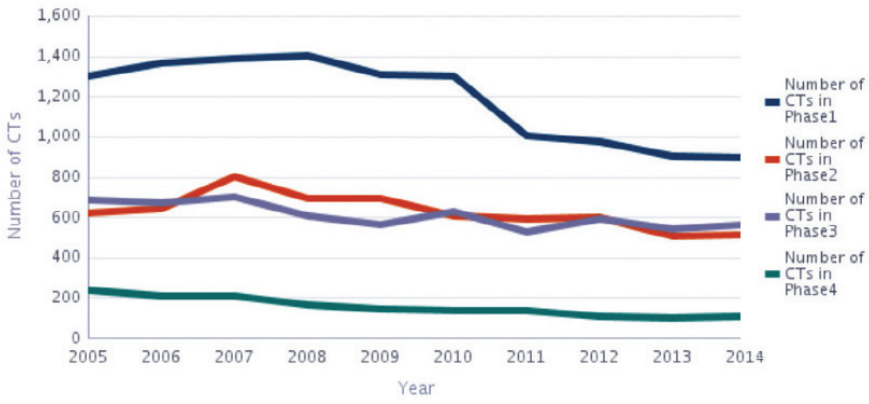
Clinical research is important to countries as a measure of the translational capacity of a healthcare system to bring concepts for new medicinal treatments into care. In the UK, the health research authorities in England, Scotland, Wales and Northern Ireland have been working to improve the environment and procedures for conducting clinical research, and progress is being made. In this section, we will review the measures for clinical research and medicine authorisations, using publicly available measures for the UK and globally.

5.1 A recent presentation by the European Medicines Agency presented data on the number of clinical trials (CTs) undertaken by Phase of research and by sponsor (commercial and non-commercial) registered on EudraCT, the European register of clinical research. **For commercial sponsors, the number of clinical trials declines over the period, but most noticeably for Phase 1** clinical trials and relative less so for Phase 2 and 3. Non-commercial clinical trials appear to have experienced a recent decline in numbers (2012-2014) across all phases.

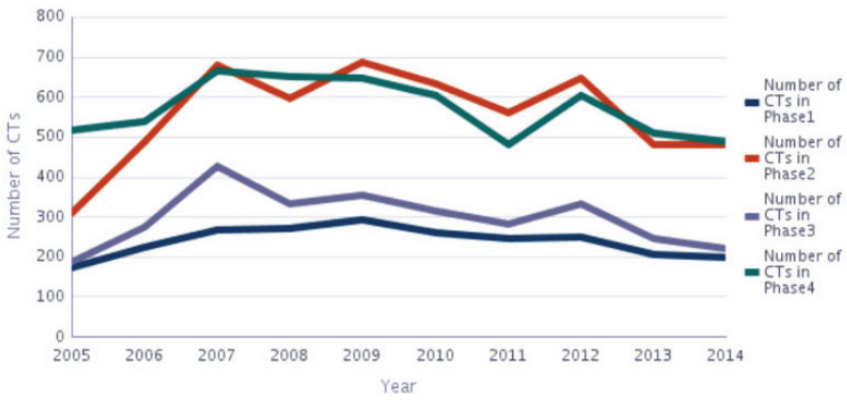
SOURCE: European Medicines Agency, The Clinical Trials Regulation EU No 536/2014 and Phase I Trials http://eufemed.eu.dedi884.your-server.de/fileadmin/user_upload/PC_1-1.1_Sweeney.pdf last accessed August 2015

NOTES: For further details, please see https://eudract.ema.europa.eu/ .

No of CTs by Comm vs Non-comm by year (2005 to 2014) and by phase (I-IV) Sponsor status: Commercial



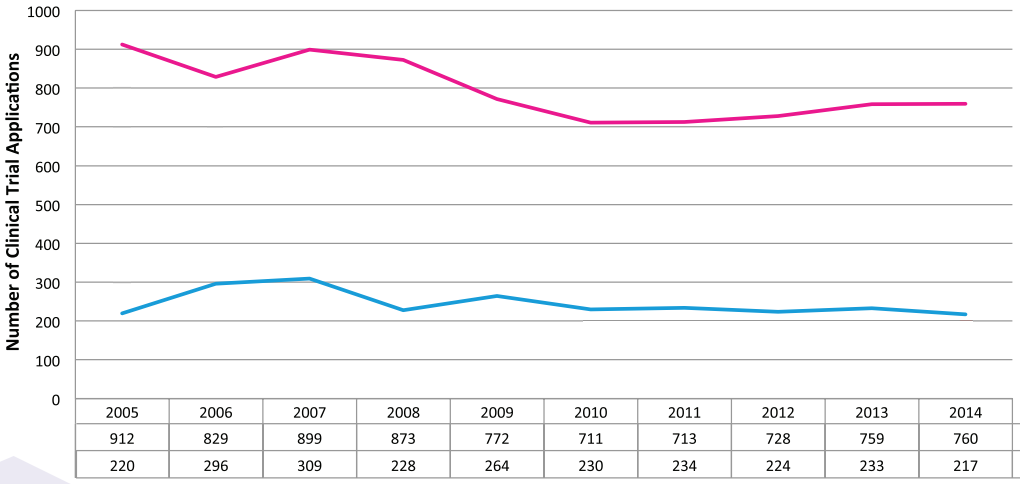
No of CTs by Comm vs Non-comm by year (2005 to 2014) and by phase (I-IV) Sponsor status: Non-commercial



5.2 In the UK, the Department of Business, Innovation and Skills recently published the Life Science Competitiveness Indicators, which reviewed the relative shares of patients recruited to global studies across all trial phases. This evidence revealed that the **UK has seen a decline its share of patients over time (2008 to 2012);** by 2012, this UK share was still substantially less than the US share, lower than Germany and Poland, and greater than France and the Czech Republic[2]. However, the data reveal that any analysis has to look at trends over a longer period, as there is considerable volatility in the numbers by year.

One way to measure clinical research is to review the clinical trial applications received by the UK regulator, the Medicines and Healthcare products Regulatory Authority (MHRA). According to the MHRA's figures, the **number of applications for clinical trials in the UK has declined** since 2005 but amounted to 760 applications received in 2014. Not all of these applications will have been supported, so the final number of clinical trials will be less. The UK National Institute for Health Research (NIHR) calculated that **more than 618,000 people participated in clinical research in the NHS in England in 2014,** with 35,000 participants recruited to studies sponsored by the biopharmaceutical industry (an increase of 35% over the previous year)[3]. To put this in global context, in 2013, biopharmaceutical companies sponsored 6,199 trials across the US involving 1.1 million participants[1].

Clinical Trial Applications Received by MHRA 2005-2014
All phases; Commercial and Non-Commercial



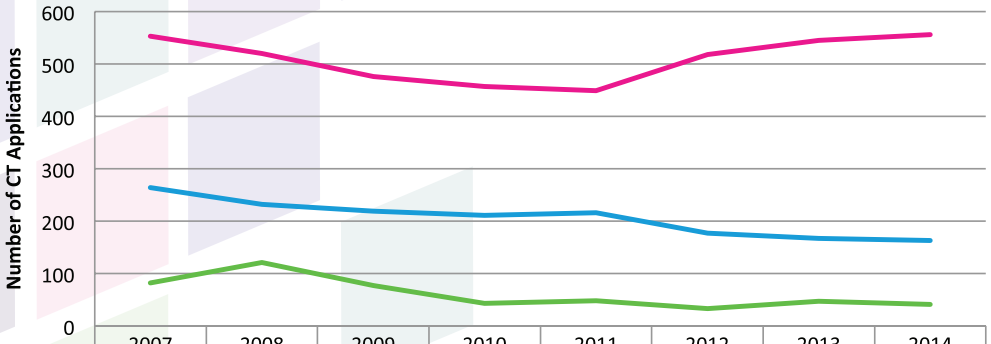
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Commercial	912	829	899	873	772	711	713	728	759	760
Non-commercial	220	296	309	228	264	230	234	224	233	217

SOURCE: Adapted from MHRA Clinical Trials for medicines: authorisation assessment performance; https://www.gov.uk/government/publications/clinical-trials-for-medicines-authorisation-assessment-performance last accessed August 2015

NOTES: MHRA last updated the data in July 2015. The data sets out the number of applications assessed by MHRA split out by phase and commercial and non-commercial sponsors.

5.3 The MHRA data for clinical trial applications by phase seems to mirror the EudraCT data described in 5.1. There is **a decline in Phase 1 and Phase 4** applications, but the **number of Phase 2/3 applications appears more consistent over time**, having returned in 2014 to their starting values in 2007.

UK Clinical Trial Applications by Phase



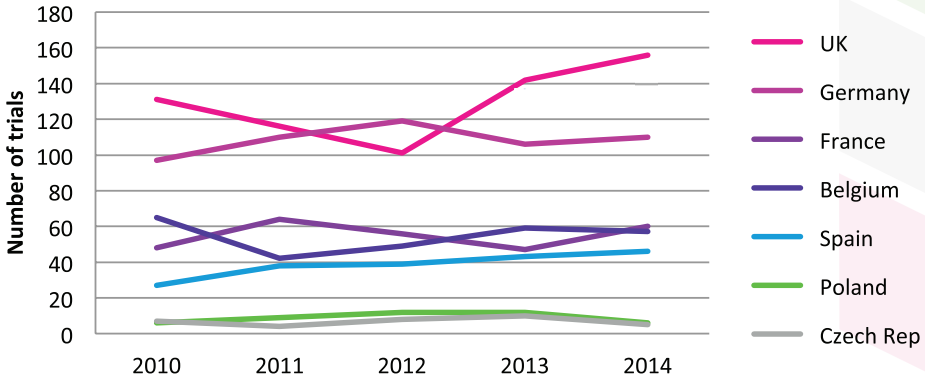
	2007	2008	2009	2010	2011	2012	2013	2014
Phase 1	264	232	219	211	216	177	167	163
Phase 2/3	553	520	476	457	449	518	545	556
Phase 4	82	121	77	43	48	33	47	41

SOURCE: Adapted from MHRA Clinical Trials for medicines: authorisation assessment performance; https://www.gov.uk/government/publications/clinical-trials-for-medicines-authorisation-assessment-performance last accessed August 2015

NOTES: MHRA last updated the data in July 2015. The data sets out the number of applications assessed by MHRA split out by phase and commercial and non-commercial sponsors.

5.4 Using Thomson Reuters Cortellis data, the evidence for the number of trials conducted for **Phase 1 clinical research clearly shows the strength of the UK**, relative to other EU countries including Germany.

Phase 1 Clinical Trials UK vs Europe

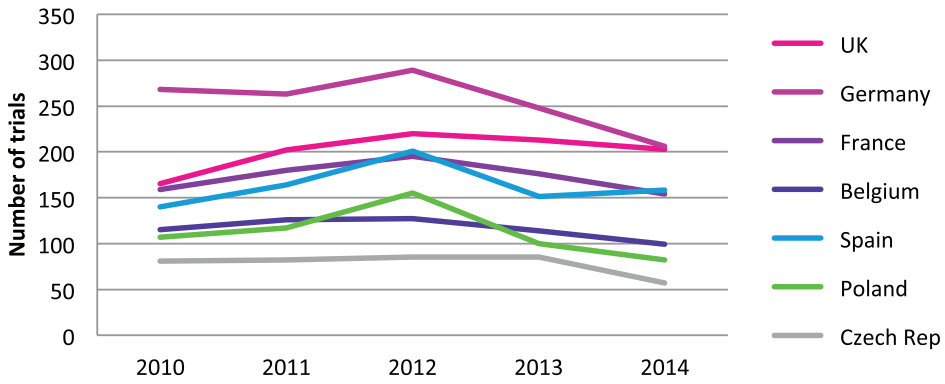


SOURCE: Thomson Reuters Clinical Trial Intelligence™, accessed September – October 2015.

NOTES: Data was collected from the Thomson Reuters Clinical Trial Intelligence™ using the following criteria: trial start date (1st January 2010 – 31st December 2014), phase (1,2, 3, unspecified), and country (UK, Germany, France, Belgium, Spain, Poland, Czech Republic). Only trials related to pharmaceutical drug development and molecular/ biological entities were included. Only commercial trials were included. Collaborative trials were only included if one or more partners were a commercial organisation.
All therapeutic areas were included in this analysis.

5.5 The **UK is competitive for Phase 2 clinical trials** in Europe, according to the Thomson Reuters analysis. By 2014, the number of Phase 2 trials in the UK was roughly equal to that of leading country, Germany.

Phase 2 Clinical Trials UK v Europe

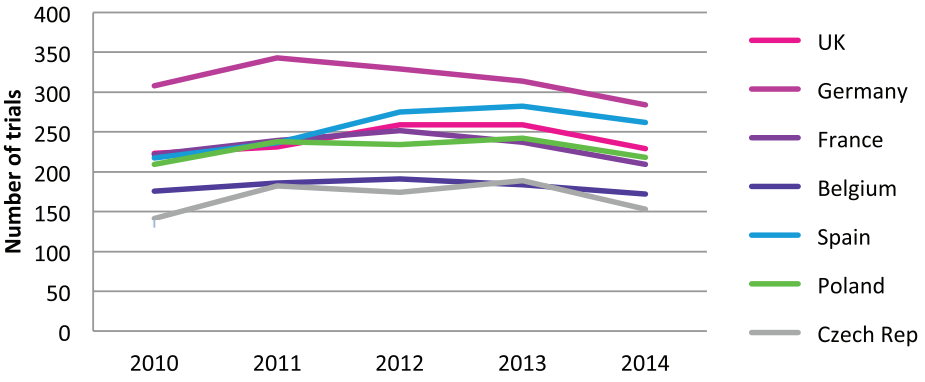


SOURCE: Thomson Reuters Clinical Trial Intelligence™, accessed September – October 2015.

NOTES: Data was collected from the Thomson Reuters Clinical Trial Intelligence™ using the following criteria: trial start date (1st January 2010 – 31st December 2014), phase (1,2, 3, unspecified), and country (UK, Germany, France, Belgium, Spain, Poland, Czech Republic). Only trials related to pharmaceutical drug development and molecular/ biological entities were included. Only commercial trials were included. Collaborative trials were only included if one or more partners were a commercial organisation.
All therapeutic areas were included in this analysis.

5.6 According to this data, the **UK has been the site for fewer Phase 3 trials** than in other countries in Europe, but still averaging ahead of some notable competitors (France, Poland). What is interesting about this evidence is the overall recent decline in the number of Phase 3 trials for all compared countries in Europe. This may not be a "vote away" from Europe, but a reflection of the strong global competition for clinical trials.

Phase 3 Clinical Trials UK v Europe

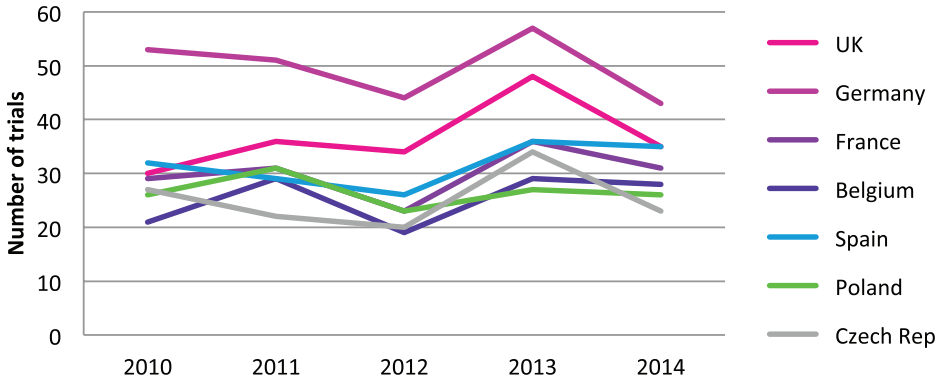


SOURCE: Thomson Reuters Clinical Trial Intelligence™, accessed September – October 2015.

NOTES: Data was collected from the Thomson Reuters Clinical Trial Intelligence™ using the following criteria: trial start date (1st January 2010 – 31st December 2014), phase (1,2, 3, unspecified), and country (UK, Germany, France, Belgium, Spain, Poland, Czech Republic). Only trials related to pharmaceutical drug development and molecular/ biological entities were included. Only commercial trials were included. Collaborative trials were only included if one or more partners were a commercial organisation.
All therapeutic areas were included in this analysis.

5.7 Exploring the data for clinical trials by therapeutic focus, we can see areas where specific countries may have competitive advantage based on scientific excellence and clinical opportunity. For **cardiovascular treatments, Germany and the UK are both significant sites for clinical research.**

Clinical Trials for Cardiovascular Treatments

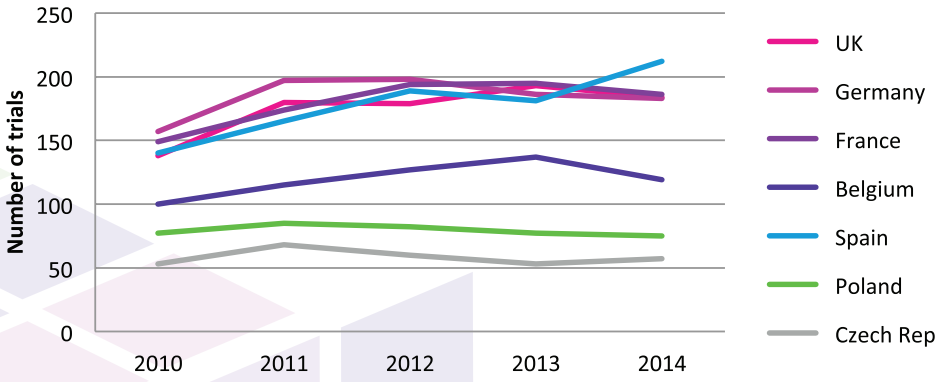


SOURCE: Thomson Reuters Clinical Trial Intelligence™, accessed September – October 2015.

NOTES: Data was collected from the Thomson Reuters Clinical Trial Intelligence™ using the following criteria: trial start date (1st January 2010 – 31st December 2014), phase (1, 2, 3, and 4), and country (UK, Germany, France, Belgium, Spain, Poland, Czech Republic). Only trials related to pharmaceutical drug development and molecular/ biological entities were included. Only commercial trials were included. Collaborative trials were only included if one or more partners were a commercial organisation. This analysis focused on cardiovascular treatment trials only. Trials across multiple therapy areas were only included once. The therapy area in which they were included was determined by the trial's main purpose for study.

5.8 **Oncology clinical trials represent a higher share of clinical trials** in the dataset for all countries. The leadership position in Europe for oncology trials is clearly contested, with an interesting **increase in the number of trials in Spain** over the period. With all types and phases of trials included, it is difficult to explore whether there is any differentiation amongst countries in their comparative advantage for oncology clinical research. However, we note that the UK remains competitive for oncology trials, and the **number of trials in the UK increased** over the period.

Clinical Trials for Oncology Treatments

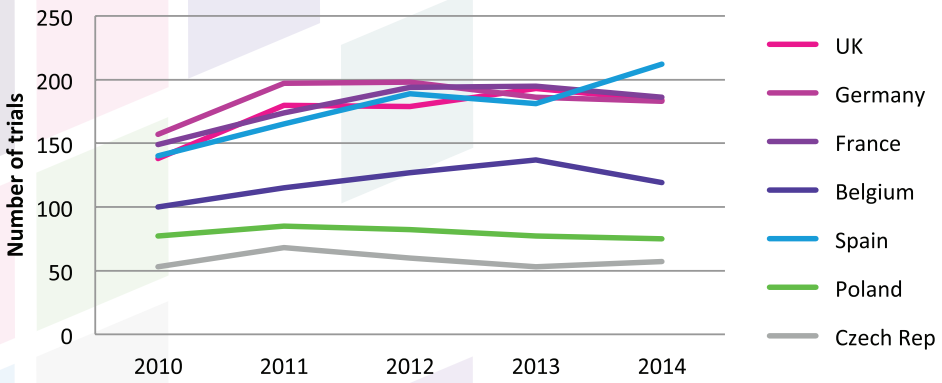


SOURCE: Thomson Reuters Clinical Trial Intelligence™, accessed September – October 2015.

NOTES: Data was collected from the Thomson Reuters Clinical Trial Intelligence™ using the following criteria: trial start date (1st January 2010 – 31st December 2014), phase (1, 2, 3, and 4), and country (UK, Germany, France, Belgium, Spain, Poland, Czech Republic). Only trials related to pharmaceutical drug development and molecular/ biological entities were included. Only commercial trials were included. Collaborative trials were only included if one or more partners were a commercial organisation. This analysis focused on oncology treatment trials only. Trials across multiple therapy areas were only included once. The therapy area in which they were included was determined by the trial's main purpose for study.

5.9 Apart from the UK, **most countries saw a fall in the number of clinical trials** for treatments related to **diseases of the nervous system.** This decline was particularly marked in Germany and France. Overall, the number of trials reported was fewer than oncology, but more than for cardiovascular disease. The **UK had the same number of trials by 2014 as the leading country, Germany.**

Clinical Trials for Treatments related to the nervous system



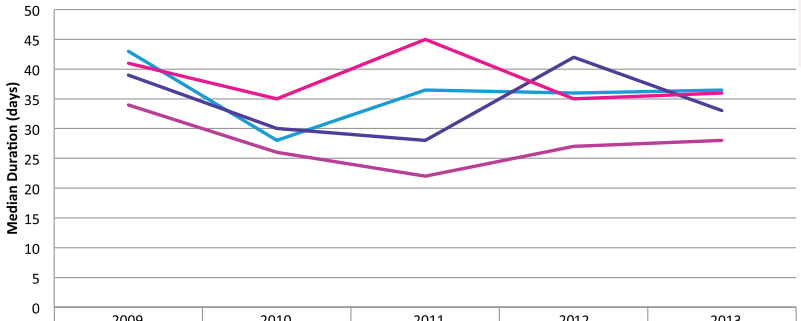
SOURCE: Thomson Reuters Clinical Trial Intelligence™, accessed September – October 2015.

NOTES: Data was collected from the Thomson Reuters Clinical Trial Intelligence™ using the following criteria: trial start date (1st January 2010 – 31st December 2014), phase (1, 2, 3, and 4), and country (UK, Germany, France, Belgium, Spain, Poland, Czech Republic). Only trials related to pharmaceutical drug development and molecular/ biological entities were included. Only commercial trials were included. Collaborative trials were only included if one or more partners were a commercial organisation. This analysis focused on trials for treatments related to the nervous system only. Trials across multiple therapy areas were only included once. The therapy area in which they were included was determined by the trial's main purpose for study.

5.10 Companies look for key metrics in comparing the relative performance of clinical research across countries. One such measure is the **time elapsed between site initiation to the first patient enrolled in a trial.** Using the Thomson Reuters CMR database, we have an indication of the comparative performance across some key European countries. This database is limited though, and so these data should be seen as indicative rather than definitive.

Reviewing the data, again it is clear that a moving average for such assessment is preferable. Averaging across the five years, **Poland has the shortest time lapse (average of 27.4 days) between site initiation and first patient enrolled,** followed by Germany (average of 34.4 days), France (average of 36 days) and the UK (average of 38.4 days). However, we note the improvement in performance in the **UK and that the UK, France and Germany are very similar in the time lapse between site initiation and first patient enrolled.**

Site Initiation to First Patient Enrolled 2009 - 2013



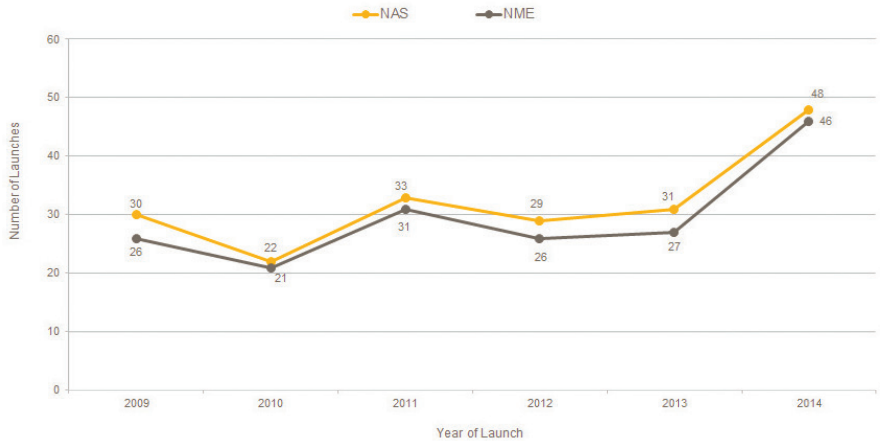
2009	2010	2011	2012	2013	
43	28	36.5	36	36.5	France
39	30	28	42	33	Germany
34	26	22	27	28	Poland
41	35	45	35	36	UK

SOURCE: Thomson Reuters CMR Database, accessed September – October 2015.

NOTES: The Thomson Reuters CMR Database reflects the responses of 26 participating companies, including a range of major companies (R&D expenditure greater than $2 billion) and smaller pharmaceutical companies. There are no Clinical Research Organisations (CROs) included in the sample, although the programme does collect data on outsourced studies. The CMR clinical programme only collects data on studies that are conducted to support a regulatory submission, and the data include Phase 1, 2, 3 and some Phase 4 trials (post-marketing / post-approval commitments). The majority of studies in the database are interventional, as the data collected are for studies that utilise an active substance.

5.11 The aim for all clinical research is to provide the evidence needed to secure marketing authorisation. Over the period 2009 to 2014, industry has seen a **growth in the number of new molecular entity and new active substance launches** worldwide. This is a good measure of the innovative activity of the industry, and the confirmation of welcome new treatments for patients.

Industry NAS and NME launches 2009 - 2014

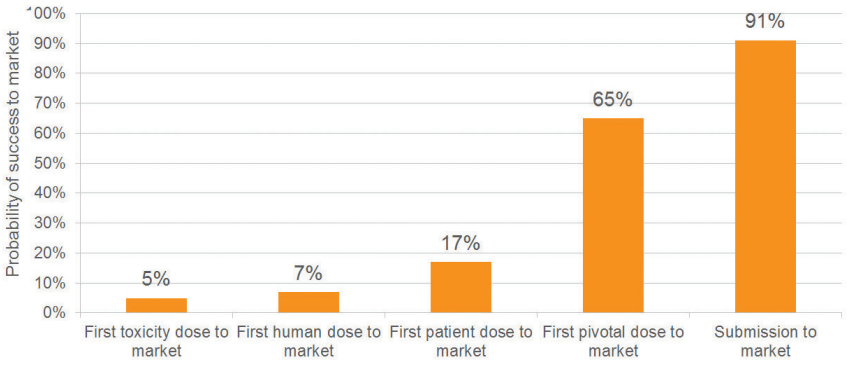


SOURCE: Thomson Reuters CMR International Pharmaceutical R&D Factbook 2010 and 2014; Drawn from the Industry R&D Investment Programme and reproduced with permission. Thomson Reuters CMR International Performance Metrics Programme/Source, Annual Survey of New Molecular Entity First Launches / New Medicine Launches 2009-2014: A complete guide to New Molecular Entities (NMEs) launched world-wide

NOTES: Number of New Molecular Entities (NME) / New Active Substances (NAS) launches: To compile this analysis, a survey of the global pharmaceutical industry was undertaken to identify all new molecular entities launched for the first time anywhere in the world for each year between 2009 and 2014.

5.12 The drug development cycle continues to be challenging and highly uncertain. Assessing outcomes for active substances filed previous, Thomson Reuters **CMR Factbook 2014** sets out the probability rates for any given medicine to achieve market authorisation and be potentially available for patients. Upon reaching the **first pivotal dose (e.g. Phase III), almost two-thirds of active substances are expected to make it through to market authorisation,** but a third will not progress. Thomson Reuters CMR International assessment over time suggests that there have been improvements in probabilities for early and late development stages over the past decade, but the process remains still very uncertain.

Probability of Success to Market for Active Substances



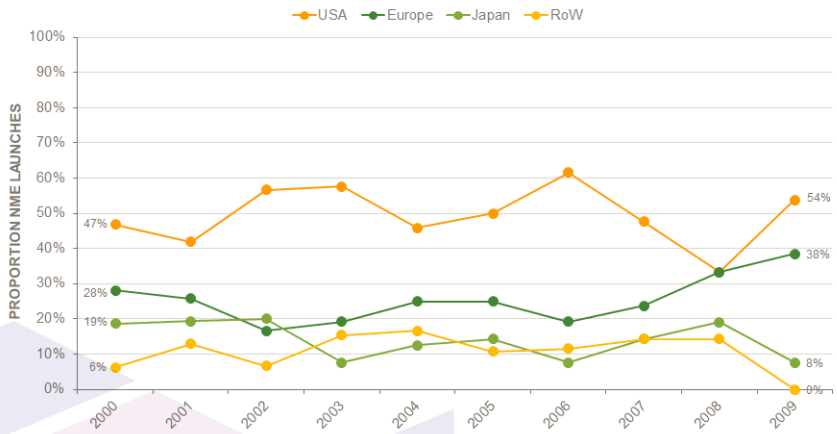
Probabilities of success to market were calculated using success rates between phase for active substances entering phase between 2008 and 2010 and year of assessment 2013.

SOURCE: Thomson Reuters CMR International Pharmaceutical R&D Factbook 2014; Drawn from the Industry R&D Investment Programme and reproduced with permission.

NOTES: Between phase success rates were calculated using the CMR methodology. The fate (progressed/ terminated) of active substances that entered phase between 2008-2010 were assessed as of 31st December 2013. Displayed are the probability of success to market values, which are a product of the between phase success rates from the start milestone to market.

5.13 Comparing across regions over the period 2000 - 2014, the **United States has remained the principal region for the first launch of New Molecular Entities (NME)** and this trend has been more pronounced since 2009. The United States retains a key innovative draw for new medicines over other regions around the world. After increasing its share of first launches up to 2009, **Europe now sees very few, with only 9% of NMEs first launched in Europe in 2014.**

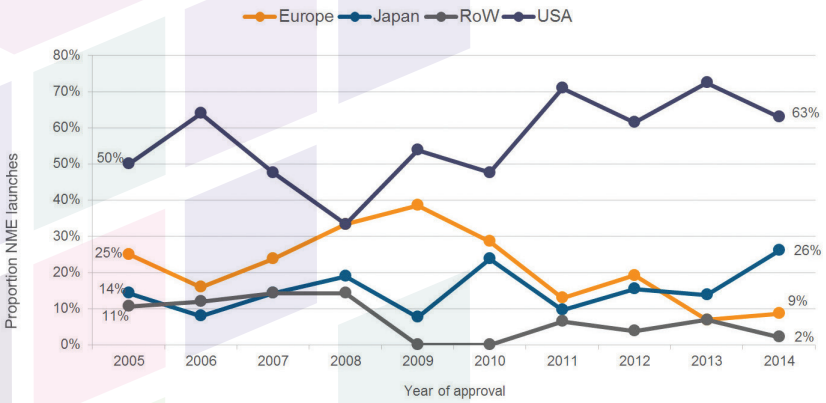
Region of First Launch for New Molecular Entities 2000 - 2009



SOURCE: Thomson Reuters CMR International Pharmaceutical R&D Factbook 2010 and 2014; Drawn from the Industry R&D Investment Programme and reproduced with permission.

NOTES: CMR International Performance Metrics Programme / Source. Annual Survey of New Molecular Entity First Launches / New Medicine Launches 2014. A complete guide to New Molecular Entities (NMEs) launched world-wide. Annual surveys of the global pharmaceutical industry were undertaken to identify all new molecular entities introduced for the first time anywhere in the world. Presented is the proportion of each year's output between 2000-2009 and in the second figure, 2005- 2014, according to the geographical region of the first launch.

Region of First Launch for New Molecular Entities 2005 - 2014



[1] New Molecular Entity (NME): A new chemical entity or biological (including products of biotechnology) that has not been previously available for therapeutic use in man and are destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in man. Vaccines, new salts, pro drugs, metabolites and esters of existing compounds and certain biological compounds (e.g. antigens) are not classified as NMEs. Combination products are excluded from the list unless one or more of the constituents of the combination product has never been previously available.

[2] New Active Substance (NAS): A chemical, biological, biotech or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans. The term NAS also includes: An isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available / a biological or biotech substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process and which will require clinical investigation. A radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.

References

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3 National Institute for Health Research. Key Statistics <https://www.crn.nihr.ac.uk/about-crn/our-performance/key-statistics-2/> (2015).

Collaborating for Innovation

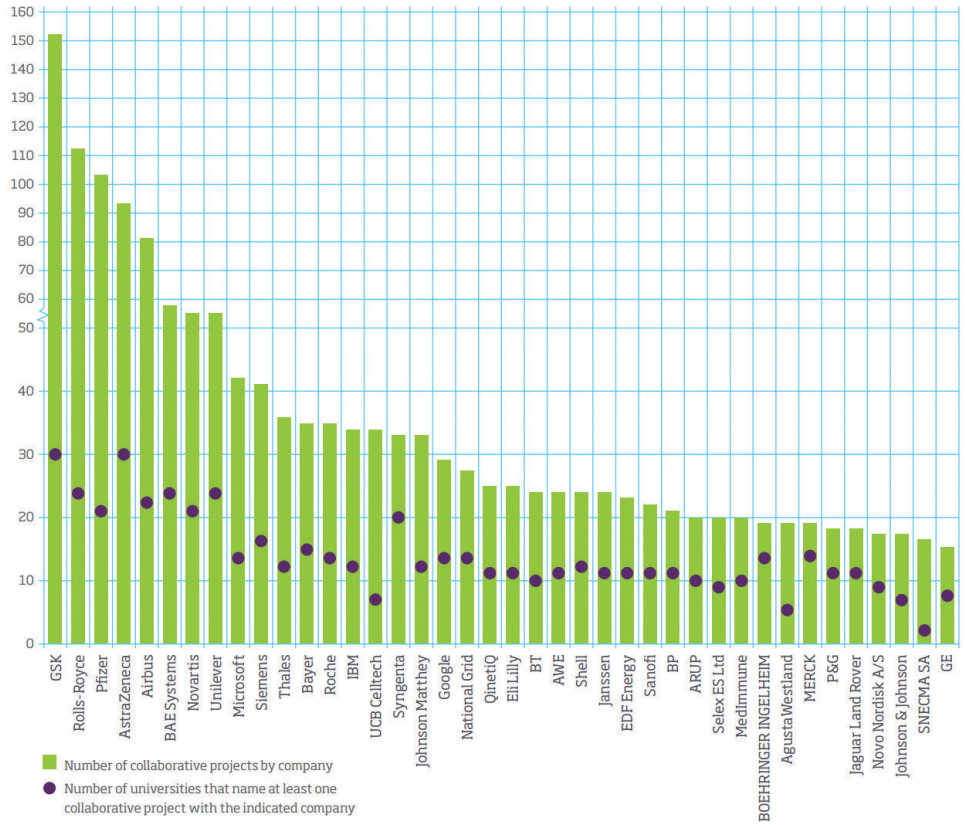
Today's biomedical innovations rely on a broader number of disciplines than ever before. In order to meet this breadth of opportunity and scientific challenge, biopharmaceutical companies are collaborating across the process of discovery, development, manufacture and commercialisation. This collaboration is increasing not only in frequency, but also in the range of collaborative agreements and scope for engagement with academia, healthcare professionals, other businesses and patients.

Collaboration is more than just a division of labour; to be truly effective, collaboration requires both parties to share the 'absorptive capacities'[1 2] to transfer ideas and co-create new knowledge and technology. Simply put, we need to have common ground in our knowledge bases to interact and the networks in place to bring us together. In this chapter, we consider some measures of the experience and potential for collaboration in the UK.

6.1 The British Government recently asked Professor Ann Dowling to consider how it could better support relationships between businesses and the UK's world-leading university researchers. In this study, which identified areas for improvement to encourage greater collaboration[3], research was collected about current collaboration between academia and industry. The study noted that "[t]he UK has a vibrant research environment, with a range of collaborations taking place between universities and business across many disciplines, but there is more to be done to help existing efforts evolve from short-term, project-based collaborations to longer-term partnerships focussed on use-inspiring research." [3: P.3]

In their analyses, the Dowling Report team identified that compared to other sectors, the life sciences were represented by a relatively small number of companies but for which collaborations are many. **Seven of the top 15 companies by number of collaborations are biopharmaceutical companies.**

Top 40 companies by number of collaborations

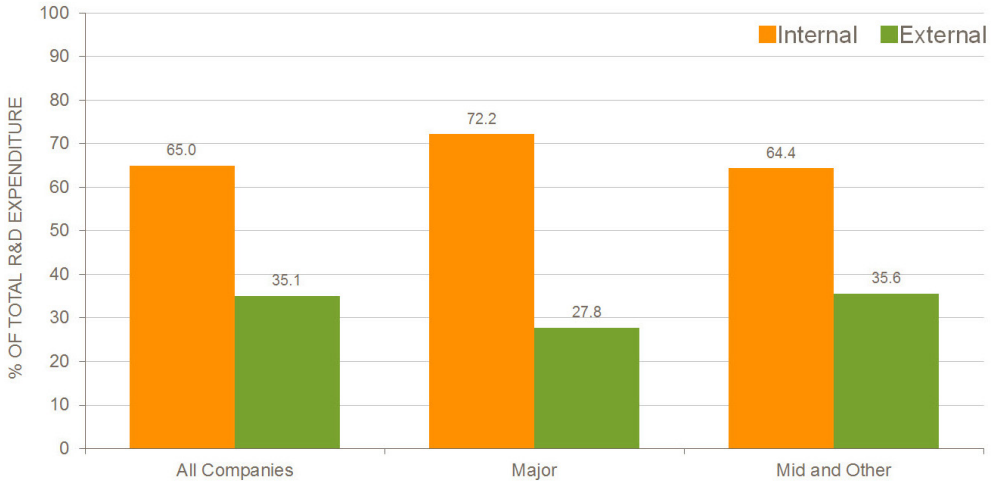


SOURCE: The Dowling Review of Business-University Research Collaborations (July 2015), Figure 9, p.40

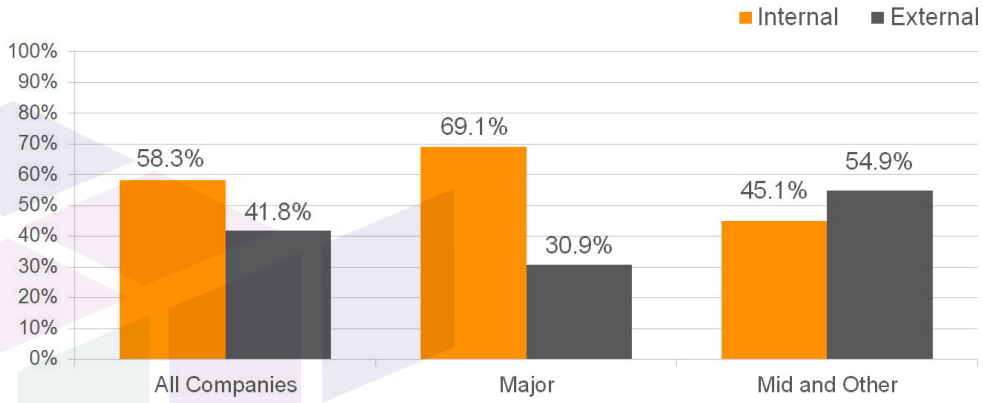
NOTES: A methodological note of how collaborations were identified to companies can be found on the Dowling Review website: http://www.raeng.org.uk/publications/other/dowling-review-collaborations-methodology-note

6.2 Biopharmaceutical companies have been increasing collaboration and extending R&D investment to external projects and partners. As the Thomson Reuters CMR International data shows, between 2009 and 2014, all companies have increased the share of **external spend within total R&D expenditure to an average of 41.8% across surveyed companies.** This change towards external spend has been **greatest for the smaller biopharmaceutical companies** ("Mid and other" companies spend less than $2 billion on R&D), for whom the share of external spend was the greater part of R&D at an average of 54.9% in 2014.

Allocation of R&D Expenditure between Internal and External Spend by Company Size in 2009



Allocation of R&D Expenditure between Internal and External Spend by Company Size in 2014



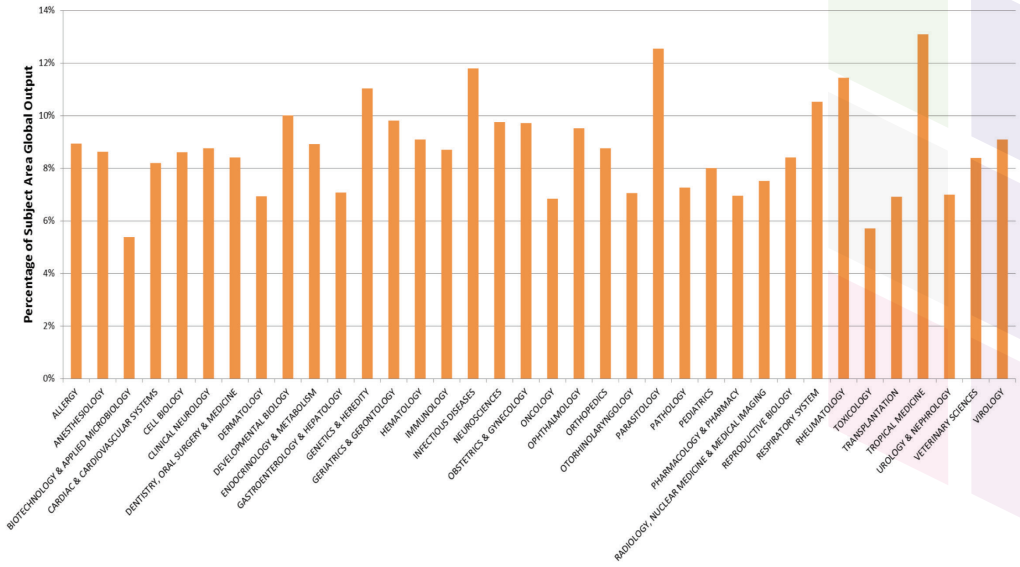
SOURCE: Thomson Reuters CMR International Pharmaceutical R&D Factbook 2010 and 2014; Drawn from the Industry R&D Investment Programme and reproduced with permission.

NOTES: Presented is the proportion of total R&D expenditure in 2009 and 2014 allocated either internally or externally, calculated as a median of the data provided by a minimum of 5 companies. Data are also shown for Major or Mid and Other companies where at least 3 companies are represented. Major companies are defined as those spending ≥US$ 2 billion in 2014 on ethical pharmaceutical R&D. Mid companies are defined as those spending ≥US$ 0.7 billion and <US$ 2 billion in 2014 on ethical pharmaceutical R&D. Other companies are defined as those spending <US$ 0.7 billion in 2014 on ethical pharmaceutical R&D. The 2009 data presented in this graph is based on data from 19 companies (6 Major and 13 Mid and Other) and 2014 data from 11 companies (8 Major and 3 Mid and Other).

6.3 One measure to understand **the relative scientific strengths of a community is to review their publications and the standing these have in international peer groups.** To explore this for the UK life sciences, bibliometrics are used, drawing on the Thomson Reuters Web of Science™ and the techniques of Thomson Reuters to allow comparisons across fields of science. Citations to prior work are a normal part of publication and reflect the value placed on a work by later researchers. Highly cited work is recognised as having a greater impact and Thomson Reuters has shown that high citation rates are correlated with other qualitative evaluations of research performance, such as peer review.

Assessing the performance of the UK scientific output with regard to 36 life science categories over the period 2010 to 2014, the UK scientific community represents a **significant share of global output across a range of subjects, notably (over 10% of the global output) in genetics & heredity, infectious diseases, parasitology, respiratory system, rheumatology and tropical medicine.** In fact, in detailed analysis, Thomson Reuters found that the UK output for the life sciences is higher than the global average for 23 of the 36 categories in both number of papers and citation impact, and although lower that the global average in terms of numbers of papers, higher than the global average in terms of citation impact for a further 12 categories.

UK Share of Global Publications by subject area, 2010-2014



SOURCE: Thomson Reuters Web of Science™. Research and analysis conducted for ABPI October – November 2015.

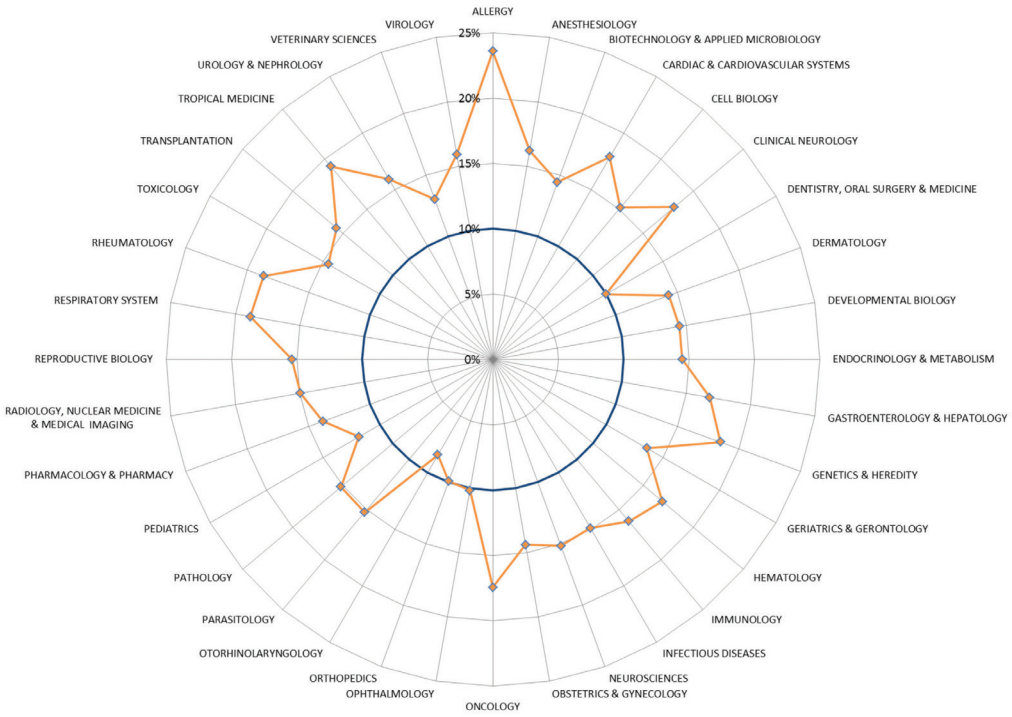
NOTES: Thomson Reuters abstracts publications including editorials, meeting abstracts and book reviews as well as research journal articles. The terms 'paper' and 'publication' are often used interchangeably to refer to printed and electronic outputs of many types. In these analyses the term 'paper' is used exclusively to refer to substantive journal articles, reviews and some proceedings papers and excludes editorials, meeting abstracts or other types of publication. Papers are the subset of publications for which citation data are most informative and which are used in calculations of citation impact.

6.4 Although publication in a journal is already a measure of success, citations are an important measure of peer value. Highly cited work is recognised as having a greater impact. Thomson Reuters has shown citation rates are correlated with other qualitative evaluations of research performance (e.g. peer review). We consider here the **percentage of publications by the UK scientific community which are amongst the world's most highly cited papers**, within the top 10% of publications in a given field and within the top 1% of publications in a given field.

The figure below shows the share of the UK publications in a given field which have citations that rank them in the top 10% and 1% of their field. The strengths of publications in **allergy, oncology, genetics and heredity science** are obvious, but it is also worth noting that in almost all fields, more than 10% of a **UK field's publications are in the global 10% by citation, which suggests that UK science is indeed world leading and more highly represented in in terms of impact in comparison to numbers of papers**.

Key scientific areas of strength are more clearly defined in comparing publications in the top 1% of publications in terms of citations. Allergy, clinical neurology, genetics & heredity, oncology and rheumatology are leading areas for UK science, but indeed for **all fields, UK science is more represented amongst the world's highly cited literature** in comparison with the numbers of papers published.

Share of Publications in the Top 10% of Field



SOURCE: Thomson Reuters Web of Science™. Research and analysis conducted for ABPI October – November 2015.

NOTES: 'Citations per paper' is an index of academic or research impact (as compared with economic or social impact). It is calculated by dividing the sum of citations by the total number of papers in any given dataset (so, for a single paper, raw impact is the same as its citation count). Citation rates vary between research fields and with time, consequently, analyses must take both field and year into account. The standard normalisation factor is the global average citations per paper for the year and journal category in which the paper was published. A value of 1.0 indicates performance equal to the global average and publication year.

Share of Publications in the Top 1% of Field

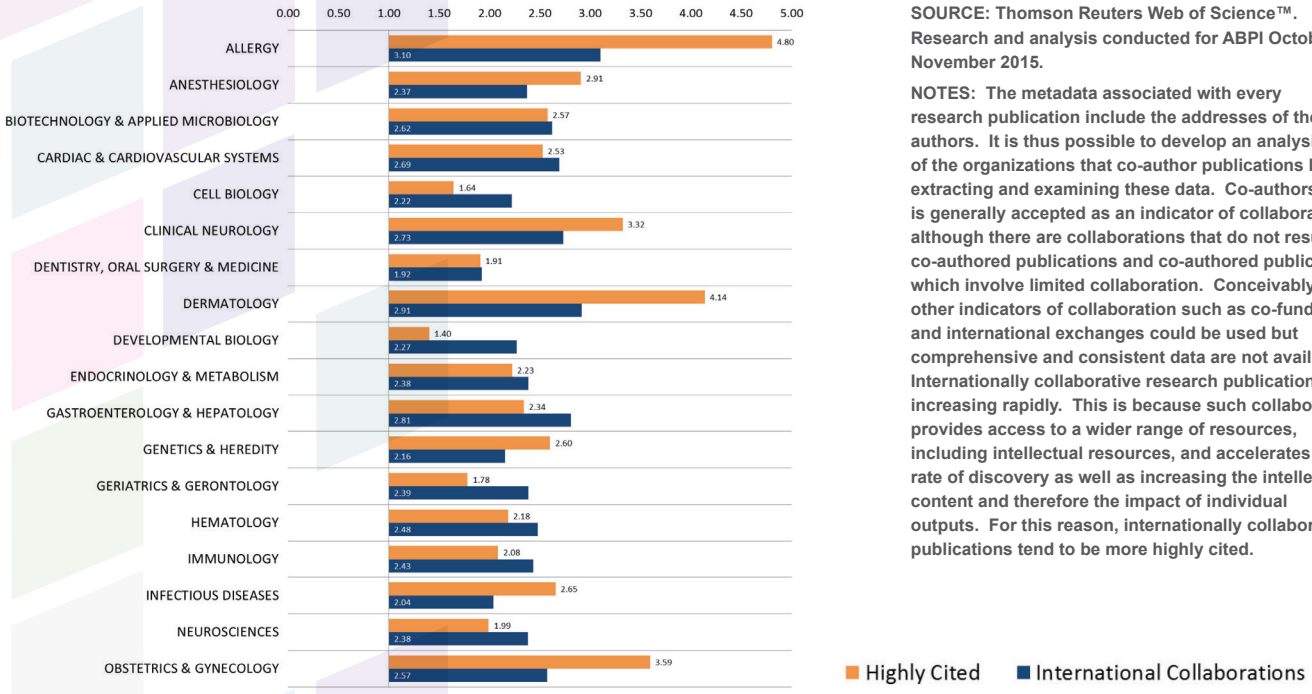
SOURCE: Thomson Reuters Web of Science™. Research and analysis conducted for ABPI October – November 2015.

NOTES: 'Citations per paper' is an index of academic or research impact (as compared with economic or social impact). It is calculated by dividing the sum of citations by the total number of papers in any given dataset (so, for a single paper, raw impact is the same as its citation count). Citation rates vary between research fields and with time, consequently, analyses must take both field and year into account. The standard normalisation factor is the global average citations per paper for the year and journal category in which the paper was published. A value of 1.0 indicates performance equal to the global average and publication year.

6.5 Previous research has shown that collaboration (particularly at the international level) leads to greater impact of science. Undertaking a comparison of citations for UK publications and whether publications involved international collaboration, Thomson Reuters have compiled the following charts by field of life sciences to compare the ratios of UK shares (for highly cited publications and for international collaborations) to global averages. By "highly cited" we mean the percentage of publications that are assigned as Highly Cited in Thomson Reuters InCites: Essential Science Indicators (ESI) (top 1% by citations for field and year).

The tables below confirm the analysis from 6.4 in terms of international impact (highly cited) for the UK research community. What this analysis shows is that the **UK scientific community are also more active in international collaborations** than the global average. There is a likely correspondence between the two, but both measures are **strong evidence of the potential for the UK science community to continue playing a leadership role for life sciences globally** if investment and engagement continues.

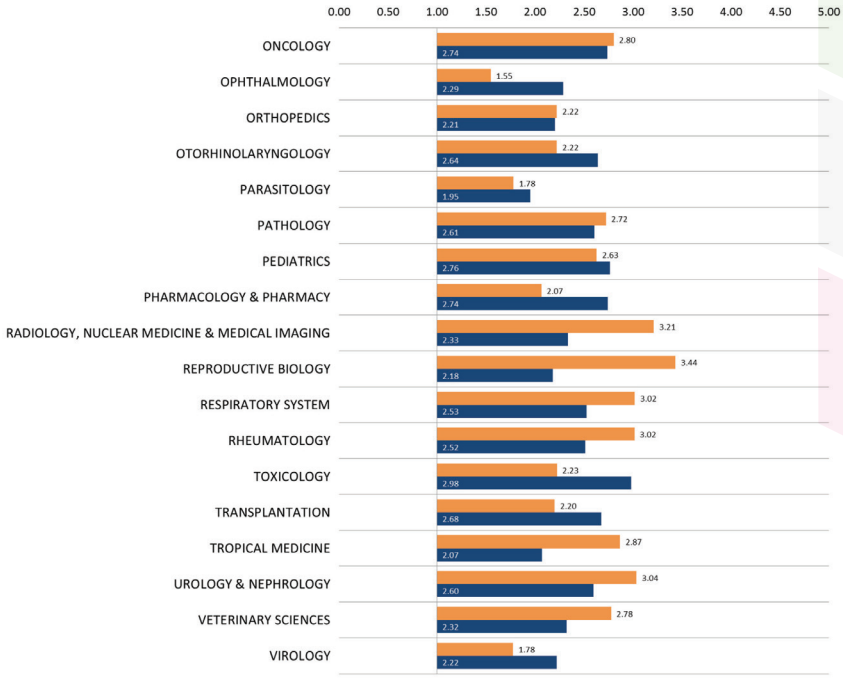
Highly Cited and International Collaborations: Ratios of UK Percentage to Global Percentage



SOURCE: Thomson Reuters Web of Science™. Research and analysis conducted for ABPI October – November 2015.

NOTES: The metadata associated with every research publication include the addresses of the authors. It is thus possible to develop an analysis of the organizations that co-author publications by extracting and examining these data. Co-authorship is generally accepted as an indicator of collaboration, although there are collaborations that do not result in co-authored publications and co-authored publications which involve limited collaboration. Conceivably other indicators of collaboration such as co-funding and international exchanges could be used but comprehensive and consistent data are not available. Internationally collaborative research publication is increasing rapidly. This is because such collaboration provides access to a wider range of resources, including intellectual resources, and accelerates the rate of discovery as well as increasing the intellectual content and therefore the impact of individual outputs. For this reason, internationally collaborative publications tend to be more highly cited.

Highly Cited and International Collaborations: Ratios of UK Percentage to Global Percentage



SOURCE: Thomson Reuters Web of Science™. Research and analysis conducted for ABPI October – November 2015.

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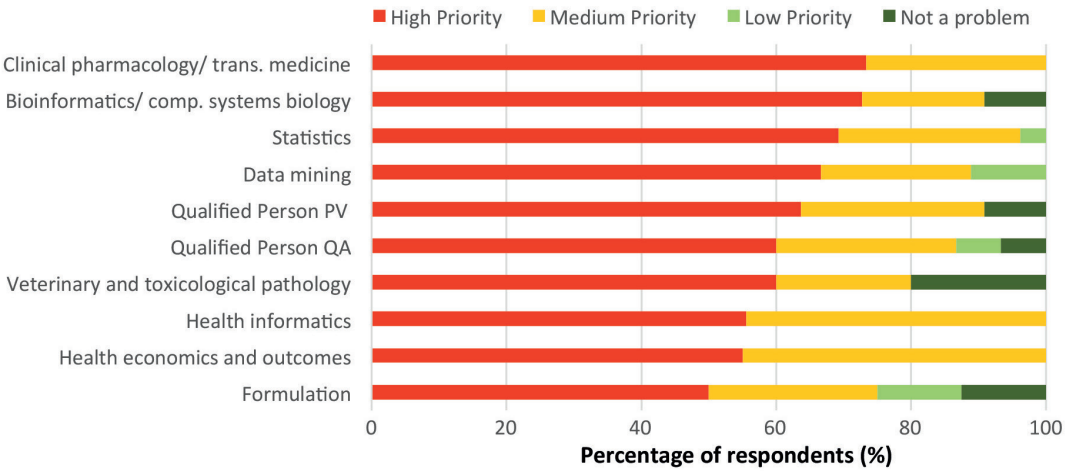
6.6 As the **Global Innovation Index 2014** emphasises, "[t]he fundamental driver behind any innovation process is the human factor associated with it."[4] The UK academic community is world-leading in the life sciences in general, but there are still educational areas where new skills are required. The current skills imperatives of biopharmaceutical companies, contract research organisations, professional bodies and recruitment companies were identified through an online survey from the Association of the British Pharmaceutical Industry (ABPI) in 2014/15. Many of the highest priority areas fell into the informatics, computational and mathematical category. This included **statistics, health informatics, health economics and outcomes, data mining, and bioinformatics/ computational systems biology.** For these disciplines, over 90% of respondents rated them medium or high priority, and raised concerns around both quantity and quality of candidates.

Skills: Priority Areas for the Life Sciences



SOURCE: Bridging the skills gap in the biopharmaceutical industry; maintaining the UK's position in life sciences, ABPI 2015

NOTES: The online survey was conducted between September 2014 and May 2015, and was designed to be comparable to a similar survey undertaken in 2008. In total there were 93 respondents from 59 different organisations, most of which were biopharmaceutical companies but also included contract research organisations, SMEs, higher education institutions, learned societies, recruitment companies and healthcare agencies.

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3. The Dowling Review of Business-University Research Collaborations, Department for Business Innovation & Skills, Editor. 2015, HM Government: London. p. 84.
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