THE CHANGING ROLE OF CHEMISTRY IN DRUG DISCOVERY

Thomson Reuters has produced this report commemorating the International Year of Chemistry 2011.

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The role of the drug discovery chemist has changed significantly over the past 50 years - workflows have been reinvented while the same goals remain to find and test novel molecules that can reach and act on disease targets. In this, the International Year of Chemistry (IYC 2011), Thomson Reuters offers a timely report that examines how life in drug discovery has changed and how it will continue to change and adapt in the future. The report analyzes and develops the major themes identified and highlighted by key players in the global pharmaceutical industry. Many of their insights are fully supported by analysis of data taken from the *Thomson Reuters Integrity*℠ drug discovery database for the period 2001-2011.

In this report, we ask who will emerge as the major drug discoverers and the major drug developers during the next decade. What is the driver for change in the industry and will globalization and regulation have far reaching consequences for the role of the chemist? How will the numbers stack up in 2020 when we count the number of new chemical entities (NCEs): will the balance shift from conventional small molecule Pharma products to the burgeoning area of biologicals?

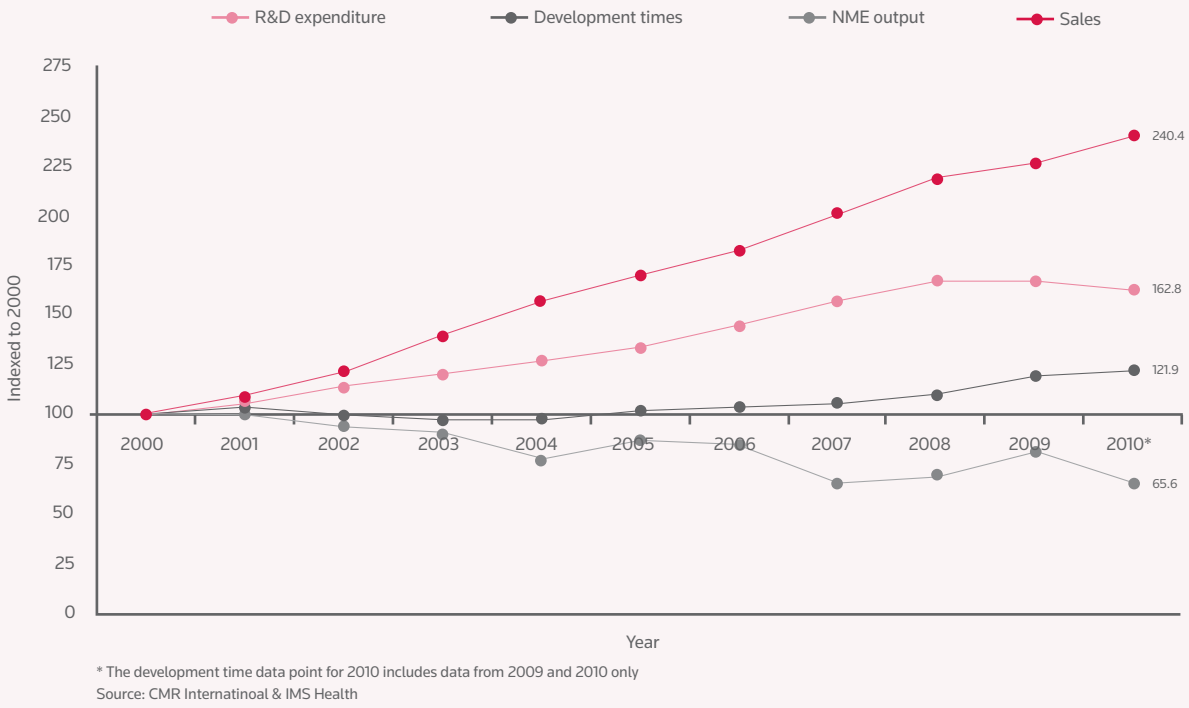
We will discuss how the future skills base will evolve and whether or not there will be a shift in the balance of traditional disciplines. We will calculate the rate-limiting steps and ask if that will affect changing role of chemists. Does a dearth of experience in Pharma, biotech, or academia impact on the changes and what role, if any, might the professional bodies play in the future development of the industry.

THE END OF AN ERA

There has been much focus in recent years on how Pharma pipelines are drying up and the era of the blockbuster product coming to an end.

Over the last 10 years, industry productivity has been declining with both time taken to market and R & D costs rising. With a number of major blockbusters about to lose the protection that intellectual property rights convey, several of the largest manufacturers in the industry, faced with potential significant reductions in revenue streams, have undergone a major effort reduce costs (Fig. 1). Site closures, restructuring and consolidation have become all too familiar terms in the industry in recent years.

PHARMACEUTICAL INDUSTRY PRODUCTIVITY 2000 -2010



* The development time data point for 2010 includes data from 2009 and 2010 only
Source: CMR Internatinoal & IMS Health

Fig. 1 Sales of Pharmaceutical products have increased almost two and a half times since 2000 with R &D spend rising almost 175 percent in the same time. However being challenged with increasing costs and falling output the trend for the last two years has been one of R&D decline. Over the same period of time it is taking almost over 20 percent longer to get new drugs to market. At the same time output has been declining over the last ten years forcing most major companies to reexamine their development strategies.

Whether this is an entirely valid summary of the current state of the industry is still the source of debate, but there are new hopes in the realm of rare and forgotten diseases, as well as among orphan and repurposed drugs that might contribute to cost reduction across the pharmaceutical industry. Nevertheless, forecasting exactly where the industry might be in years to come is proving as difficult as ever. (Fig. 2, Fig. 3)

MOST POPULAR TARGETS (BASED ON UAD FROM PHASE I TO REGISTERED)			
YEAR	1ST	2ND	3RD
2001	Reverse transcriptase	Cyclooxygenase 2	Microtubules
2005	Kit (c-Kit)	VEGFR-2	DNA polymerase II
2007	Tubulin	VEGFR-2	Microtubules
2011	VEGFR-2	RNA-directed RNA polymerase (NS5B)	Kit (c-Kit)

Fig. 2 The Most popular targets based on drugs under active development from phase 1 to registered during the period 2001 – 2011. This data reveals that apart from VEGFR-2 there hasn't been a phased progression of targets from year to year, making it difficult to spot the trends (data sourced from *Thomson Reuters Integrity*)

MOST POPULAR TARGETS (BASED ON PATENTS PUBLISHED ON 2001, 2005, 2007 OR 2011)			
YEAR	1ST	2ND	3RD
2001	TNF alpha	Phosphodiesterase IV	Coagulation Factor Xa
2005	Phosphodiesterase IV	Dipeptidlyl peptidase IV	p38 MAPK
2007	Dipeptidyl peptidase IV	Coagulation Factor Xa	Vanilloid VR1 receptor
2011	Phosphatidylinositol-3-kinase	11-beta-Hydroxysteroid Dehydrogenase	RNA-directed RNA polymerase (NS5B)

Fig. 3 Most popular targets based on patents published during the period 2001 – 2011. These data demonstrate the increase in popularity of Phosphodiesterase IV at the start of the decade and Dipeptidyl peptidase IV in the middle of the decade. Apart from these two compounds it appears difficult to spot trends. Taking the data from fig 2 and fig 3 demonstrates the difficulty we have seen in spotting the next big blockbuster during the last decade. (Data sourced from *Thomson Reuters Integrity*)

Is the era of the blockbuster drug is well and truly over or is it only just taking off? According to Dr Cathy Tralau-Stewart, Head of the Drug Discovery Centre and Pharmacology at Imperial College, University of London, and previously with GlaxoSmithKline, "Blockbusters are a thing of the past." Unfortunately, she feels that many of the pharmaceutical companies do not want to accept this fact. "They are going to have to change their model completely," she adds. "Financially, they cannot afford to take ten drugs through to market rather than one if they continue to use their current systems and processes." She points out that future drugs are more likely to be targeted at set populations conferring maximum efficacy on the target population. If you have the disease or condition and are outside this target population the drug may not work effectively or present unwanted side effects. "You will have to identify your target population using biomarkers and diagnostics," she adds. "So looking at it that way, you are going to get 10 targeted projects to full market rather than 1 blockbuster." The outcome for a drug like Avastin might have been very different if such biomarkers had been used to ensure that the product reached only the appropriate sub-population. With the biomarkers to hand, drug chemists would have been better equipped to target only the cohort for which the drug was entirely suited.

COMPARISON BETWEEN THE TOP 5 ACTIVE RESEARCH THERAPEUTIC AREAS AND BLOCKBUSTER DRUGS FROM EACH AREA				
	2005	2007	2010	NO. OF BLOCKBUSTER DRUGS
CANCER	217	313	312	1
INFECTIONS	76	106	113	0
NEUROLOGICAL	74	84	85	4
GASTROINTESTINAL	55	78	66	1
ENDOCRINE	-	75	57	2
CARDIOVASCULAR	53	-	-	3

Fig. 4 Comparison between the top 5 active research therapeutic areas and blockbuster drugs from each area.

Figure 4 demonstrates most active development over the past 5 years has been in the cancer field. At the same time this has only seen one drug that would be classified as a blockbuster. Interestingly, Neurological disorders and Cardiovascular disease have delivered 4 and 3 blockbusters respectively. Neurological disorders rank number 3 in the active development stakes while cardiovascular dropped out of the top five active development areas in 2007. The second most active area for research has been infection. Communications with many of the interviewees suggest that with the rise in multiply resistant hospital infections, the new treatments coming to market are often put on the shelf and used as a last resort when other drugs fail. This practice if continued, will severely limit the future ability of these drugs to reach blockbuster status.

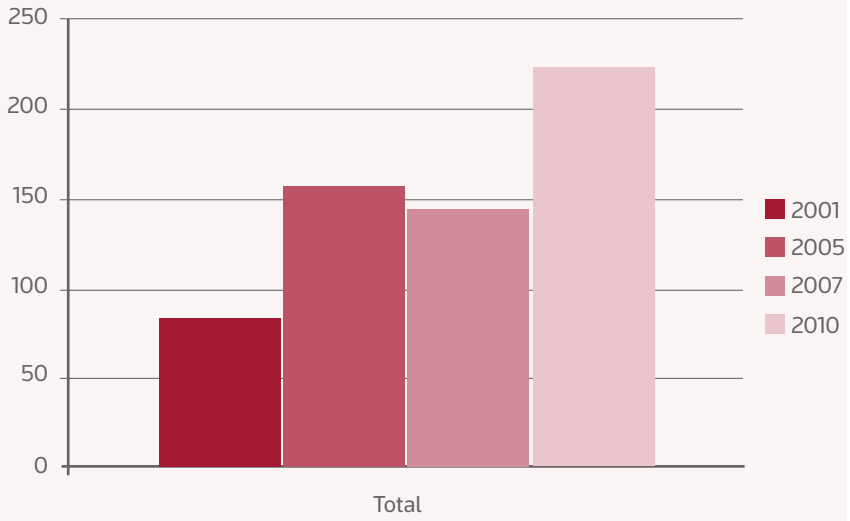
Medicinal chemist Dr Derek Lowe who works on preclinical drug discovery in the US is not convinced that the term blockbuster is a useful concept in the first place. "If some company comes across a drug that they think can sell $10 billion, they can decide that the era of the blockbuster is very much alive," he says. However, he adds, "If there is a company that has decided that the only thing that it is going to pursue is $10 billion drugs, blockbuster or nothing, then yes, I think that has been dead for quite a while."

ORPHANS TO THE RESCUE?

With the high cost of drug discovery, companies are turning to repurposing drugs for rare diseases that have been almost entirely neglected until now. The numbers of these drugs has risen 300 percent since the start of the decade (Fig 5).

The "rationale" for drug repurposing is to short circuit the drug development process by developing existing therapeutic agents for conditions other than those for which they were first developed.

INCREASE IN REPURPOSED DRUGS

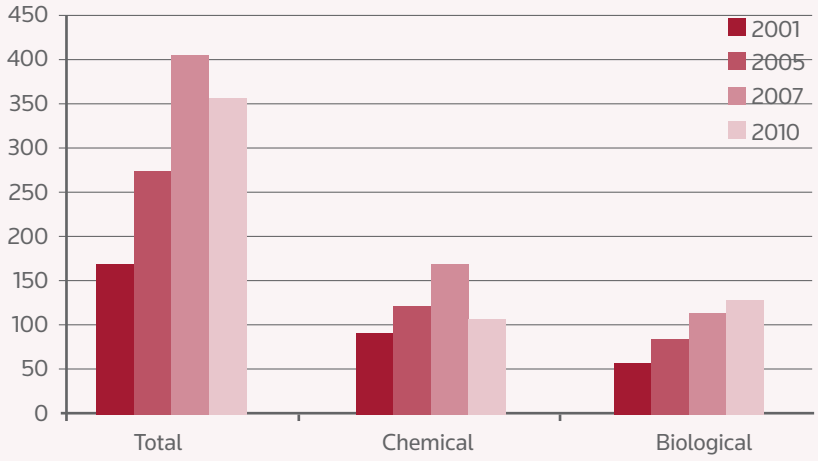


Source: *Thomson Reuters Integrity*

Fig. 5 Repurposed drugs have grown from around 80 in 2001 to 222 by 2010 demonstrating close to 300 percent increase.

Even orphan diseases may not be the answer to industry woes, one computational chemist working on preclinical drug discovery in the US suggests. The high costs of drug design and maintaining a big corporation in the face of putative but unproven revenues has always been a major barrier. "It is," he suggests, "better to decide on population, who is catered for, which population will change, to focus on that, and not to approve a drug for a wealthy population." Paradoxically, he adds, "The more money that Pharma throws into research, the fewer new compounds appear for approval." (Fig 6). Demonstrates the rise in compounds entering Phase 1 from 2001 – 2010.

COMPOUNDS IN PHASE I 2001-2010



Source: *Thomson Reuters Integrity*

Fig. 6 Since 2001 there has been over 100 percent growth in compounds in Phase I, reflecting the increase in R&D spend. Biologicals have risen year on year since 2001. Data suggests that while NCEs are still the main focus for research into therapeutics overall, their position is being challenged by the rise of biologics.

However, just because a condition was considered an orphan disease at one time doesn't necessarily mean it will remain so. Cystic fibrosis was once considered an orphan disease and that, along with hepatitis C, is beginning to find growing markets. As technology and diagnostics develop, together with our ability to stratify patients, our definitions of what is classified as an orphan disease will undoubtedly evolve.

Moreover, Lowe points out that there are already blockbuster orphan drugs, "We have drugs out there like Gleevec which is, under US law, an orphan drug but it is a $billion orphan drug, and you have Genzyme until recently making a very good living off orphan indication." He suggests that the orphan drug concept is simply predicating on health insurance companies being willing to pay a tremendous amount for these orphan drugs. "If it wasn't for that," Lowe adds, "I don't know what kind of incentives would have to be in place but they would have to be bigger than they are now."

Ten to fifteen years ago, Big Pharma aimed for big products. But, as David Leahy, CEO Molplex, Chairman Inkspot Science and formerly of AstraZeneca, reminds us that era is over. Now, orphan diseases and drugs offer much smaller returns individually but each can add to the portfolio. "What we are going to see will be more of a dispersal of lots more smaller advances, drugs that offer smaller advances and smaller but numerous markets, more niches in terms of disease and population," Leahy says. "There will be more $50-200 million/year targets and hopefully there will be a lot more of them as the industry has got to grow."

Allan Moorman, formerly Senior Director of Medicinal Chemistry at King Pharmaceuticals Inc, Research & Development (now part of Pfizer), in Cary, North Carolina, USA agrees that as far as blockbusters are concerned by 2020, the number of drugs entering the market that become blockbusters is going to be smaller. "This is a combination of increased emphasis on more personalized medicine," he says, "and the simple fact that you are going to have niche companies looking at targets that are ultimately likened to Big Pharma for marketing, and they are going to be multiple parallel efforts being brought forward. So I think that there are going to be fewer and fewer first-in-class blockbusters that really are able to dominate the market."

Of course, while the golden age of billion-dollar drugs may be gone, it is certainly not forgotten. Should a new blockbuster come along, no Pharma company is going turn away from the opportunity it brings. Paul Leeson, Consultant with GSK, Director of Medicinal Chemistry at AstraZeneca, Charnwood, UK at the time of interview, explains that shooting for blockbusters is certainly no longer an option, but suggests, "They will come along but in a different way, and you will also find drugs that make a lot of money but they will build that position over time, rather than starting out saying that we are going to make say $20 billion in the next 5 years on this, and it is very difficult to find molecules like this." He suggests that it is more likely that more usable molecules will be found and that organizations will accept bigger portfolios for smaller income for each molecule they market.

In the next ten years more and more drug companies will be looking to repurposing as a means to drive their development costs down. Investigation of drugs that were developed for one indication and being repurposed for another can shortcut several of the development steps. An example of this over the last decade has been Thalidomide, originally developed in the late 1950s as a sedative to treat morning sickness was withdrawn in the early 1960s because of teratogenic effects. In 1998, the FDA approved the use of thalidomide for the treatment of lesions associated with Erythema Nodosum Leprosum (ENL) and again in, 2006 it granted accelerated approval for thalidomide in combination with dexamethasone for the treatment of newly diagnosed multiple myloma patients.

As the ability to stratify patients within particular diseases becomes ever more possible through new and improved diagnostic tests, it will undoubtedly see older drugs being

repurposed and targeted at specific sub populations and rare diseases. With smaller populations or few sufferers of a rare disease, the costs associated with developing a novel therapeutic may be prohibitive relative to the future sales prospects. By adopting a repurposed drugs strategy significant cost has already been taken within the earlier development, meaning the repurposed drug should be cheaper to develop.

SCALING UP OR SCALING DOWN

The landscape across which drug discovery will function is an important question for the future. Traditionally, big multinationals have been at the forefront of a major industry, but academic spin out companies, research institutes, charitable organization, public-private partnerships (PPP), small and medium-sized enterprises (SMEs) in Pharma and Biotech, even government research laboratories are taking on increasing roles as well as finding new market niches and collaborating with the bigger companies on a more equal footing.

There are issues of falling levels of in-house R&D in Big Pharma and the outsourcing and virtualization of research usually in collaboration with the aforementioned smaller enterprises and organizations. This is becoming apparent across the European Union, the United States and in Asia, as well as among emerging economies. A parallel issue is the relocation of company R&D to sites in those emerging markets, with the likes of early drug discovery within Pfizer, Novartis, GSK, and AstraZeneca in the UK all closing or downsizing sites, a pattern also seen in other countries. The resulting effect is the inevitable loss of skilled chemists to the industry, although many of these will find employment in smaller ventures, academia, or start-up businesses of their own. These interwoven factors are all leading to a current wave of contraction and geographical shifts as well as a wholesale reassessment of financial stability, investment decisions and expected returns. Indeed the relative costs of small molecules compared to those of biologicals for both development and procurement is being continually reassessed.

The unfortunate side-effect of outsourcing R&D to the emerging nations is the negative impact this will inevitably have on the economies of the UK and USA, for instance. “They will lose leadership in an industry where we have traditionally led and which contributes very significantly to UK Plc,” adds Tralau-Stewart, “We urgently need to address this and fund the academic/biotech early R&D centers now to supply the Pharma pipelines in 2020,” she adds.”

THE WHOLE WIDE WORLD

Local economics aside, Moorman points out that, "Drug discovery will largely occur at small niche biopharmaceutical companies around the world, whether in the UK, US, Western Europe, Eastern Europe, China, India, Brazil, South Africa, Mexico." He adds that all of those nations will continue to have ongoing drug discovery efforts. "But, it will not be at Big Pharma," he asserts, "it will occur at small niche biopharmaceutical companies."

It is perhaps inevitable that a much larger proportion of drug discovery will take place outside North America and Western Europe. "I don't think that drug discovery is going to disappear in these countries," says Lowe, "but by the same process of all the outsourcing that has been going on for many years, we can have all these companies opening up serious research centers in countries like China." China is rapidly heading towards a population of 1,400 million people. That is an enormous market waiting to be opened, which will require good relations between the industry and the Chinese government. "The Chinese market is so huge and the government is so intimately tied into access to it that anything that you can do to be friendly with the Chinese government is a good thing, that is how [the companies] look at it," adds Lowe.

Recent patent data bears out the rise in Asia as a driving force in drug discovery. Figure 7.) In the period 2005-2010. Chinese drug related patents are up 7 fold compared to a mostly static figure in Europe and the US. In the same period Japan showed a 28 percent decline while other developing parts of Asia showed growth, albeit not on the scale of China. Clearly drug research is developing at a rapid rate in parts of Asia with new centers opening and existing locations expanding which offers skilled chemists in those countries opportunities to practice their art.

One interesting point to note is the rise of infection -based patents in Europe and US in recent years. This demonstrates a 16 percent increase in activity in Infection based patents here. This may be early indication of a shift in focus towards infection in an attempt to fight antibiotic resistant strains of microorganisms which are a growing threat to public health in both Europe and the US. A similar statistic can also be seen if you look at Alzheimer's disease in Europe US and Japan. There seems to be an increased in focus in these regions which are all concerned

PATENTS: GEOGRAPHICAL LOCATION OF DRUG DISCOVERY PATENTS ISSUING 2005-2010

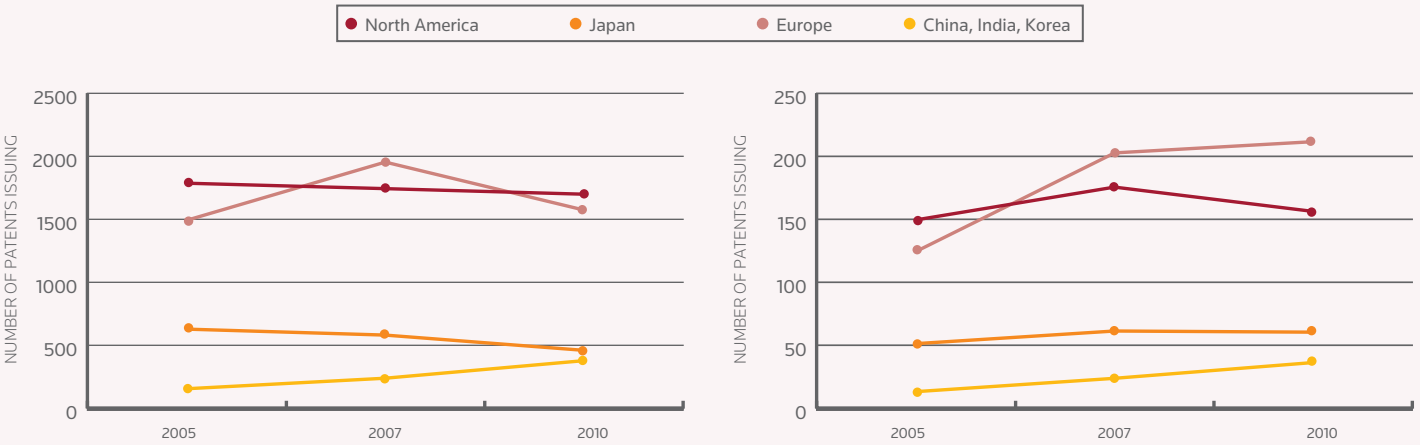


Fig. 7a Global trends in all drug discovery patents.

Fig. 7b Global trends in Cardiovascular drug discovery patents.

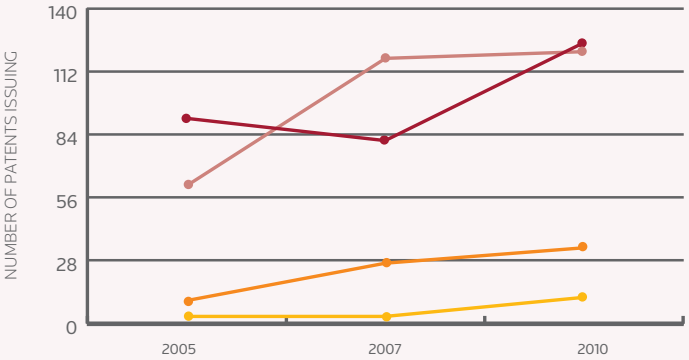


Fig. 7c Global trends in Alzheimer drug discovery patents.

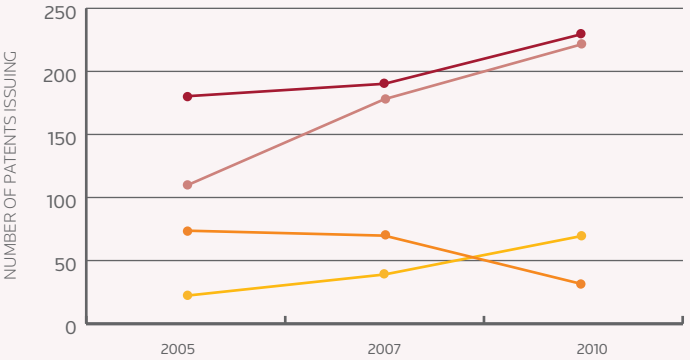


Fig. 7d Global trends in Infection drug discovery patents.

Source: *Thomson Reuters Integrity*

Together with total numbers of patents issued, we have displayed patents for Cardiovascular, Alzheimers and Infection to demonstrate the trend of Asian growth is evident across many therapeutic areas. Trend data taken from Thomson Reuters Integrity. Figure 7a displays data for all therapeutic areas by region, these data clearly demonstrate a rise in patents published in Asian countries but showing a decline in Japan at the same time. Coincident with this, activity in Europe has been reasonably stable while North America demonstrates a small decline. Figs 7b,7c,7d reveal similar results for some of the most active therapeutic areas in recent years – Cardiovascular, Alzheimers and Infection. In these graphs activity is increased in all regions except Japan. This may be indicative of the economic climate in Japan in the last decade. However, in all cases Asia has increased its output of published patents in excess of 300 percent in the last five years.

with the effects of ageing populations. Given that success in reducing the incidence and mortality of infectious disease over the last few decades and with improvement in medical care overall, it was inevitable that the demographic would shift to a more elderly population. As it does, the incidence of diseases classed as gerontological are on the increase and thus a growing market for companies that can find potent treatments to ward off symptoms and perhaps even reverse the often debilitating and lethal effects of such diseases.

TECHNOLOGICAL ADVANCES

It is never possible to predict which new technologies will have the biggest impact on the industry and drug discovery. There are, however, signs that the range of druggable targets is expanding, especially given the notion of an aging population that survives the diseases of youth and poverty to find itself exposed to diseases of age, cancer, pain, cardiovascular, diabetes, and brain diseases, such as Alzheimer's and Parkinson's. Chemistry and target selection and validation can ward off attrition and perhaps even refill those pipelines. Many additional directions could be taken in the sense of pre-competitive initiatives, data collection, management, and interpretation, areas that will, of course, require increased investment.

Some in the industry, such as Leeson, believe that the notion of new drug discovery technologies is nothing but a white elephant. He suggests that no approach is going to succeed in isolation and, more to the point, technology is not necessarily a route to any kind of success. "We have had the whole genome sequence, combinatorial chemistry, drug screening, molecular modeling, fragment-based drug design," he says, "These are fantastic capabilities and yet our output is dropping. New technology is not the answer."

DESPITE SUBSTANTIAL INVESTMENT IN INNOVATIVE R&D, FEW DRUGS HIT NEW TARGETS

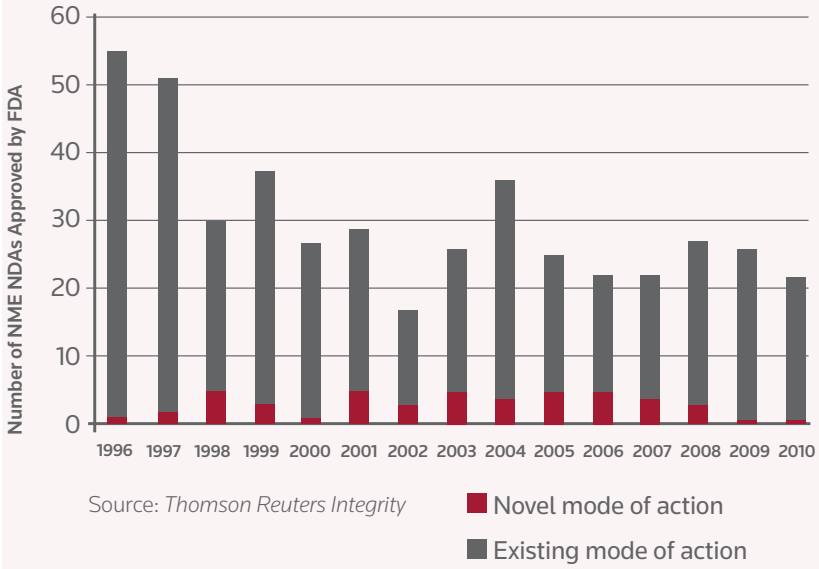


Fig. 8 Despite significant investment in R & D (See fig 1) there are fewer drugs coming to market. With only 22 reaching the market in 2010 compared to almost 40 per annum in the late nineties. In the first decade of this century we have seen this figure reduced on average, to the low twenties with 2004 being the exception. Novel modes of action have been very low during this time with values of 2-5 being typical. Together this suggests novel approaches should be considered to drive up innovation.

AD HOC APPROACH

For the last decades, Pharma has been carrying out drug discovery on an ad hoc basis where a lead may emerge from traditional medicine, high-throughput screening, or molecular modeling. Fundamentally, however, it has been, says Tralau-Stewart, "based on a very poor understanding of our targets." This has led to a high potential for failure at every stage of the process."[Leads] are often going to fail on getting to the clinic after millions or billions of dollars have been spent on each target if they don't work at the clinic," she says. Totally new paradigms are now needed for this decade with academia playing a much stronger role than ever before, particularly at the early stages of drug discovery. Indeed, critical to success in 2020 will be the increased focus on understanding drug discovery, bringing it closer to the clinic, and trying to understand the biology a lot more before putting chemistry into the picture, with much of that effort being in academia. However, academia alone cannot undertake this multiple paradigm shift. "I would suggest that academia cannot do this on its own," adds Tralau-Stewart, "this has got to be done in collaboration with industry, perhaps biotech, a collaboration of public private healthcare partnerships (PPP) trying to focus the right areas and move projects forward, and maybe move chemistry forward as well."

However, Moorman suggests that the paradigm shift from small molecules to so-called biologicals is not as clear cut a changes as one might suspect. "We have brought out combinatorial chemistry, we have brought out high-throughput screening, we've brought forward overexpression of receptors in various cell lines," he says. "We are consistently failing to identify suitable molecules to bring forward, to failing at ever-increasing rates, due to issues initially of safety, and in Phase 2 and Phase 3, they are failing for lack of efficacy." There are claims that biologicals will somehow, by definition, be more successful in the clinic than their small molecule cousins, but this is not yet proven. "All of this technology has got us to a situation where scientists aren't thinking about what they are doing, they are just doing it," he adds. Moorman also believes that while it might be a matter of semantics and how you define the products of biotech, the drug discovery effort will not instantaneously shift from a chemical approach involving small molecules to a biological approach that uses biological solutions in the form of engineered antibodies, peptides and proteins to tackle disease targets. "Small molecules will continue to be a major component of the drug discovery effort," he says."Internally, biopharmaceuticals will play a role and it will grow over time, but I think that in the next 10 years small molecules are still going to be the dominant component of drug discovery/drug development, new medicines that are coming to fruition."

SPACE - THE FINAL FRONTIER

With such a thought, there is a need to expand chemical space, to find entirely novel fragments, backbones and drug-like leads; which is where the organizational and collaborative diversity alluded to above might help. We are yet to see how the consortium approach will work, how open innovation and large-scale collaborations will facilitate drug discovery and development. Moreover, after years of acquisitions of smaller operations by the large Pharma companies, there remains some uncertainty as to how such alliances might form in a non-incestuous manner. Indeed, consolidation of large Pharma is yet to reach equilibrium, where the balance will lie ultimately is an unknown.

ACADEMIC FAILINGS OR A REBIRTH?

Unfortunately, there are suspicions among some in the industry that despite the enthusiasm for academic-industry collaboration, academia is failing in its training role and universities are not supporting synthetic chemistry adequately. "What we are seeing less of now is total synthesis, the intellectual challenge of doing so," says Leeson, "What that provided was a fantastic training ground for chemical problem-solving." He points out that the future crops of PhD students are not likely to be as well-trained in chemical problem-solving as they need to be to cut it in drug discovery.

"Coupled with industry, academia can probably make a good medicinal chemistry course," he concedes, "but is that the right thing to do for students in terms of time and resources, or is it better for them to learn organic chemistry, become independent researchers capable of problem solving and cutting-edge synthesis and acting as a basic skill set, and then adding a medicinal chemistry layer on top?" Given that most observers feel that small molecules are here to stay, AstraZeneca remains 70-75 percent small molecules, for instance, it is more important that we have capable chemists than PhDs with weak synthetic skills in drug discovery.

PATENTS: PHARMA VS. ACADEMIA				
		2005	2007	2010
TOTAL	Academia	602	1371	2025
	Pharma	4135	9187	9647
INFECTION	Academia	104	178	217
	Pharma	305	353	395
CARDIO	Academia	38	55	82
	Pharma	311	425	416
ALZHEIMER	Academia	19	30	75
	Pharma	147	191	223

Fig. 9 The acceleration of patenting in academia is up 3 fold on the last 5 years while in industry it has doubled. Again this is across all the therapeutic areas we looked at. This trend data seems to show that Pharma is patenting more than ever in efforts to protect its intellectual property developments but also academia is waking up to the need to protect itself and raise its ability to generate revenue streams.

In contrast, Professor Alex Tropsha, Associate Dean for Research, at the University of North Carolina, Chapel Hill, USA, is convinced that academia will provide the major training for drug discovery. Ironically, this could prove to be true as there is currently an influx of experienced industrial scientists moving from down-sized Pharma R&D. However, he also insists that chemistry skills alone are not enough for modern drug discovery. "We need 'enriched training of chemists' to understand the complexities of the biology," he says, "We also need human biologists and bacterial biologists from academia. We should not be talking about training of organic chemists, chemists must also be able to understand biology of small molecule drugs, biochemistry; training in chemistry, biology, and informatics is needed."

THE ERA OF THE DRUG HUNTER

Leahy has to agree. "The medicinal chemist skills base is now coming to an end," he says, "and will be replaced by 'drug hunters'." By this he means scientists with drug design backgrounds who bring more intellectual diversity to the laboratory bench that pure synthetic organic chemistry or molecular biology alone. This new generation of drug designers will come from a wider range of disciplines. "They will come from the life sciences, some synthetic chemists, but with more people in computer science and general micro and molecular biology and other disciplines, and DMPK (drug metabolism/

pharmacokinetics) and analytical backgrounds also," he suggests. "The core skills will move more to judgments on understanding target profiles, Leahy adds "how to deliver them rather than synthetic chemistry."

Tropsha emphasizes that, "Chemistry continues to be very important but it will be more biologically enriched chemistry. This also hints at a likely shift in the balance of conventional Pharma against biologicals. "For biological and small molecule drugs, there will be much more contribution from peptide chemistry and molecular biology," he adds, "In future the balance will be more on biologicals."

Most of the big companies have a target for 50 percent biological, but most drugs are still small molecules. Biologicals are large, complicated molecules, expensive to develop, and Big Pharma will like that because it promotes their strengths. However, if the Pharma ecosystem moves to the kind of balance Leeson foresees, or with the kind of environment of lots of small players suggested by Leahy, then they will not be covering biologicals but mostly small molecules.

FOCUS ON DISEASE

The Pharma industry, by its very nature is disease-focused, but it has gradually and in some cases summarily withdrawn from those therapeutic areas that failed to sustain keen profits, such as bacterial infection or else became unmarketable because of saturation, patent expiries and the emergence of generics. There are "new" diseases that have opened up markets, such as various syndromes and illnesses of unknown etiology and in some cases uncertain symptoms, such as restless-legs syndrome and social anxiety.

20/20 VISION — BEYOND THE VALLEY OF DEATH

There will also be what Tropsha refers to as the "valley of death", the gap between the discovery of a bioactive molecule at the initial drug discovery stage and the conversion of that entity through Phase 1 and 2 trials to a commercially viable drug candidate. "Due to scarce funding, scores of promising new medicines have floundered and not made it through the valley of death," he says. "To overcome this, drug discovery will occur in academia or academic start-ups, in an academic environment, covered by PPP, NIH, venture capital and foundations."

According to Leeson, however, the industry will not be too different in 2020 from what it is today. He is optimistic that the number of NCEs will go up. "Thinking of the timescales for drug development, it takes a decade from invention of the compound to reaching the marketplace, before that is the innovation part from the biology breakthrough to the drug which is nearly 20 years," he says. "So what we are talking about in 2020 is what we are doing today...based on what we know, the pipelines will improve in the next decade compared to the last decade." By 2020, we should be seeing the start of that and things will get better afterwards, especially with the pickup in rare diseases that have been studied over the last few years.

Important areas of drug discovery do remain. In particular, biomarkers have a potent but still emerging role to play. They will home in on mode of action and give us the option of patient selection for specific personalized drugs. The post-genomic concept of personalized medicine continues to entice and is gaining traction as more biomarkers are identified. There are then the diseases on which no research program is apparently focused; there could be significant unmet medical need among such health problems.

BIOMARKERS MODULE RECORD COUNTS CUMULATIVE CHART FROM 2008 TO DATE

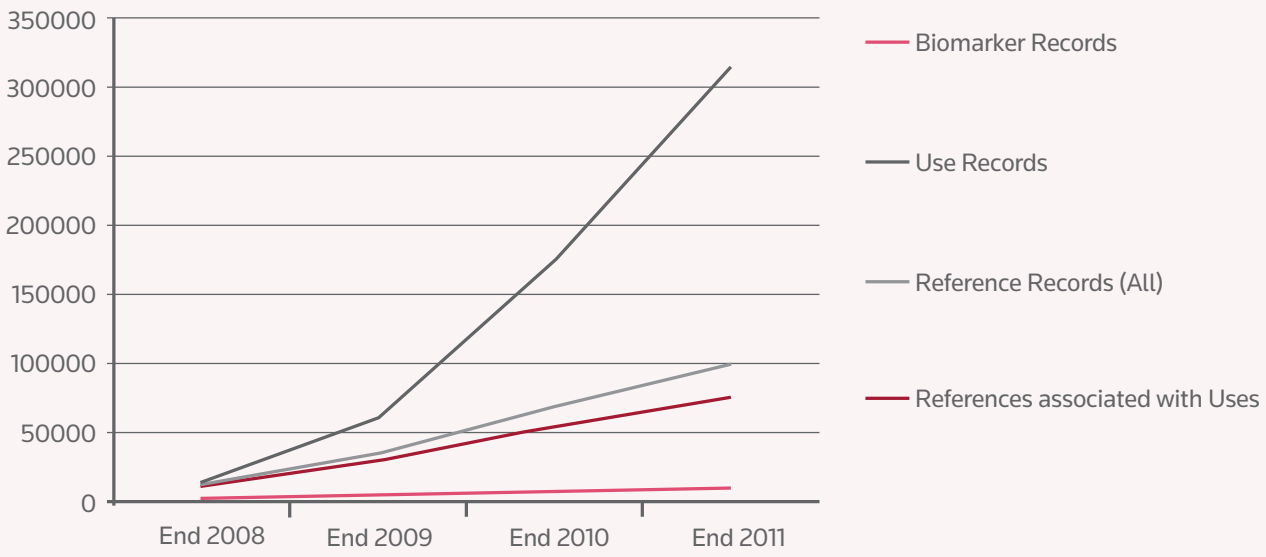


Fig. 10 Data from the *Biomarkers Module of Integrity* demonstrates the rise in reported biomarkers related to drug development projects. This data is for trending purposes only and reveals how Biomarker numbers and Biomarker uses have accelerated in recent years.

PATIENT DISSECTION

It is a complicated enough matter to dissect the Pharma industry in terms of pipelines, orphans and blockbusters. But perhaps the most important factor of all in understanding the history of the Pharma industry and, if not predicting, then assessing as best as we can, its future, is often ignored - the customers. The customers are, of course, the patients, any Pharma product's end users; ensuring that the right drug gets to the right patient will be the paradigm shift away from the scattergun prescribing that has been the mainstay of medicine for decades.

"The customer will still be the patient, of course," says Leeson. However, the disease focus will probably move to some smaller and smaller niche areas. It is possible that biotech will take over the areas from which Pharma has withdrawn but, he adds, it is always about trying to choose the right drug for the right patient whether through better diagnostics, gene profiling or biomarkers. "We can still make the right drugs and already have an army of 2000," he says. All we have to do is select the right one based on diagnostics.

THE MORE THINGS CHANGE...

Drug discovery has changed, the age of the blockbuster drug is long gone, although we might still long for those days. The Pharma industry has evolved, merged and demerged and gained a smaller sibling, the biotech industry, with its focus on so-called biologicals rather than small molecules. The changes mean that today drug discovery is often best-served by collaborations, among companies, with the bio industry, and with academia.

The pipelines and patents have in some cases run dry. Nevertheless, the realms of the post-genomic world with its opportunities for high-speed diagnostics and personalized medicine are opening up new markets. Rare diseases and repurposed drugs are providing novel opportunities that were previously hidden from view or ignored. Moreover, where one blockbuster may have sustained a single multinational for a decade or more, today, a dozen lesser, but equally as important products, whether small molecule or biological, will be on the front line of our attack on disease. Evidence points to a reduction in drugs to market despite a substantial increase in targets, but this could be a turning point as the smaller markets open up in diverse areas.

Given this rapidly evolving environment, the people needs of the industry are changing too, although at this point the need for skillful organic synthetic chemists is just as strong as the growing need for more non-specialist scientists who understand the business of carbon in terms of its small molecules, its biochemistry and its economics. The role of the chemist in Pharma is changing and the concepts of who will train the future scientists is very much open to debate with some observers claiming that academia has softened what was a hard science by folding in biological sciences and related fields. Yet others foresee the academic-industrial collaborations as improving the breadth of knowledge and the quality of those entering the industry.

In the next 10 years we will see greater use of in silico techniques, the number of biologicals will continue to rise. Already the job description for many chemists has changed from the pure synthetic chemist to include more computational chemistry. In the future this role will evolve further as awareness of the relevance of biology becomes more and more apparent. Indeed, biologicals are on the increase relative to new molecular entities as we have discovered.

Companies will continue to look to low-cost regions to drive costs down, which is corroborated by patent data showing the rise of Asian patent numbers. With seemingly endless mergers and acquisitions and the advent of countless start-ups with a biological spin, it seems that there will be greater diversity than at any point in the history of the Pharma industry. However, closures in Europe and US and the outsourcing and relocation of R&D to low-cost regions by Pharma will also play a role in the globalisation of the industry and a shift away from the West as the powerhouse of drug discovery. Indeed, while in the past academia seems to have driven fundamental science, discovery is increasingly the focus of academics and they too have increased their patent output substantially during the last ten years, their collaborators, and spin-out companies, while development becomes the remit of the industry.

The last fifty years have witnessed incredible changes in drug discovery, in the approach taken by the industry and academia in addressing disease targets and in the evolution of scientific diversity.

In this the International Year of Chemistry, IYC2011, we can foresee new targets, new ways to tackle them, and a world of strife that will perpetuate change over the next fifty years and beyond. Nevertheless, despite all the changes we have seen and the changes to come, the ultimate focus of the industry, academia, the science remains, as always, the patients.

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Interviewees

[1] **Dr Cathy Tralau-Stewart**, Head of the Drug Discovery Centre and Pharmacology at Imperial College, University of London, previously with GlaxoSmithKline

[2] **Dr Derek Lowe** who works on preclinical drug discovery and a frequent blogger of the Pharmaceutical industry

[3] **David Leahy**, CEO Molplex, Chairman Inkspot Science and formerly of AstraZeneca

[4] **Allan Moorman**, Founder Alta Vetta Pharmaceutical Consulting, L.L.C.,Durham, North Carolina and formerly Senior Director of Medicinal Chemistry at King Pharmaceuticals Inc, Research & Development (now part of Pfizer) , North Carolina

[5] **Professor Alex Tropsha**, Associate Dean for Research, at the University of North Carolina, Chapel Hill, USA

[6] **Paul Leeson**, Consultant with GSK, Director of Medicinal Chemistry at AstraZeneca, Charnwood, UK at the time of interview

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