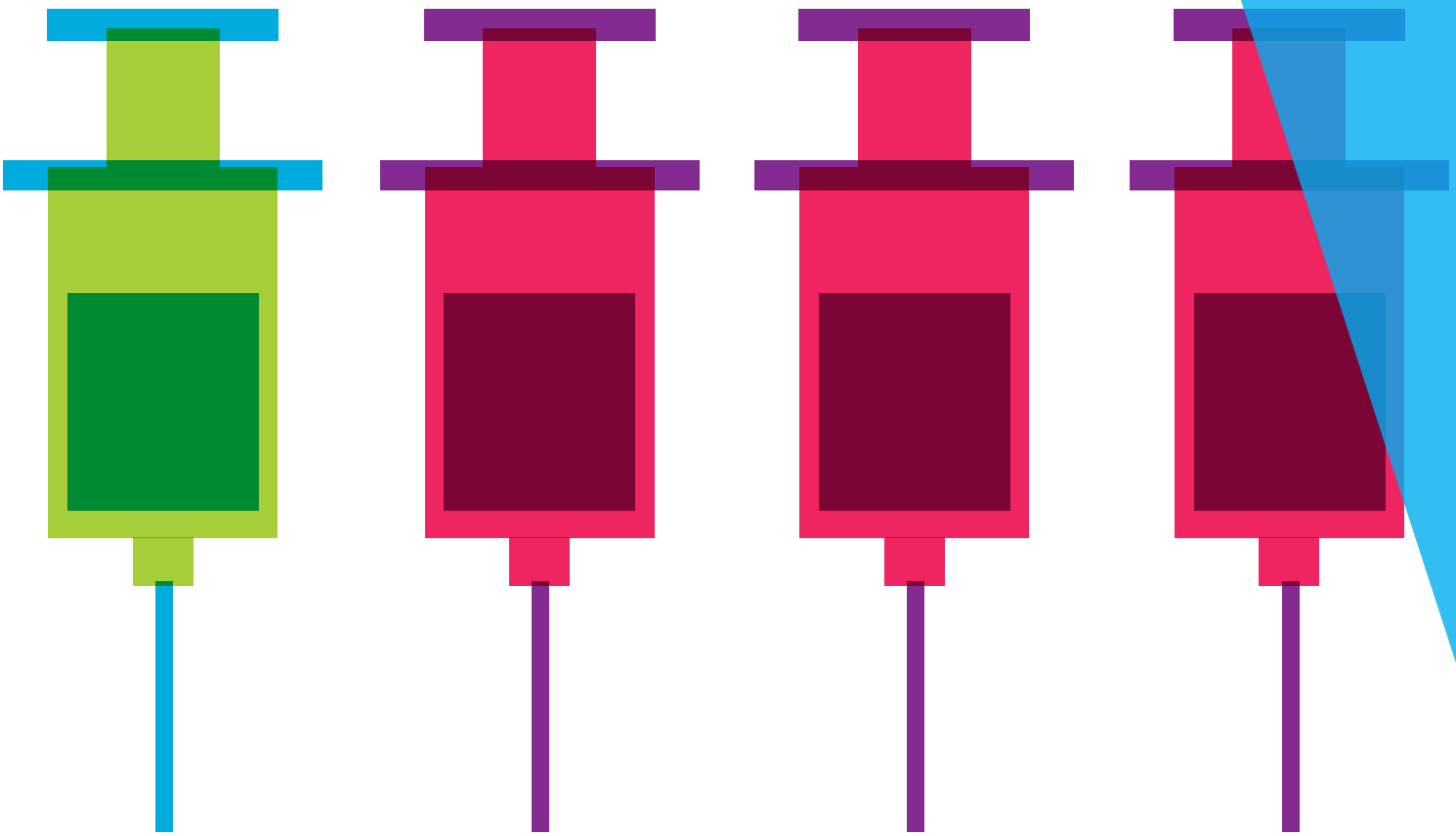
Marks&Clerk

From rare to routine



Life Sciences Report 2015

Medicines for rare diseases, vaccines and antibiotics

Contents

Introduction

Dr Gareth Williams

Welcome to the 2015 Marks & Clerk Life Sciences Report.

The theme of this year's report is "From rare to routine" – a study in innovation in therapeutics for rare diseases to common disorders. We have chosen to look at the patent landscape for three sectors of the life sciences industry which face different challenges and demands in the business of healthcare – rare diseases, antibiotics, and vaccines.

Rare or orphan diseases affect only small proportions of the population, restricting the size of the market for corresponding treatments, potentially making financial return on investment in R&D difficult. However, as we see from the patent filing data, we have been through a decade of intense research into treatments for rare diseases. To counteract the impact of market size on R&D levels for orphan drugs, many governments offer incentives to investment in rare diseases – for example, granting periods of market exclusivity. While patent filings have slightly decreased in this area over the last 10 years, numbers are still much higher than in either of the other areas analysed. It is clear that the research here is driven by "big pharma" companies, despite the growth of niche companies dedicated solely to rare diseases.

The antibiotics sector tells a very different story. In contrast to drugs to treat rare diseases, antibiotics are typically viewed as cheap and useful for treating widespread conditions. However, research levels are extremely low, particularly for new classes of antibiotics. The approaching crisis in antibiotic resistance has the potential to be catastrophic for human healthcare. If incentives for innovation are needed anywhere, research into new antibiotics is one such place. Increasing pressure is being placed on healthcare companies to innovate in this area, and we are beginning to see incentives beyond patent protection being offered by governments. There is also a growing body of research into alternatives to conventional antibiotics, which may help avoid the growth of resistance.

Our report shows that numbers of patent families filed in the antibiotics space have remained generally static over the last 10 years. While many patents are filed around modifications of known antibiotics (penicillins being the most active field, despite the age of such antibiotics), there is some research into new classes. This latter research shows much more volatile patent filing trends, reflecting the uncertainty of innovation, and a distinct set of applicants from patent filings on existing antibiotic classes, suggesting it is the domain of specialists. Here we also see large volumes of filings from Chinese companies like the Tianjin Shengji Group and Shandong Xuanzhu Pharmaceutical Technology. The value of non-patent incentives can be seen from our interviews with NovaBiotics and MerLion Pharmaceuticals, both antibiotics companies and both of which use incentives such as orphan drug designation or qualified infectious disease product designation to ensure that patent protection is aligned with regulatory protection.

The third sector we investigated was vaccines. These perhaps occupy a middle ground between cheaper antibiotics and costlier rare disease therapies. The vaccine field has seen a number of changes recently, with company mergers and divestments, as well as a growing focus on therapeutic vaccines rather than pure prophylaxis. A growing range of diseases are now largely preventable through vaccination, although searches for vaccines against some diseases – notably malaria – continue. Our review of patent filing data showed an increased role played in patenting vaccine technology by public institutions or governments compared with antibiotics or rare diseases. There are also some significant entities clearly involved only in animal health, rather than human health. Vaccine innovation benefits from some regulatory incentives, but also promises a robust and broad

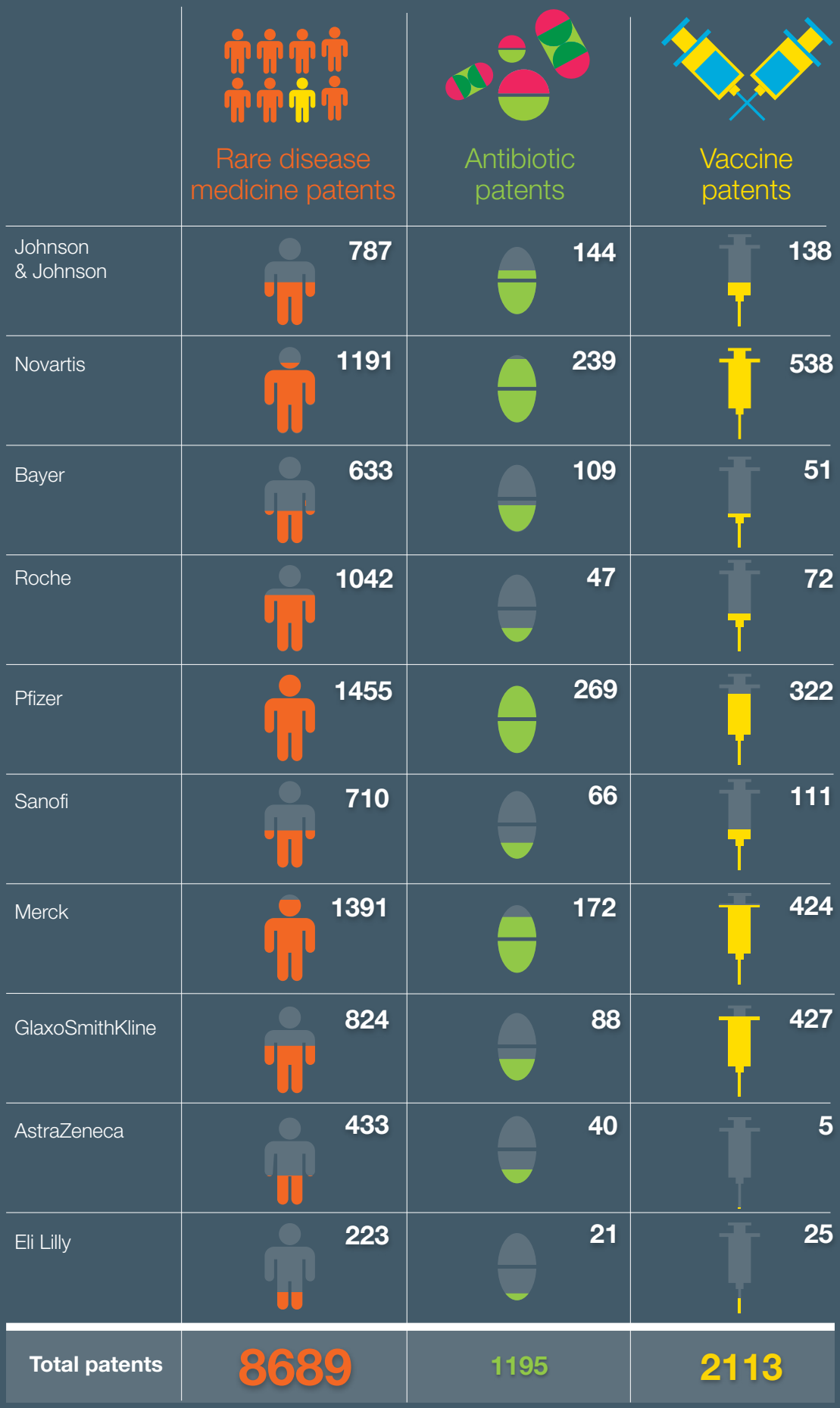
Introduction (cont.)

marketplace if approved, perhaps indicating that this technology hits the sweet spot between insufficient return on investment and high barriers to innovation.

As awareness of the growing threat from antibiotic resistance increases and recommendations from government initiatives like the UK Review on Antimicrobial Resistance are implemented, we expect, and hope, to see research into antibiotics increase. Meanwhile, incentives for R&D into rare disease treatments will likely lead to a continual, if gradual, recovery of patent filing levels associated with orphan drugs. It will be interesting to see how far the story has moved on in a decade's time.

Dr Gareth Williams
Partner, European Patent Attorney
Marks & Clerk

Fig. 1 Patents filed by world's top 10 pharmaceutical companies over the last decade – medicines for rare diseases, antibiotics and vaccines



1 data point per patent family. Data for 2013-2015 incomplete due to 18-month publication delay. List of companies from *Scrip 100* 2014. Numbers include patents filed by subsidiaries

Medicines for rare diseases

While there are clear commercial and ethical drivers for healthcare companies to focus their R&D resources on therapies, treatments and diagnostic tools for prevalent diseases and conditions, the commercial driver for research into therapies that target rare diseases may not be immediately apparent.

Taking into account normal market and economic conditions, research into medicines to treat rare diseases would, potentially, be *de minimis*, due to a lack of any realistic commercial return on the R&D investment. Yet, as our patent data analysis shows, R&D into treatments for rare diseases has been significant over the last decade. We set out below potential explanations for this.

Over the past 15 or so years, governments via their national and supranational regulatory bodies worldwide have introduced various incentives intended to induce companies to invest in developing treatments for conditions only affecting small numbers of people. The incentives offered vary from jurisdiction to jurisdiction, but range from protocol assistance, fee reductions, tax credits, or protection from competing products in the form of market exclusivity periods. Drugs and therapies in development or on the market which meet the specific criteria laid out under legislation receive special “orphan designation”. Such drugs and therapies are often termed “orphan drugs” or “orphan products”.

We list the incentives offered in USA, Europe and Japan (Fig. 2). On an initial glance, no one territory looks particularly more favourable than the other, save that the USA has a seven year exclusivity period, whereas the EU and Japan have 10 years. This is, in part, deliberate, as shared practices and filing strategies are encouraged to promote investment. Arguably, more could be done to bring consistency worldwide to ensure that developers of orphan drugs have similar incentives. A key feature of each programme is the ‘pseudo-monopoly’ established by the market exclusivity periods, designed to give the first mover in a particular therapeutic area a reasonable period of time to make a return on its investment without fear of similar therapies being granted marketing authorisation.

Using the list of rare diseases on Orphanet, the European reference portal for information on rare diseases and orphan drugs, we conducted the following patent data analysis on rare diseases. What is clear from the analysis is that, over the last decade, there has been a huge amount of research into treatments for rare diseases. Whether the overall increase in development is a direct result of the regulatory incentives is difficult to conclude, but there appears to be a correlation.

Fig. 2 Rare Disease definitions and treatment incentives in the EU, USA and Japan

	EU	USA	Japan
Definitions			
Rare Disease	Life threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people (equivalent to <250,000 people in the EU)	Any disease or condition that affects <200,000 people in the USA	Serious and/or difficult-to-treat diseases that affect <50,000 patients in Japan
Orphan designation criteria	Drugs and biologics intended for treatment, prevention or diagnosis of a Rare Disease. OR where, without incentives, the marketing of such drugs will be unlikely to generate sufficient returns to justify the investment in its development. AND no satisfactory method of diagnosis/prevention/ treatment is authorised or if a method does exist, the medicinal product will be of significant benefit to patients.	Drugs and biologics intended for treatment of a Rare Disease. OR the disease or condition affects more than 200,000 people but for which there is no reasonable expectation that the cost of development and making available in the USA will be recovered from sales of the drug in the USA. (The designation can be assigned to a previously unapproved drug or for a new use of an already marketed drug.)	Drugs and medical devices intended for treatment of a Rare Disease. WHERE the disease for which the drug is claimed must be incurable. AND where there is no appropriate alternative device or treatment available OR the efficacy and expected safety of the drug is higher in comparison with other available drugs.
Incentives			
Market exclusivity	Medicines assigned as a 'designated orphan medicinal product' and have marketing authorisation will receive 10 years orphan drug market exclusivity in the EU – approved by the European Commission. An extra two years' exclusivity is added for therapeutics with a paediatric indication. Market exclusivity is assigned to one orphan medicinal product in relation to one indication. Therefore, if one product gains orphan status for multiple indications, it will receive multiple orphan drug market exclusivities upon its market authorisation.	A seven year period of marketing exclusivity is granted for a designated orphan drug, where the FDA will not approve another sponsor's marketing application for a drug with the same active moiety, for the same indication. More than one sponsor can receive designation for the same drug for the same indication however the seven year marketing exclusivity is given to the first sponsor to apply for marketing authorisation. Competitors are not prevented from making the drug available for different uses during the seven year period of exclusivity.	The usual re-examination period is extended from eight to 10 years for a designated orphan drug and four to seven years for an orphan medical device.
Grants, fee reductions and tax credits	**Research Grants** Research grants are mostly available on a member state basis. However some grants are available from the European Commission. **Fee Reduction** Sponsors will receive a fee reduction for marketing authorisation applications, inspections before authorisation, applications for changes to marketing authorisations after approval and reduced annual fees. **Tax Credit** Any tax credits towards clinical studies will be subject to individual member states' tax laws.	**Research Grants** The FDA will provide research grants to support the clinical research that tests the safety and/or efficacy of drugs, biologics, medical devices and medical foods. At this point, it is not compulsory for the products to be assigned an orphan designation. **Fee Reduction** A marketing application for an orphan-designated product is not subject to the prescription drug user fee unless the application includes an additional indication other than to the rare disease designated. **Tax Credit** 50 per cent credit for clinical study expenses per year.	**Research Grants** Sponsors can receive grants and subsidies from the National Institute of Biomedical Innovation (NIBIO) worth up to 50 per cent of the cost of clinical trials. **Fee Reduction** 25 per cent reduction in initial regulatory user fees for review of marketing authorisation application. **Tax Credits** Sponsors receive a tax exemption of up to six per cent off research costs and 10 per cent off corporate tax.
Fast-track marketing approval	Acceleration of market authorisation is only provided if the Committee for Medicinal Products for Human Use (CHMP) deems the product will meet a major public health need. Otherwise there is a deadline maximum of 210 days for the evaluation of an application.	There is no fast-track marketing approval. However, if the product receives approval for a rare paediatric disease the sponsor will receive a 'voucher' for a priority review of a subsequent marketing application for a different product.	Designated orphan drugs and medical devices are automatically placed on a fast-track approval process taking 10 months instead of 12.
Protocol assistance	Sponsors can obtain assistance in developing a study that best demonstrates the quality, benefits and risks of their product. The protocol assistance is available at a reduced charge and is linked to a fee reduction scale that depends on the status of the sponsor.	The FDA may provide protocol assistance for research and clinical studies.	**Pre-designation** The Ministry of Health Labour and Welfare (MHLW) provides consultation on whether a product may be eligible for orphan designation. **Post-designation** Pharmaceuticals and Medical Devices Agency (PMDA) and NIBIO provide advice on clinical trial design for marketing approval and the use of data derived from foreign and/or Japan- based clinical studies.

Despite this, over the past 10 years the number of patent families has gradually declined (Fig. 3). The number of families peaked at 4,436 in 2005. However, close analysis shows that this is the result of a dip in filing numbers in 2008 and 2009 – a result of the financial crisis. Since then, numbers have slowly begun to rise again. We have also seen a decline in the total number of patent applications filed, the peak being in 2006 with 44,197 applications filed, dropping to just over half that number in 2012 (24,482). This suggests that in addition to fewer families being filed in this area, where they are filed, fewer applications are being filed per family.

Nonetheless, the annual numbers of patent families filed relating to rare disease research overall remain far higher than for vaccines and antibiotics. This indicates a much larger interest in these diseases than arguably might have been expected.

The geographical distribution of patent filings in this field unsurprisingly shows the USA is the top jurisdiction for filing patents related to rare diseases research, with 87,491 applications being filed between 2004 and 2015 (Fig. 4). The USA is also the clear leader as destination of choice for priority applications. The usual players follow behind; Europe, Japan, Australia, Canada and China, although notably, the total number of applications filed in Europe was almost half that filed in the USA at 46,773 applications.

Fig. 3 Patent applications (families and total) relating to rare disease medicine research

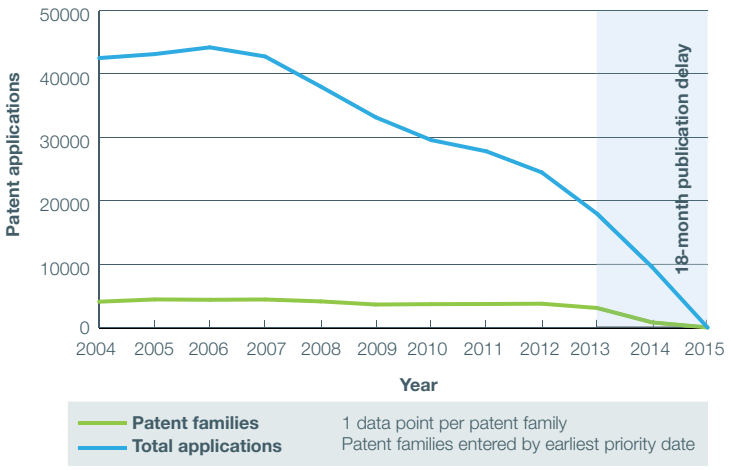
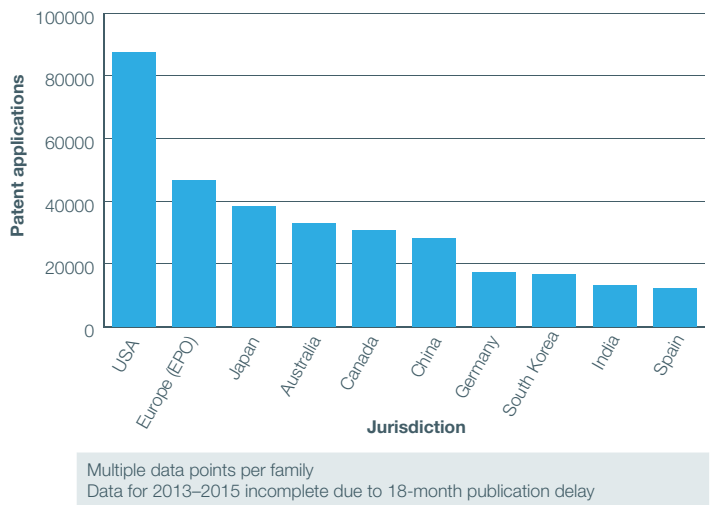


Fig. 4 Patent applications (total) relating to rare disease medicine research filed in top jurisdictions (2004–2015)



Following a general upward trend to 2010, the number of patent families related to rare diseases research containing at least one US application has since declined (Fig. 5). In Europe, numbers have remained relatively steady following an upward trend to 2008 (Fig. 6).

Numbers of families containing at least one Japanese application have demonstrated an almost uninterrupted year-on-year increase (Fig. 7). This indicates an increasing focus on Japan as a market for rare diseases treatments. In China, the numbers indicate an increasing volume of applications filed, with a recovery of the upward momentum lost by a dip in 2010 already in place (Fig. 8).

The data on the number of patents being granted seems to tell a different story to the downward global trend in total patent applications. From 2004 to 2014 the total number of patents granted rose considerably, from just 7,821 to 20,532. This is also reflected in the numbers of families with at least one patent granted in each of the USA, Europe, Japan and China. One possible explanation could be that applicants are changing their filing behaviour, filing fewer speculative applications and more (although less frequent) robust applications, perhaps directed to their core technologies. However, this upward trend is expected to reverse in the coming years as the decrease in total patent applications takes its toll.

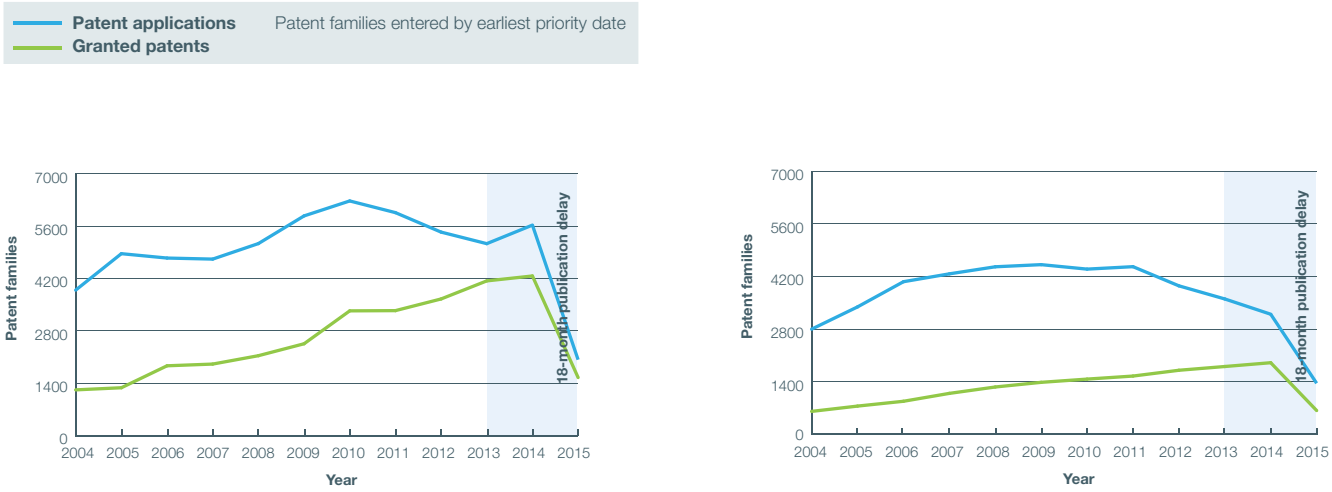


Fig. 5 Patent families containing at least one US application and at least one granted US patent relating to rare disease medicine research

Fig. 6 Patent families containing at least one European application (at the EPO) and at least one granted European patent relating to rare disease medicine research

Fig. 7 Patent families containing at least one Japanese application and at least one granted Japanese patent relating to rare disease medicine research

Fig. 8 Patent families containing at least one Chinese application and at least one granted Chinese patent relating to rare disease medicine research

Fig. 9 Top Filers of patents relating to rare disease medicine research (2004–2015)

1	Novartis	778
2	Merck	736
3	GlaxoSmithKline	516
4	University of California	439
5	Roche	435
6	Boehringer Ingelheim	362
7	Janssen Pharmaceuticals	350
8	Sanofi	340
9	Genentech	323
10	Pfizer	322
11	L'Oréal	274
12	Abbvie	266
13	University of Texas	251
14	Amgen	233
15	Vertex Pharmaceuticals	227
16	AstraZeneca	224
17	Allergan	223
18	Bristol-Myers Squibb	212
19	Johns Hopkins University	210
20	Wyeth	200

Data for 2013–2015 incomplete due to 18-month publication delay
1 data point per patent family

The list of Top Applicants in rare diseases shows clear dominance by the world's largest healthcare companies – often referred to as "big pharma" (Fig. 9). When filings from the subsidiaries of "big pharma" companies are combined with those of their parent companies, this pattern becomes even starker (Fig. 1).

The difference in patent numbers between the list of individual Top Filers and filings when subsidiaries of the world's largest healthcare companies are combined with those of their parent companies demonstrates the large volume of patents being filed through subsidiaries. Fig. 1 clearly has Pfizer companies as filing the most patents relating to rare diseases. With Wyeth number 20 on the list of Top Filers, despite having just one priority filing recorded since its acquisition by Pfizer in 2009, Wyeth and its subsidiaries' portfolio of patents and patent applications in rare diseases provided a significant boost to Pfizer's own.

Not only does "big pharma" dominate, but 13 of the Top 20 Applicants are based in the USA. Only three are universities and there are no other public organisations present. Although Novartis, a multinational pharmaceutical company headquartered in Basel (Switzerland), is the top individual applicant with 778 patent families, US-based Merck is very close behind with 736. This result goes some way to explaining the results in Fig. 4.

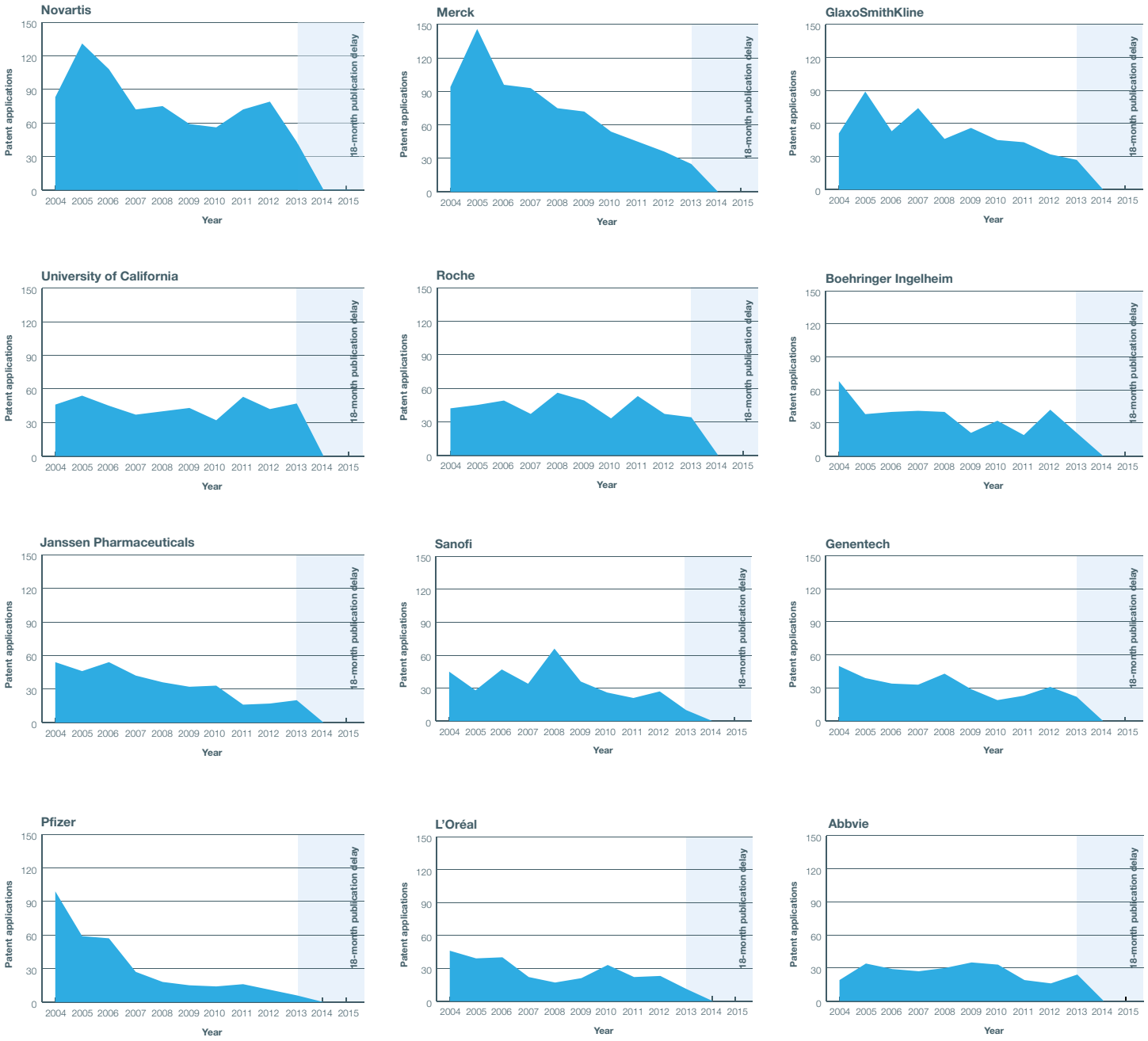
A perhaps unexpected entrant in the list of Top Filers, L'Oréal filed applications for 274 patent families in the field of rare diseases between 2004 and 2015, according to our search parameters. Most of L'Oréal's applications appear to relate to cosmetic-related inventions, with some having secondary uses for medical treatments of rare conditions. These include, for example, treatments for inflammatory skin disorders and methods for promoting epidermal stem cell multiplication or epidermal renewal, which can be used in anti-ageing cosmetic products.

While year-on-year analysis of the patent families and total patent applications filed by the Top Filers over the last decade shows that many are filing fewer patents related to rare diseases, this may be explained by the number of patents being applied for by subsidiaries (Fig. 10).

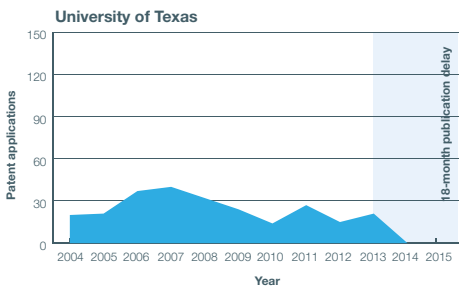
The generalised downward trend for Top Filers is not reflected among the universities, where numbers of patent filings have remained consistent across the period studied. For example, in 2004, the University of California filed 46 applications. This number also peaked in 2005 at 54 applications, but until 2013 at least, the University of California consistently filed between 30 and 55 applications each year in this field.

There is clear recognition from the relevant authorities regarding the importance of these therapeutic areas, clinically, ethically, economically, and politically. Despite the overall decrease in patent filings, there has been a general upward worldwide trend in investment into rare disease. What remains to be seen is whether the slight downward trend now being experienced is in any way reflective of the current incentive schemes offered, and not just a blip due to the harsh market conditions since 2007. What the data analysis does show, however, is that when the individual rare diseases are viewed together, the footprint is vast, and appears to provide pharmaceutical companies with a viable avenue for streams of R&D.

Fig. 10 Patent applications (families) relating to rare disease medicine research by Top Applicants



1 data point per patent family
Patent families entered by earliest priority date


University of Texas
Patent applications
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18-month publication delay
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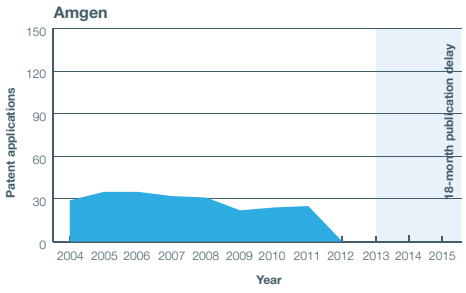
Amgen
Patent applications
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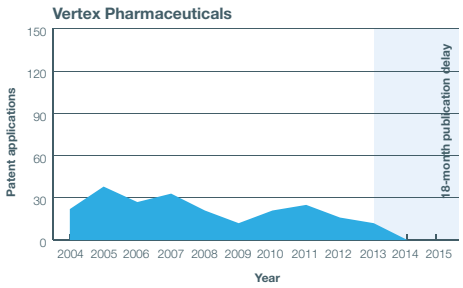
Vertex Pharmaceuticals
Patent applications
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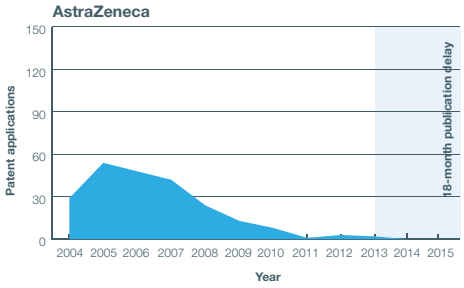
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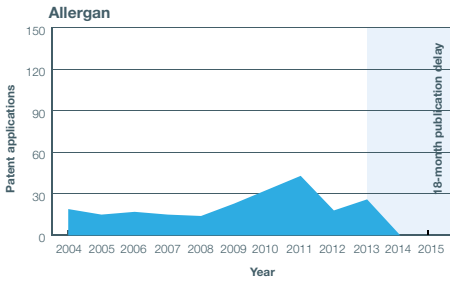
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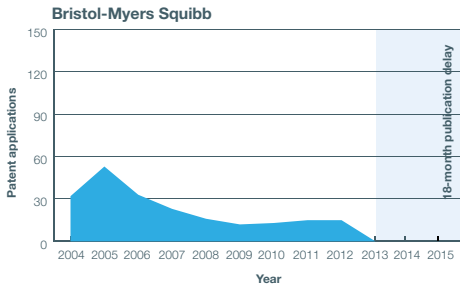
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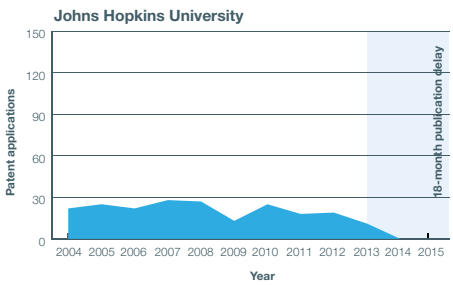
Johns Hopkins University
Patent applications
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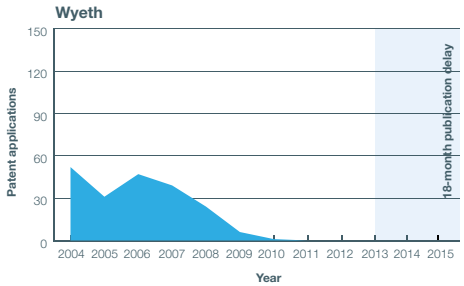
Wyeth
Patent applications
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Year

Antibiotics

Since first discovered and used early in the 20th century, antibiotics have revolutionised medicine. Where once microbial diseases were a death sentence, antibiotics have offered a safe and reliable treatment. In almost 100 years of use, we have discovered and developed a battery of compounds with potent activity.

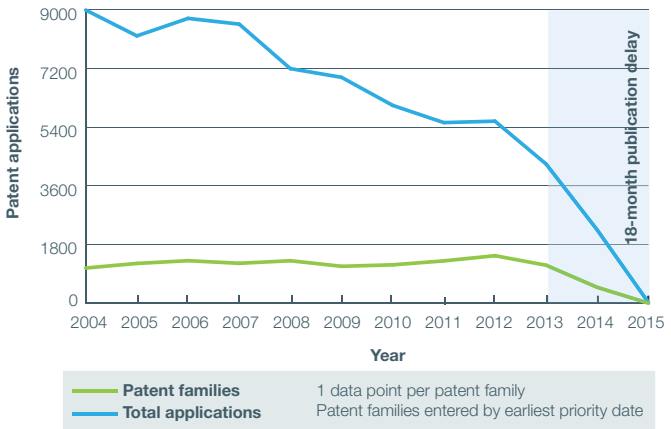
Antibiotics are frequently classed according to their mechanisms of action. Those that are bactericidal tend to target and affect components of the microbial cell wall or membrane or inhibit the action of enzymes essential to microbial function. For example penicillin (an antibiotic belonging to the β-lactam class) inhibits the formation of essential peptidoglycan cross-links in the bacterial cell wall. The bactericidal family of antibiotics also includes those belonging to the quinolone, cephalosporin, aminoglycoside and polymyxin classes. Other antibiotics are bacteriostatic and these include the macrolide and tetracycline antibiotics.

Through over-use in human health and animal husbandry, recent decades have seen the emergence of microorganisms resistant to antibiotics from virtually every available class. Today there are numerous examples of clinically significant antibiotic-resistant microorganisms posing a significant health risk. Over-use and mis-use of antibiotics in hospitals has created a microclimate in which organisms such as *C. difficile* and *S. aureus* can develop resistance. In 2013, the World Health Organisation reported that there were an estimated 480,000 new cases of multi-drug resistant tuberculosis. Further strains of *Mycobacterium tuberculosis* classed as extensively drug-resistant (that is, multi-drug resistant and resistant to any fluoroquinolone and any second-line injectable drug) have been identified in 100 countries, in all regions of the world.

While legislation and education are being used to curb the unnecessary use of antibiotics, there is an urgent need to identify not just effective derivatives of antibiotics currently in use, but novel antibiotics and new classes. Between 1940 and 1962, more than 20 new classes of antibiotics were marketed. Since then, very few new classes have reached the market. However, a heightened awareness of the problem of resistance is driving new R&D in this field.

The number of patent families being filed in the field of antibiotics has been steady over the last 10 years (Fig. 11), with numbers remaining in the region of approximately 1,200 families filed each year.

Fig. 11 Patent applications (families and total) relating to antibiotic research



NovaBiotics – an interview with Deborah O'Neil, CEO and CSO

NovaBiotics spun out of the Rowett Institute (now part of the University of Aberdeen) in 2004. It remains Aberdeen (UK)-based, but in 2014 established a wholly owned US subsidiary, NovaBiotics Inc., to facilitate upcoming trials for its clinical candidate for the treatment of cystic fibrosis. The company focuses on the development of novel anti-infective agents for clinically challenging bacterial and fungal infections. Its most advanced products are its clinical candidates Novexatin®, an antifungal cationic peptide for the treatment of fungal nail infection and Lynovex®, its cystic fibrosis candidate, with clinical development of Novexatin® having been led by NovaBiotics' exclusive global licensee/ partner Taro Pharmaceuticals since 2013. Its earlier-stage candidates include Novamycin®, an antifungal peptide developed for treatment of yeast and mould infections, and anticipated to enter clinical trials in 2016; and Novarifyn®, a family of antibacterial peptides active against a range of difficult-to-treat pathogens including *MRSA*, *P. aeruginosa*, *C. difficile*, *A. baumannii* and *E. Coli*. We spoke to Dr Deborah O'Neil, who is both CEO and CSO at NovaBiotics, not to mention inventor or co-inventor on many of the company's patents, to discuss the company's IP and regulatory strategy.

IP strategy

"NovaBiotics' core IP is its expertise in relation to antimicrobial cationic peptides platform technology to which our initial patent filing was directed. Novexatin® is covered by this filing, as well as three subsequent patent filings, which focus on the cyclic structure of Novexatin®, the organisms against which it is targeted and an infection model. Novamycin® and Novarifyn® are also cationic peptides, and also protected by our initial filing as well as subsequent patent filings, which illustrates the value of this technology to NovaBiotics.

"Our cystic fibrosis candidate Lynovex® arose from our finding that a very small (molecular weight less than 80 Da) molecule cysteamine allows amounts of antimicrobial agents, including antibiotics, to be minimised in the treatment of microbial infections. This is because cysteamine potentiates the effects of currently available antibiotics; a finding with application not only in the context of NovaBiotics' antimicrobial cationic peptides but also in other antibiotic classes. Separately, our research has applicability to other chronic respiratory conditions. As with our cationic peptides, we have aggressively pursued patent protection for this technology"

Repurposing and Orphan Drug designation

"Cysteamine is already approved for use in the rare metabolic disease cystinosis. Its repurposing, for use in treating cystic fibrosis, offers the potential for fast-track clinical development of the drug. Our successful applications for Orphan Drug designation for Lynovex® in both the USA and Europe, and the accompanying market exclusivities, offer tangible commercial benefits to our pursuit of a milestone treatment for this debilitating disease. Moreover, the Orphan Drug designations we have received for cysteamine extend to its use both as an active pharmaceutical ingredient (API) or as an adjunct, for example with other antimicrobial therapies, which illustrates the alignment of our patenting and regulatory strategies"

Partnering strategy

"We recognise that we cannot do everything and view our strategic partnering with Taro Pharmaceuticals as taking risk out of the business; it allows each of us to play to our strengths, with us as a small company retaining our focus on our innovation. In other technology, however, we aim to retain more control of commercialisation and thereby to retain more value. We believe that our pragmatism in seeking to translate our pipeline to the clinic may be appealing to investors; a potential investor in NovaBiotics once told me it was refreshing to meet a company that 'doesn't think gravity doesn't apply to them'!"

Resurgence in antimicrobial research, and rare diseases

"Clearly, it is an incredibly exciting time to be a leading innovator in the anti-infectives space, notably (but not exclusively) antibiotics. After years of neglect and indeed a number of major players exiting this technology, it seems clear that we are at the beginning of a resurgence in activity, likely to be driven by SMEs such as NovaBiotics. Although we think reformulation of some existing APIs, for example into topical treatments, are likely to become more frequent at the "pharma" end of the spectrum, we also think the development of novel APIs and novel disruptive technologies such as those of NovaBiotics by SMEs and academia are also likely to play an increasing role, often with genuine partnering at mid- to late-stage development.

"NovaBiotics has a pipeline of both clinical and preclinical antimicrobial candidates for a diverse group of medically unmet and difficult-to-treat conditions, developed from novel technologies developed in-house using rational drug design principles. Although we are proud of the technology behind our pipeline, we are more excited about the huge difference we hope these technologies will make to traditionally neglected therapies. In clinical and commercial terms, NovaBiotics technology is very much in the right place at the right time."

"Clearly, it is an incredibly exciting time to be a leading innovator in the anti-infectives space, notably (but not exclusively) antibiotics."

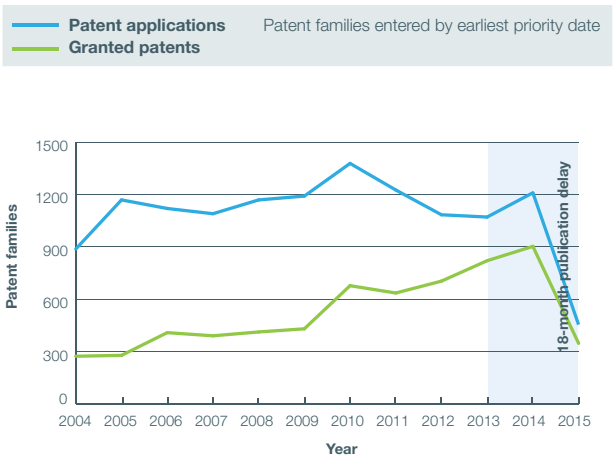


Fig. 12 Patent families containing at least one US application and at least one granted US patent relating to antibiotic research

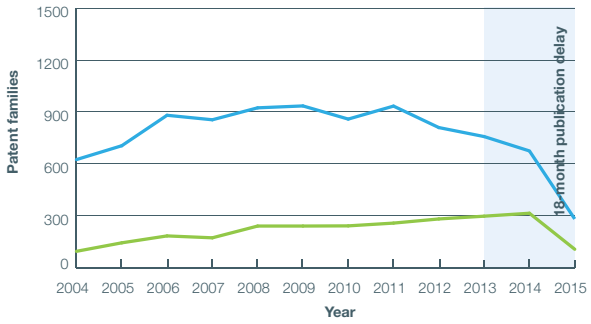


Fig. 13 Patent families containing at least one European application (at the EPO) and at least one granted European patent relating to antibiotic research

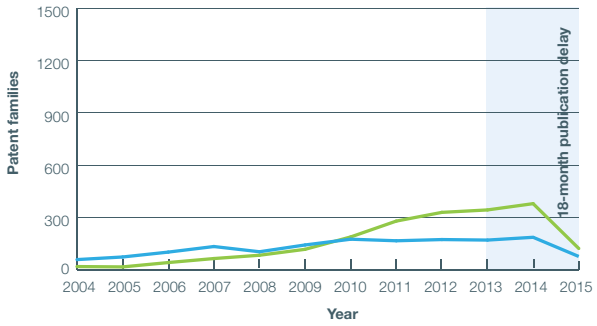


Fig. 14 Patent families containing at least one Japanese application and at least one granted Japanese patent relating to antibiotic research

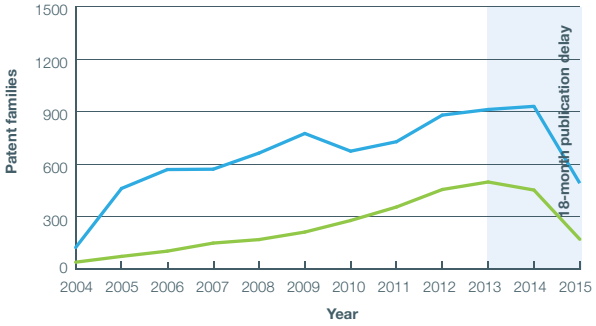


Fig. 15 Patent families containing at least one Chinese application and at least one granted Chinese patent relating to antibiotic research

In contrast, the total number of patent applications filed worldwide each year has seen a drop from 2007 (8,565) to 2012 (5,586). It is tempting to suggest that as a consequence of increasing financial pressure resulting from the recent economic downturn, applicants are beginning to adopt increasingly restricted filing strategies (i.e. fewer patent applications per family), with a focus on a smaller number of key jurisdictions. However, a further factor may be a general apathy towards antibiotic innovations. A potentially poor return on the money and time required to bring new antibiotics to market may be turning private industry towards more lucrative research projects.

Of the Top Jurisdictions, the year-on-year numbers of patent families filed in this area containing at least one US application have remained the steadiest, varying between 888 and 1,378 (Fig. 12). Families with European applications have also remained relatively steady since 2006 at around 900 per year (Fig. 13).

The number of families containing applications filed in Japan (Fig. 14) was increasing year-on-year from 2004 to 2010, with the exception of 2008. However, since 2010, it has remained relatively steady. Families with applications in China show a clear upward trend, despite a dip in 2010 and 2011 (Fig. 15).

Fig. 16 Top Filers of patents relating to antibiotic research (2004–2015)

	Organisation	Patents
1	Tianjin Shengji Group	92
2	Shandong Xuanzhu Pharmaceutical Technology	81
3	University of California	77
4	Novartis	73
5	Merck	66
6	Wyeth	63
7	Sulur Subramaniam Vanangamudi *(individual)*	62
8	Ranbaxy Laboratories	52
9	University of Texas	52
10	Hainan Weikang Pharmaceuticals (Qianshan)	47
11	Bilgic Mahmut (Neutec)	41
12	Pfizer	40
13	Medtronic	35
14	Amgen	31
15	Foamix Pharmaceuticals	30
	Janssen Pharmaceuticals	30
17	GlaxoSmithKline	29
	Abbvie	29
	Achaogen	29
	Auspex Pharmaceuticals	29

Data for 2013–2015 incomplete due to 18-month publication delay
1 data point per patent family

Nevertheless, despite the worldwide decline in the number of filings in the area of antibiotics, the number of granted patents has been increasing year-on-year since 2004. This is consistent across the USA, Europe, Japan and China. Factors contributing to this may include, for example, a reduction in the number of speculative applications that never reach grant, indicating a greater understanding among applicants of where to focus research efforts as well as how to navigate the legal obstacles to patenting inventions in this field. Other possible explanations include a reduction in the backlog of patent applications in the major patent offices. However, taking into consideration the four to five (or more) year period between filing and grant, we may soon start to see deceleration and possibly a decline in the number of patents being granted in this field.

Unsurprisingly, the USA was the territory that saw the highest number of patent filings in the period between 2004 and 2015, with a total of over 19,500 filings (Fig. 17). This was almost twice the number of filings in Europe – the second highest ranked jurisdiction. While the USA received the most number of filings by some distance, numbers were relatively close between the next highest territories, including Europe, China, Japan, Australia and Canada, all of which saw between approximately 9,500 and 6,000 filings.

It is also notable that, despite the current uncertainty surrounding patentability in the field of medical compositions in India, this territory remains a jurisdiction of interest for many applicants.

Further analysis of the data reveals that the USA was also the territory that saw the highest number of priority filings in the period between 2004 and 2015 (6,891 first filings). This was consistent with the nationalities of the Top Applicants. China followed in second place (4,400 first filings for the same period). All other jurisdictions represented a minor proportion of global first filings in comparison, the EPO being the next closest with fewer than 700 first filings.

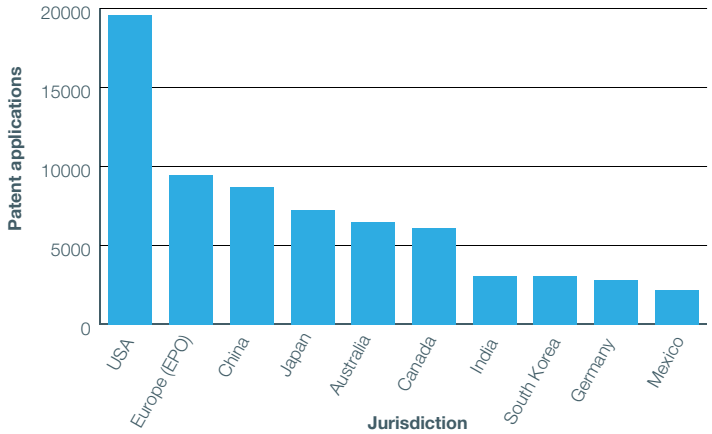
The 20 Top Filers in this field are dominated by private companies, with only two being classed as public entities, both of which are US universities (the University of California and the University of Texas) (Fig. 16).

Just over half of the 20 Top individual Filers are USA-based, with the remaining organisations originating from China (three), India, the United Kingdom, Switzerland, Turkey and Israel (one each).

The two largest individual filers of patent applications (families) related to antibiotics are both Chinese companies: Tianjin Shengji Group and Shandong Xuanzhu Pharmaceutical Technology. Further examination reveals that these companies are adopting relatively restrictive filing strategies, indicating China-centric behaviour. Of the world's largest pharmaceutical companies, Novartis, Merck, Pfizer, GlaxoSmithKline and Janssen Pharmaceuticals (a Johnson & Johnson company) are all individually present among the 20 Top Filers.

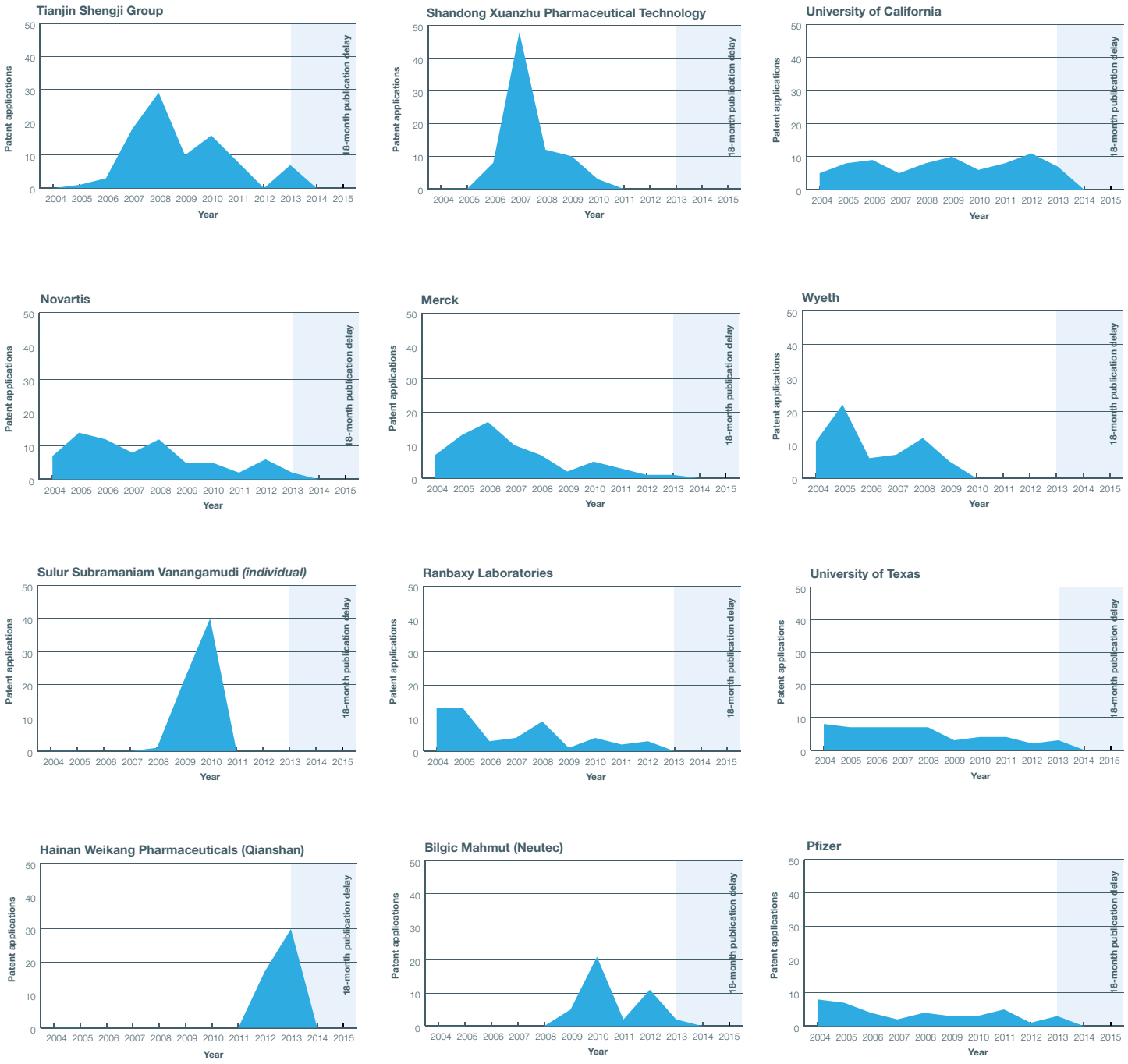
When filings from the subsidiaries of "big pharma" companies are combined with those of their parent companies, it becomes clear that together "big pharma" groups are more active in this field than any individual player (Fig. 1). Pfizer companies filed the most applications (269), with Novartis, Merck, Johnson & Johnson and Bayer companies all filing more than 100 families each (239, 172, 144 and 109 respectively).

Fig. 17 Patent applications (total) relating to antibiotic research in Top Jurisdictions (2004–2015)

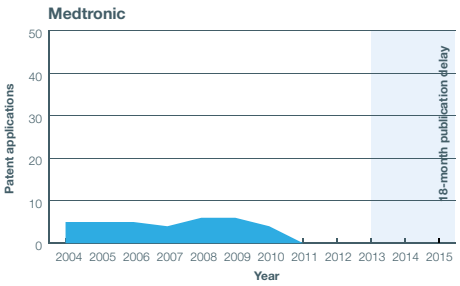


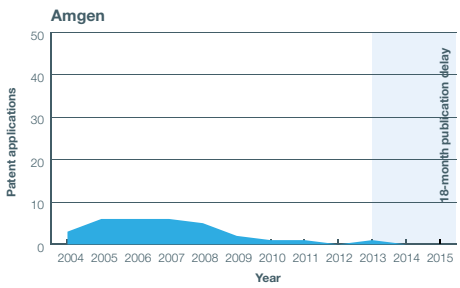
Multiple data points per family
Data for 2013–2015 incomplete due to 18-month publication delay

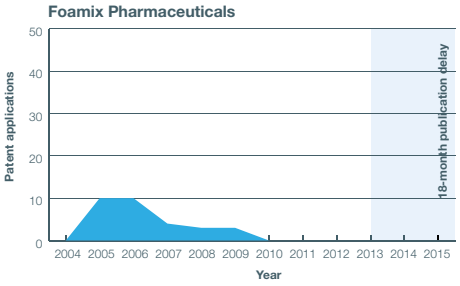
Fig. 18 Patent applications (families) relating to antibiotic research by Top Applicants

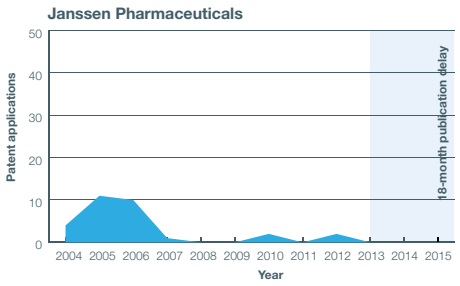


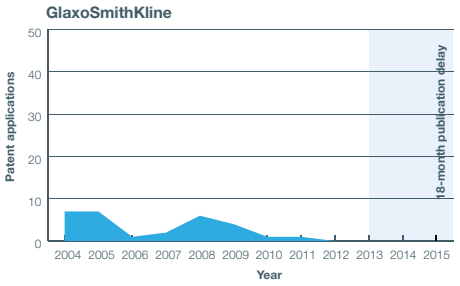
1 data point per patent family
Patent families entered by earliest priority date

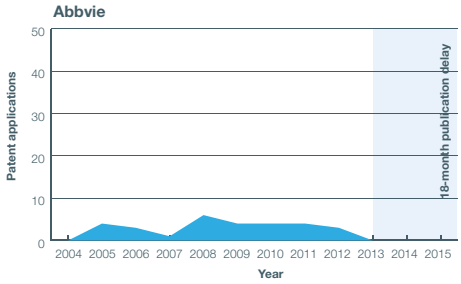


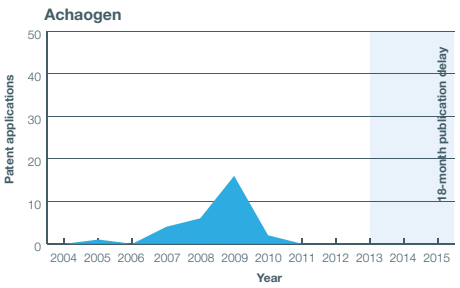


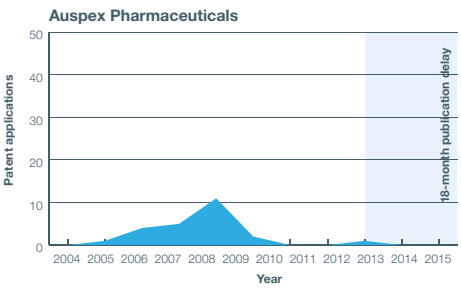












Analysis of individual applicants' filing levels over the years indicates varying behaviours (Fig. 18).

The majority of Top Filers have experienced a decrease in their total number of patent families filed in recent years, including the top two filers, Tianjin Shengji Group and Shandong Xuanzhu Pharmaceutical Technology. However, a number of Top Filers have maintained a relatively steady number of family filings since 2007. A notable example of this latter behaviour is the University of California. The University of Texas has also consistently been filing patent applications in this area, although numbers have decreased from a high of eight in 2004 to two in 2012. This may well indicate that these public organisations have suffered less of an impact from the financial crisis or that they are generally less concerned with the problems and cost associated with bringing antibiotics to market.

Several applicants demonstrate filing behaviour associated with "disruptive technologies" – where there has been a sudden increase in patent filings: Hainan Weikang Pharmaceutical (Qianshan), Bilgic Mahmut (Neutec), Harbin Pharmaceuticals, and Chongqing Lummy Pharmaceutical. With three of these organisations being Chinese, it is unsurprising China is seen as emerging as a major force in the field of antibiotics.

Research into known classes of antibiotics

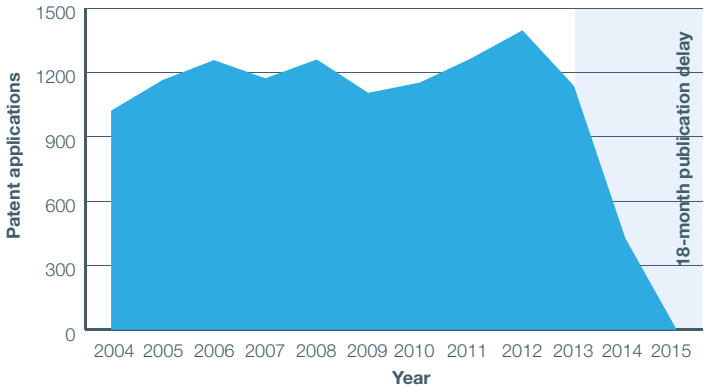
Since the mid-1980s, the world has relied on the efficacy of antibiotics derived from a finite number of established and well-used antibiotic classes. However, the emergence of antibiotic-resistant microorganisms and the threat this poses to human health place an immense pressure on this resource. The solution lies in part with finding new antibiotic classes or more active derivatives of existing compounds. With no new class of antibiotics making its way into general use in the last 20 years, many companies might see that innovations from within the existing pool of effective compounds offer the best chance of success.

Known classes of antibiotics	
Penicillins	• Group of antibiotics produced by fungi. • Common to all is a four-membered β-lactam ring which inhibits bacterial cell wall formation. • Still widely used but resistance has developed in many bacterial species.
Aminoglycosides	• Group of antibiotics that includes gentamicin, kanamycin and streptomycin. • Mode of action is inhibition of protein synthesis. • Mainly used against gram-negative aerobic bacteria such as *Pseudomonas*, *Acinetobacter* and *Enterobacter* species. • Highly toxic, although there is revived interested in their use due to increasing resistance to other antibiotics.
Macrolides	• Belong to the polyketide class of natural products. • Antibiotic macrolides, such as erythromycin, are mainly used to treat infections caused by Gram-positive bacteria. • Some macrolides are not antibiotics but have antifungal or immunosuppressant activity.
Cephalosporins	• A class of β-lactam antibiotics which are less susceptible to β-lactamases than other β-lactams such as penicillins. • Members are grouped into "generations" based on their spectrum of activity. Fourth generation cephalosporins have broad-spectrum activity.
Fluoroquinolones	• Broad-spectrum synthetic antibiotics belonging to the wider quinolone family. • Recommended for use in cases of multi-drug resistance when other antibiotics have failed to be effective.
Against mycobacteria	• The genus *Mycobacterium* includes the pathogens which cause tuberculosis and leprosy. • *Mycobacterium* species have a characteristic thick cell wall which makes infection difficult to treat. • Antibiotics active against mycobacteria include rifampin, ethambutol, isoniazid, pyrazinamide and streptomycin.
Sulfonamides	• Bacteriostatic agents that act by inhibiting an enzyme (DHPS) involved in folate synthesis. • Used to treat a variety of infections, including ear infections, urinary tract infections and bacterial meningitis.
Tetracyclines	• Broad spectrum polyketide antibiotics, commonly used in the treatment of acne. • Mode of action is through inhibition of bacterial protein synthesis. • Resistance has emerged through at least three mechanisms, including enzymatic inactivation of the antibiotic, efflux, and ribosomal protection.
Glycopeptides	• Class includes vancomycin, which is used to treat MRSA. • Narrow spectrum of activity, being mainly effective against Gram-positive cocci. • Restricted use due to their toxicity.
Lincosamides	• Include the natural product lincomycin and its semi-synthetic derivative clindamycin. • Clindamycin is active against anaerobic bacteria and can also be used to treat malaria. • Inhibit bacterial protein synthesis by binding to the 23s part of ribosomes. • Resistance occurs through methylation of the 23s binding site.
Carbapenems	• β-lactam antibiotics which are the drug of last resort against many infections, such as *E. coli*. • Although highly resistant to most β-lactamases, there are concerns over resistance due to the spread of genes encoding carbapenemases – enzymes that hydrolyse carbapenems.
Polypeptides	• Examples include actinomycin, bacitracin, colistin, and polymyxin B. • Actinomycin D was the first antibiotic shown to have anti-cancer activity. Bacitricin is widely used as a topical agent.
Ansamycins	• A family of secondary metabolites, which includes streptovaricins and rifamycins. • Rifamycins are widely used against infections caused by mycobacteria, including tuberculosis and leprosy.
Monobactams	• β-lactam antibiotics in which the β-lactam ring is not fused to another ring. • Aztreonam, the only commercially available monobactam, is active against some gram-negative bacteria, including *P. aeruginosa*.
Nitrofurans	• A class of antibacterial drugs defined by a five-membered aromatic ring with a nitro substituent. • An important member of the class is nitrofurantoin, which is a first-line agent for the treatment of urinary tract infections due to its efficacy and low rate of bacterial resistance.
Oxazolidinones	• Considered as the treatment of last resort against gram-positive infections such as MRSA. • Prevent protein synthesis by disrupting translation. • Their unique mechanism of action means that cross-resistance with other protein-synthesis inhibitors is rare.
Carbacephems	• Synthetic antibiotics similar in structure to cephalosporins. • Loracarbef was the first carbacephem to undergo clinical development.
Lipopeptides	• Class includes Daptomycin, which is a naturally occurring compound active against gram-positive bacteria by interfering with cell membrane function.
Others	Including: • Arsphenamine • Chloramphenicol (broad spectrum bacteriostatic agent) • Fosfomycin • Fusidic acid (used in combination therapy against MRSA) • Metronidazole • Mupirocin (polyketide antibiotic active against MRSA) • Platensimycin • Thiamphenicol (potent analogue of Chloramphenicol) • Tigecycline (first clinically available drug in new class of antibiotics called the glycylcyclines, designed to overcome resistance to tetracycline) • Tinidazole (member of nitroimidazole family of antibiotics) • Trimethoprim (treatment of urinary tract infections; inhibits bacterial DNA synthesis).

The data shows that while there is a regular (bi-annual) decrease in the number of patent families filed within the known classes of antibiotics, the numbers have been consistently high (Fig. 19). Since 2010, there has been a yearly increase, although it remains to be seen whether this will continue. With the numbers of patent applications directed towards research into known classes of antibiotics much higher than in new classes, it is unsurprising that the list of top filing organisations almost mirrors that for all research into antibiotics, with Tianjin Shengji Group and Shandong Xuanzhu Pharmaceutical Technology leading, followed by the University of California.

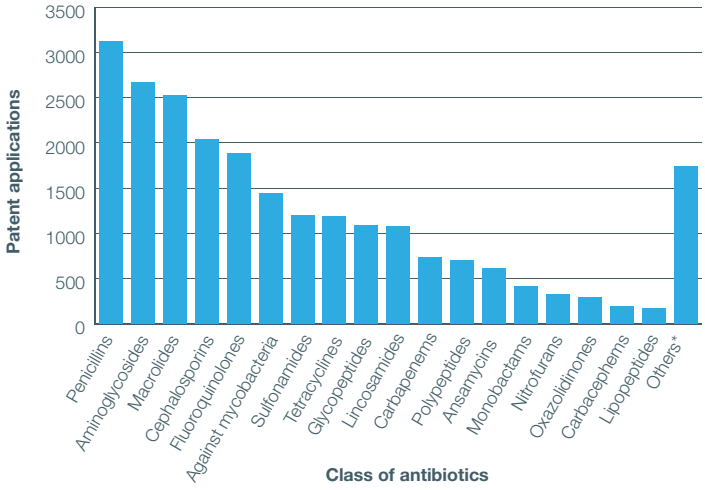
Analysis of patents relating to specific classes of antibiotics, where specified in the patent application, shows that more patent applications (families) were directed towards the penicillin antibiotics than any other known class (Fig. 20). Despite widespread resistance and their almost persistent use for 70 years, it is clear that the penicillin antibiotics remain an important tool in medicine. The emergence of resistance has perhaps reduced the utility of traditional forms of penicillin but it would seem that there is still a keen interest in this drug with research into new derivatives and formulations finding therapeutic application. The data further shows significant innovation within the field of aminoglycoside and macrolide antibiotics.

Fig. 19 Patent applications (families) relating to research into known classes of antibiotics



1 data point per patent family
Patent families entered by earliest priority date

Fig. 20 Patent applications (families) relating to research into specific known classes of antibiotics (2004–2015)



1 data point per family
Data for 2013–2015 incomplete due to 18-month publication delay
*Arsphenamine, Chloramphenicol, Fosfomycin, Fusidic acid, Metronidazole, Mupirocin, Platensimycin, Thiamphenicol, Tigecycline, Tinidazole and Trimethoprim

Fig. 21 Top Filers of patents relating to research into new classes of antibiotics (2004–2015)

1	Amgen	21
2	Pfizer	12
	Schering Corporation	12
	Merck	12
5	HE Han *(individual)*	11
6	US Health	10
7	Novartis	7
8	TNO	5
9	IRM	4
	Bioneer Corporation	4
	East Sunshine Pharmaceuticals Guangdong	4
	Srinivas Jegannathan *(individual)*	4
	Romark Laboratories	4
14	Dow Agrosciences	3
	Aquilus Pharmaceuticals	3
	BASF	3
	Corcept Therapeutics	3
	Qingdao Honghao Sheng Technology	3
	University of Shandong	3

Data for 2013–2015 incomplete due to 18-month publication delay
1 data point per patent family

Research into new classes of antibiotics

It is a fact that microorganisms will constantly outpace research into and development of new drugs. As such, the provision of modified versions of existing drugs can only ever provide a temporary solution to the problem of antibiotic resistance. The discovery of new antibiotic classes would undoubtedly offer the best prospect of a more permanent fix. However, the diversity of microorganisms is such that we are not looking for a single new class of antibiotics but rather a new cohort of novel drugs which, with proper management, could be effective for many decades. This next section looks at the patent filing statistics within the field of new antibiotic classes.

The number of family filings relating to new classes of antibiotics has been unsteady since 2004 (Fig. 22). Not unexpectedly, the data appears more volatile and the numbers much lower when compared to the data obtained for known classes of antibiotics. It indicates we are still struggling to repeat the success we had in the 20th century in this field. However, if we are to win the battle against antibiotic resistance, this must change and it is hoped that in the years to come, the number of patents protecting new antibiotic classes will rise. Detailed analysis of the data shows similar filing behaviours (including geographies of choice) as in other areas of research.

The Top Filers in this field largely differ from those in the known classes of antibiotics (except for Novartis), indicating that this is a specialised field attracting the interest of the few that have decided that the future of this industry may lie with novel therapies rather than further development of the existing solutions. (Fig. 21).

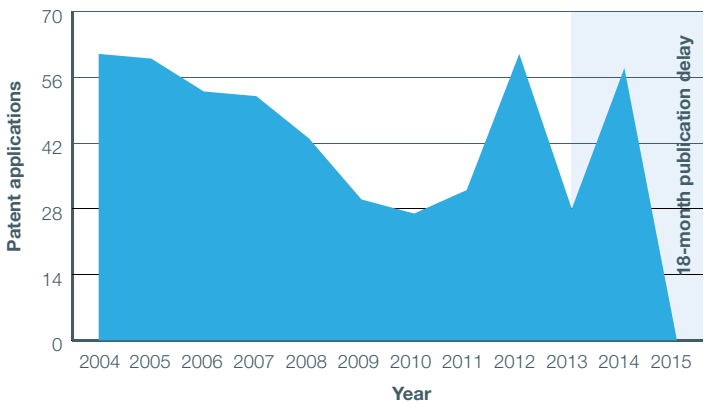
Looking more closely at the data, we note that Amgen has several patent families directed to heterocyclic compounds whereas Merck has an interest in antiviral agents. The South Korean entity, Bioneer Corporation, owns patent families in the fields of therapeutic oligo-RNA and siRNA as delivery systems for use in the treatment of cancer and other infectious disease.

The Top Applicants in this field are mainly private organisations, from the USA, although there is certain geographical distribution with other Top Filers in Europe (Novartis, TNO, and BASF) and China (East Sunshine Pharmaceuticals Guangdong, Qingdao Honghao Sheng Technology and the University of Shandong). Of the top five private organisations (Amgen, Pfizer, Schering Corporation, Merck and Novartis), none have filed any applications for new classes of antibiotics since 2008.

The only two public organisations among the Top Filers in this field are the US Department of Health and University of Shandong.

Further analysis of the data shows that Vertex, Merck, IRM LLC, Schering Corporation and Dow Agrosciences have a relatively large number of patent applications, although these are spread across a smaller number of families, which indicates that their filing strategy involves filing in more jurisdictions than, for example, Amgen.

Fig. 22 Patent applications (families) relating to research into new classes of antibiotics



1 data point per patent family
Patent families entered by earliest priority date

In addition to the University of Shandong, other filers from China include HE Han, an individual who has 11 priority publications from 2014. All of their applications were filed in China and relate to beverages comprising vegetables or natural components said to have an antibiotic effect. Similarly, East Sunshine Pharmaceuticals Guangdong and Qingdao Honghao Sheng Technology both have four applications all made in only in 2013 and 2014. This is a strong indication that the antibiotic market including novel antibiotic classes is currently of general interest in China.

While the US Department of Health did not file any applications between 2011 and 2013, in 2014 there were three priority applications published, indicating that they may have renewed interest in this field.

In May 2015, the chair of the UK Review on Antimicrobial Resistance, Jim O'Neill, announced that the world needed a global fund to drive the development of new and effective antibiotics. Our report supports the generally held view that more can be done to discover new antibiotics. The significant advances made in other fields demonstrate that despite the significant problem of resistance and the realistic prospect of untreatable infections, the antibiotic industry is not innovating at the same pace as, for example, those active in the field of rare diseases.

However, this apathy is perhaps not without good reason. As with any drug, the development of new antibiotics requires time and money, but what is markedly different in this field is that the developer is faced with the realistic prospect of a new and expensive antibiotic being so widely used that resistance develops in an unacceptably short period of time. The emergence of resistance would almost immediately negate the level of investment required to bring the drug to market in the first place. It is, therefore, likely that any single organisation is cautious of investing in the development of new antibiotics. The proposal to implement a global fund contributed to by the world's major organisations and governments is perhaps one possible solution to this problem.

"After over a decade of neglect, the problem of resistance and increasingly ineffective antibiotics is finally prompting action in the industry."

MerLion Pharmaceuticals – an interview with David Dally, CEO

MerLion Pharmaceuticals is based in Singapore, with its clinical development team in Berlin (Germany). It was formed in 2002 through the privatisation of the former Centre for Natural Product Research, part of Singapore's Institute of Molecular and Cell Biology. The company's primary focus is the development of finafloxacin, a member of the fluoroquinolone class of antibiotics to which MerLion holds an exclusive, worldwide license from Bayer, the holder of 1997-filed patents for the API. Following a sub-licence to a major North American partner in 2010 for use in otic (ear) infections in North America, the US Food and Drug Administration (FDA) approved in December 2014 an otic suspension of finafloxacin to treat acute otitis externa, commonly known as "swimmer's ear". MerLion retains the rights to intravenous and oral formulations of finafloxacin for all other indications. We spoke to David Dally, CEO at MerLion, to discuss the company's IP and regulatory strategy.

IP strategy

"MerLion's IP is based around finafloxacin. The company has been diligent in investigating the possibilities for alternative compounds, such as analogues or isomers of finafloxacin that retain its outstanding safety profile and unique activity, and to explore the possibility for process patents. We have not found such a step-change improvement in other compounds we have looked at and the possibility for process patenting did not seem appealing. However, after painstaking research, arising in part from the particularly enhanced activity and efficacy of finafloxacin under acidic conditions, we have developed specific formulations for which we are pursuing patent protection. Moreover, we are engaged in ongoing investigations into specific uses of finafloxacin against specific, difficult-to-treat disease indications, for which we are also pursuing patent protection."

Twin-track approach

"Although confident that the patent strategy MerLion is pursuing will be effective, the company recognises that powerful protection is also achievable through the use of data exclusivity. Indeed, data exclusivity offers particular benefits to a company such as MerLion focusing on antibiotic research. For example, we are mindful of the benefits achievable via the FDA's Qualified Infectious Disease Product (QIDP) designation, which provides for five additional years of exclusivity for certain antimicrobials, in addition to the normal period provided – as well as ensuring maximum protection under the corresponding provisions in other major jurisdictions, most notably Europe and Japan."

Regulatory approval

"Analogously to our approach to IP protection, in particular data exclusivity, we are exploring all options in relation to regulatory approval. For example, the company is weighing up its options with regard to restricted use labelling in the USA, allowing us to focus resources on the medical indications for which finafloxacin is most beneficial."

Looking forward

"Now is an exciting time to be an antibiotic-focused company. Of course, we have been moving forward with what we believe to be a highly differentiated antibacterial candidate for more than eight years. However, after over a decade of neglect, the problem of resistance and increasingly ineffective antibiotics is finally prompting action in the industry, for example with Merck's $9.5 billion acquisition of Cubist Pharmaceuticals in December 2014 and the proposal from a UK Government-appointed review team to establish a $2 billion innovation fund to incentivise further antibiotic research."

"MerLion, the first Singapore company to achieve FDA approval with a novel drug, is well placed to contribute to the long-overdue effort to address increasing levels of antimicrobial resistance. Although the long-term solution for addressing bacterial infection may not be antibiotics – bacteria have evolved over several billion years such that they develop resistance rapidly under antibiotic pressure – in the short to medium term, much more focus needs to be on the development of effective antibiotics. Much focus has been on MRSA, the bacterial bogeyman in recent years. However, gram-negative pathogens tend to be harder to eradicate and more resistant to antibiotics and now represent a potentially much more serious threat than MRSA and other gram-positive bacteria. Finafloxacin is effective against many resistant gram-negative bacteria that cause a number of severe infections. For example, we reported in January the encouraging results from our phase 2 clinical trials, involving treatment of complicated Urinary Tract Infections (cUTIs). The company is optimistic about the benefits to patients finafloxacin offers, not only against cUTIs but in relation to many other difficult-to-treat indications."

Vaccines

Table 23 Top Filers of patents relating to vaccines research (2004–2015)

	Organisation	Patents
1	US Health	697
2	Novartis	323
3	Harbin Veterinary Institute	123
4	Intervet	105
5	Sanofi	99
6	University of California	96
7	Merck	94
8	University of Pennsylvania	92
9	University of Texas	85
10	Institut Pasteur	81
11	Wyeth	74
12	Zoetis	63
13	Merial	61
14	Allergan	59
15	Lanzhou Veterinary Research Institut	57
16	Pulai Ke Biological Engineering	54
	Jiangsu Academy of Agricultural Sciences	54
18	Duke Univeristy	51
	Oncotherapy	51
20	Pfizer	48
	Huazhong Agricultural University	48
	US Army	48

Data for 2013–2015 incomplete due to 18-month publication delay
1 data point per patent family

"Prevention is better than cure"

Since Edward Jenner's successfully used his *Variolae vaccinae* (smallpox of the cow) preparation to vaccinate humans against the scourge of smallpox, we have stuck close to the old adage that "prevention is better than cure". Continual research and the strict implementation of global vaccination programmes have led to the successful eradication and control of a number of diseases, most notably polio, rubella and mumps.

There remain a number of challenges with certain diseases proving difficult to tackle through vaccination. Malaria remains a significant threat to health in tropical regions and while many countries offer yearly influenza vaccines to the most vulnerable, the world still faces the threat of a pandemic. Most recently the ebola outbreak in Western Africa has highlighted the need for prophylactic (preventative) therapies which prevent such contagious conditions taking hold among a population.

The recent successful development of two vaccines effective against Neisseria meningitides serotype B, Pfizer's protein vaccine "Trumenba®" and GlaxoSmithKline's "Bexsero®", is proof that vaccines effective against even the most challenging of organisms can be developed.

Today, vaccine technology has progressed to a point where in addition to an ever expanding repertoire of vaccines against bacterial, viral and fungal diseases, science is able to provide us with vaccines that are personalised. These "personal" vaccines are most commonly applied to the treatment of certain types of cancer where the vaccine stimulates an anti-cancer immune response in the patient.

Our analysis of patent data relating to vaccines research over the last decade shows that there has been a general downward trend in the total number of patent applications filed in the field of vaccine research from 9,149 applications in 2004 to 5,799 applications in 2012 (Fig. 24). However, the number of patent families applied for has remained fairly constant at around 1,200 each year. This pattern is similar to the other areas of research analysed in this report and, likewise, suggests that filers have elected to proceed in fewer territories than previously.

Whilst the number of vaccine patents granted has been on the rise since 2004, it is possible that given the year on year decline in the number of applications filed, the number of grants will decline in the next few years. However, as with all sectors of technology, new innovations can re-invigorate the patent landscape and recent developments in vaccine technology may, over the next few years lead to a resurgence in filing figures.

The USA tops the list of most popular jurisdictions in which to file patent applications directed to vaccines, with 23,437 patent applications having been filed since 2004 (Fig. 25). Whilst falling well short of the USA, other key jurisdictions for this technology area are Europe, Japan, Australia, China and Canada.

A significant number of patent applications have also been filed in India since 2004 (2,809). It is becoming increasingly difficult to prosecute biotechnology patents before the Indian Patent Office, and it will be interesting to see what impact (if any) revisions to the Indian Patent Act and recent case law will have on the total number of applications filed in this jurisdiction.

Of note is also the number of patent applications filed in Hong Kong (1,758 – not indicated on Fig. 25). Reasons why applicants might be encouraged to file in this state may include a booming medical tourist industry and the relative ease with which a patent can be obtained in Hong Kong via the straight forward registration of a European patent (validated in the UK), UK patent or Chinese patent.

Analysis of the most popular first filing territories for patent applications relating to vaccine research shows the USA and China to be on top. This may, in part, be attributable to first filing laws operating in these territories which stipulate that US and Chinese-originating inventions be the subject of first (priority) filings in these territories. The EPO is also a popular patent authority at which to file priority applications. Compared to national patent filings, European applications are often expensive. However, the quality of the EPO's search is widely recognised and for technologies positioned within a crowded landscape, a detailed and comprehensive search prior to filing an international (PCT) application is often a valuable asset.

In terms of number of patent families filed, the US Department of Health tops the list of Filers in this sector with a total of 697 families filed in the period between 2004 and 2015 (Fig. 23). While there is a collection of large multi-national companies among the Top 10 Filers (Novartis, Intervet, and Sanofi to name a few), also active in this field are the Harbin Veterinary Institute and a collection of US universities including the Universities of California, Pennsylvania and Texas.

Founded in 1948, the Harbin Veterinary Research Institute is China's first veterinary medicine research institute with a research portfolio covering many aspects of animal health.

Many of the Chinese entities appearing on the list of Top Filers have relatively low total numbers of applications in comparison to number of patent families, suggesting that these entities do not generally file overseas.

When the numbers of patent families filed by subsidiaries of "big pharma" companies are taken into account, we see that, although still behind the US Department of Health, the companies of GlaxoSmithKline (427 families), Johnson & Johnson (138), Merck (424), Novartis (538), Pfizer (322) and Sanofi (111) all have more than 100 family applications to their name. Recently, Novartis divested its vaccines business (excluding its influenza vaccines) to GlaxoSmithKline, which may leave the UK-based multinational as the major player in this area.

Fig. 24 Patent applications (families and total) relating to vaccine research

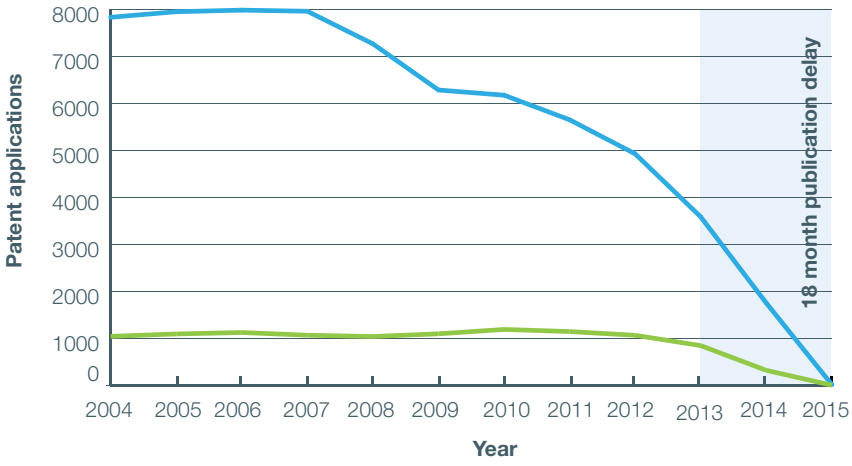
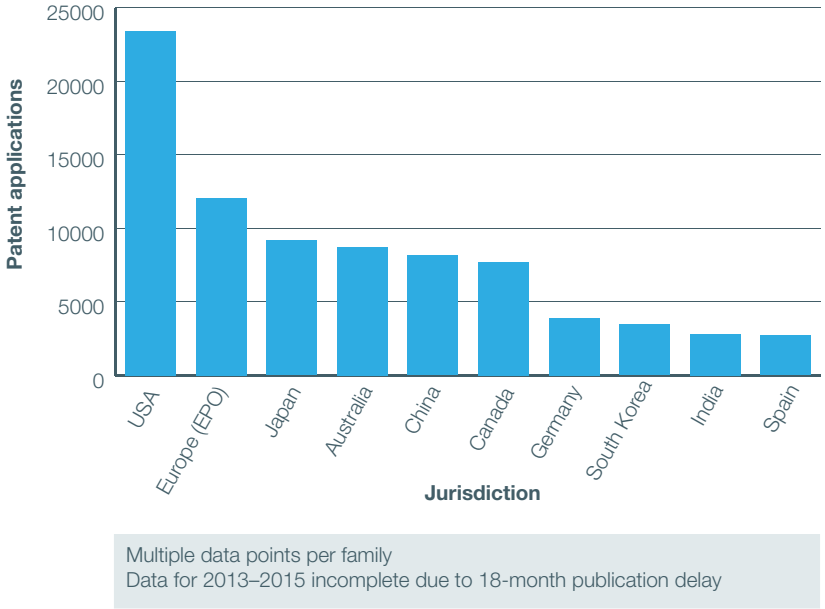


Fig. 25 Patent applications (total) relating to vaccine research in Top Jurisdictions (2004–2015)



In the years between 2004 and 2011, Europe saw steady growth in the number of patent families containing at least one application in the area of vaccine research at the EPO (Fig. 27). The numbers of patent families containing at least one application in the USA has fluctuated, with a peak in 2010 (Fig. 26). In China, numbers have grown significantly, from 202 patent families in 2004 to 911 in 2012 (Fig. 29). If the generalised rate of growth continues, China will soon overtake Europe as the second most popular jurisdiction in which to file patent family members relating to vaccine research. It is likely that this is largely thanks to the growing number of domestic Chinese filings.

In the years spanning 2004 to 2015, there has been an increase in the number of patents granted in the area of vaccine research in each of the major territories. China, in particular, has seen a spike in the number of granted patents in the years between 2012 and 2014, overtaking Europe and Japan for the first time in 2012.

Patent applications Patent families entered by earliest priority date
Granted patents

Fig. 26 Patent families containing at least one US application and at least one granted US patent relating to vaccine research

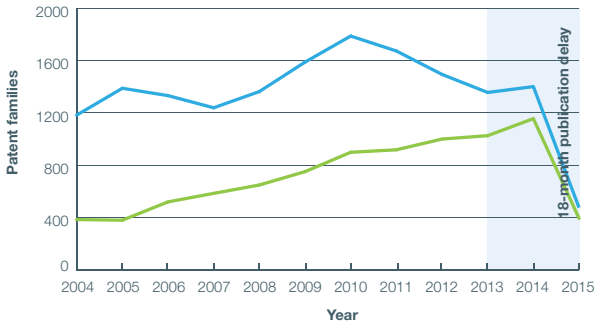


Fig. 27 Patent families containing at least one European application (at the EPO) and at least one granted European patent relating to vaccine research

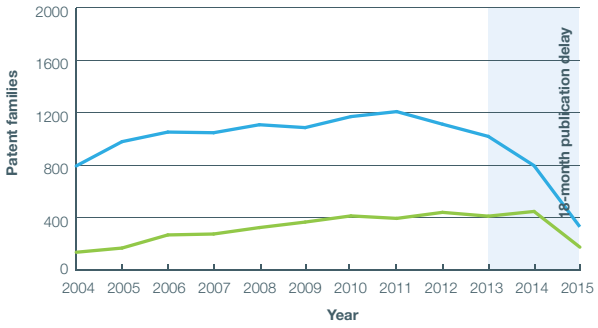


Fig. 28 Patent families containing at least one Japanese application and at least one granted Japanese patent relating to vaccine research

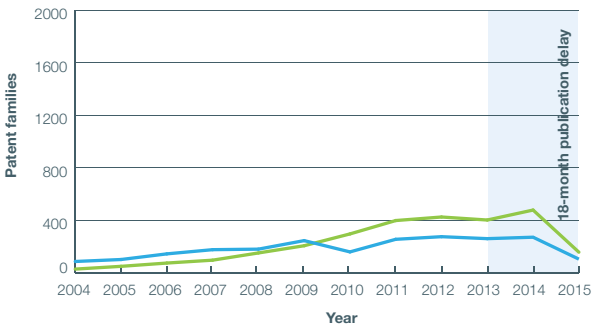
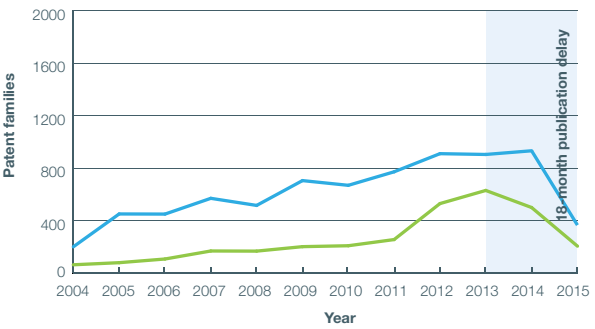


Fig. 29 Patent families containing at least one Chinese application and at least one granted Chinese patent relating to vaccine research



"There is a financial motivation for companies as well… The role of vaccines is therefore both philanthropic and profitable."

Mucosis – an interview with Tom Johnston, CEO

Mucosis is a clinical stage biotechnology company that focuses on developing vaccines for infectious diseases that can be delivered needle-free through the nose or mouth to elicit a more natural immune response with a broader base of protection. The vaccines are based on the company's core Mimopath® technology that uses a bacterium-like particle (BLP) derived from the food-grade bacterium Lactococcus lactis as an immunostimulant and/or as an antigen carrier. Mucosis' lead product, SynGEM®, is a stabilised, recombinant, vaccine against Respiratory Syncytial Virus (RSV), for which there is no current treatment. The annual global burden of RSV illness is significant, causing 253,500 deaths worldwide in 2010.

In addition to common infectious diseases such as RSV and pneumococcal, Mucosis is researching oral vaccines for the prevention of rare diseases such as diarrhoea caused by *Shigella* and ETEC (enterotoxic *E. coli)*, with support in the past from the Gates Foundation. We spoke to Tom Johnston, CEO at Mucosis, to discuss the company's IP and regulatory strategy, and changes in the vaccine field.

IP and regulatory strategy

"Since the inception of Mucosis in 2007, our IP strategy has been a two prong approach: protection of our core technology which provides a foundational platform; and then building on this platform by directing patent applications to related technologies, such as linkers for binding antigens to the core, and to the treatment of specific diseases, such as RSV.

"We develop the technology both in-house and also with partners, including the University of Utrecht with which we have collaborated for many years. We are continually exploring unmet needs across multiple disease categories where our core technology may have applications. We have recently investigated potential applications in allergies and oncology. Identifying opportunities to use our technology in a new therapeutic area is very rewarding and looks promising. However, at the same time it is important to focus on the core programs such as RSV and continue to drive this forward.

"When the company was formed, our strategy was to validate the technology in humans as soon as possible and mitigate the risk of future programs, and we accomplished this using our influenza vaccine (FluGEM®) as a proof-of-concept. Given the positive safety and immunogenicity results, the regulators are now familiar with our core technology which we believe will enable us to move quickly through the regulatory process in the future."

Changes in the vaccine field

"In the past year we have seen the consolidation of GlaxoSmithKline and Novartis, and before that the merger of Pfizer with Wyeth. These ongoing acquisitions, and the substantial expenditures to complete such transactions, show that big pharma recognises the importance of vaccines. Although vaccines still account for a relatively small proportion of drug revenue, they are still a significant part of the business.

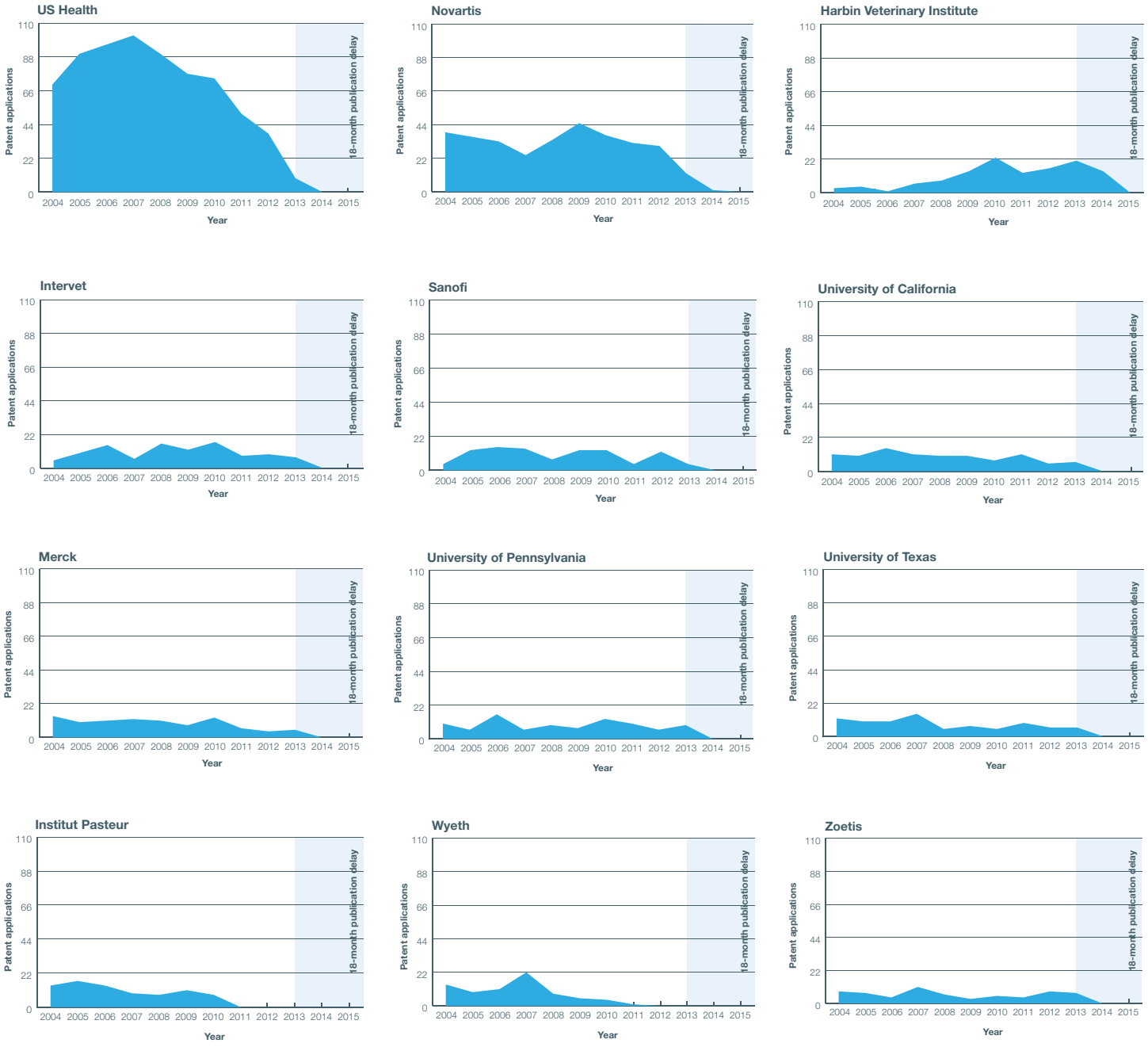
"In the last decade the overarching trend has been a shift in focus from treatment to prevention. This has been driven by consumer interest in preventing illness, increased government support through funding, investment in infrastructure to prevent pandemics and a realisation that prevention is better than more costly treatments. Additionally, non-governmental organisations are examining how to take vaccines in new directions – including expansion to parts of the world with high unmet medical needs and exploring novel approaches for emerging diseases."

Future prospects

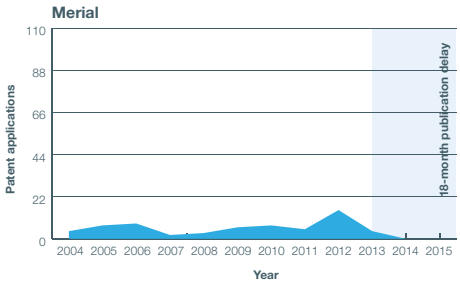
"At the moment, the focus on vaccines is increasing due to that increased emphasis on prevention. Our understanding of the human body and how we fight disease at the macroscopic and molecular levels is also better. We also understand specific disease mechanisms of action more clearly than in the past. In addition, we are now seeing innovation that was unheard of a decade ago, including cancer vaccines, and we are targeting new disease types that were once thought to be incurable. There is a financial motivation for companies as well, as evidenced by the fact that influenza alone represents a billion dollar market in the US. The role of vaccines is therefore both philanthropic and profitable.

"Over the next five to 10 years, I think we will see a mix of steady state developments and more significant disruptions in vaccines that advance healthcare overall across the globe. Incremental improvements are likely to be seen through increased effectiveness of existing vaccines. At Mucosis, we see the value of delivering vaccines through the mucosa, which not only improves the immune response but also has the potential to improve patient compliance. Additionally, we expect to see the use of vaccines continue to evolve in new disease areas, as prophylactic agents as well as therapeutic agents."

Fig. 30 Patent applications (families) relating to vaccine research by Top Applicants



1 data point per patent family
Patent families entered by earliest priority date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Patent applications
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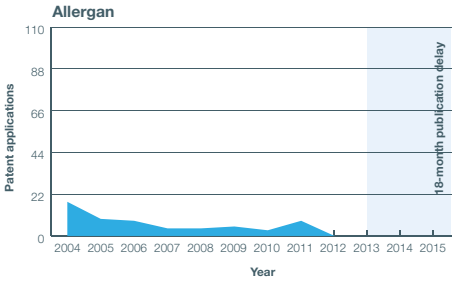
Year
18-month publication delay


Allergan
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Lanzhou Veterinary Research Institute
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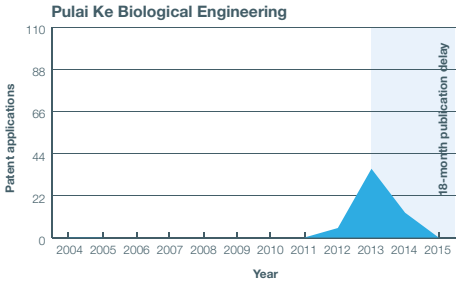
Pulai Ke Biological Engineering
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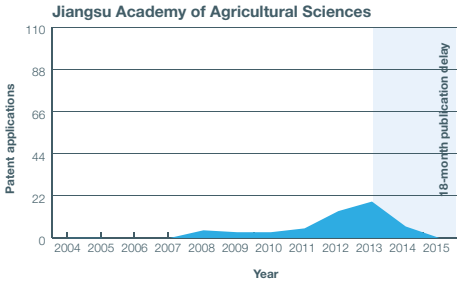
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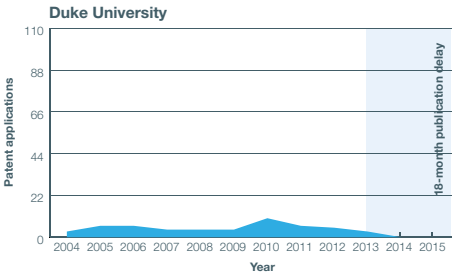
Duke University
Patent applications
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Year
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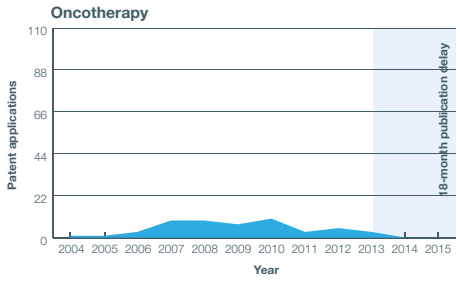
Oncotherapy
Patent applications
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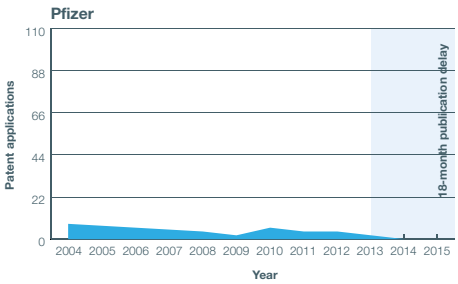
Pfizer
Patent applications
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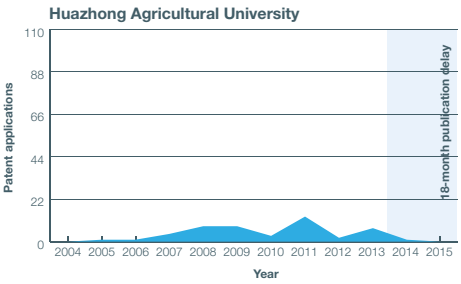
18-month publication delay


Huazhong Agricultural University
Patent applications
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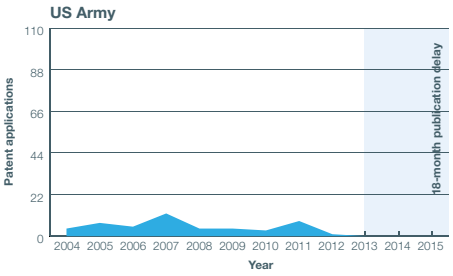
Year
18-month publication delay


US Army
Patent applications
110
88
66
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2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
Year
18-month publication delay

Fig. 31 Top Filers of patents relating to therapeutic vaccine research (2004–2015)

	Organisation	Patents
1	Oncotherapy Science	49
2	US Health	26
3	Johns Hopkins University	25
4	University of Pennsylvania	21
5	Centocor	19
6	Sloan Kettering Institute	17
	University of Texas	17
8	Immatics Biotechnologies	16
9	Genentech	15
10	INSERM	14
11	CureVac	13
	Kurume University	13
13	CNRS	12
14	University of California	11
	GlaxoSmithKline	11
	Dana Farber Cancer Institute	11
	Stanford University	11
	Mayo Foundation	11
	Health Research	11

Data for 2013–2015 incomplete due to 18-month publication delay
1 data point per patent family

Prophylactic vaccines

Looking now at the number of patent families filed specifically in the area of prophylactic vaccines, the number of patent families applied for between 2004 and 2012 has fluctuated between a low of around 1,042 families in 2004 and a high in 2010 of 1,189 families (Fig. 32).

There are relatively fewer families in the area of cancer (or therapeutic) vaccines but these show similar minor fluctuations in numbers in the period between 2004 and 2012, the number peaking with a total of 183 families in 2007 (Fig. 33).

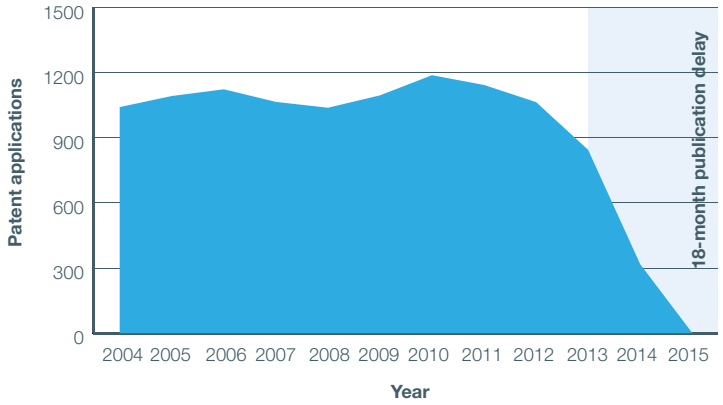
Cancer vaccines might be seen as a relatively new innovation in the field of vaccines but this exciting area of innovation is starting to show some promise and we can assume that in the years to come patent filings in this field will increase.

Antigens targeted by vaccines

A review of the numbers of families filed relating to specific antigens clearly shows that more patents relating to vaccine research are filed for vaccines acting against bacteria than any other antigen.

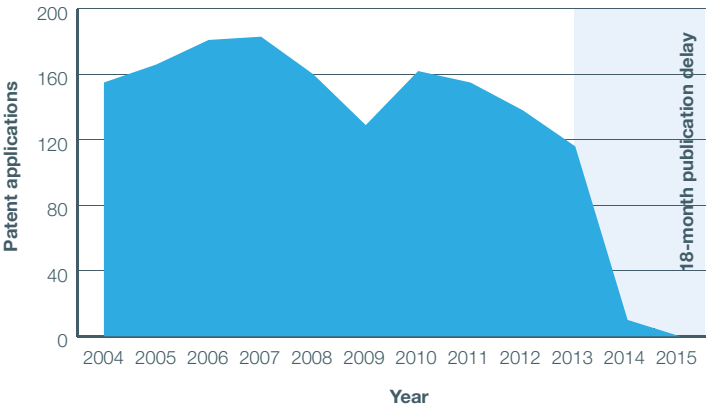
Platform technologies including those which facilitate detailed genomic and proteomic analysis have allowed researchers to mine bacteria for antigens which offer the best vaccine potential.

Fig. 32 Patent applications (families) relating to prophylactic vaccine research



1 data point per patent family
Patent families entered by earliest priority date

Fig. 33 Patent applications (families) relating to therapeutic vaccine research



1 data point per patent family
Patent families entered by earliest priority date

Absynth Biologics – an interview with Fiona Marston, CE

Absynth Biologics is a UK-based company, founded in 2007, which aims to address unmet medical needs by developing vaccines and antibodies for the prevention and treatment of bacterial infections, for which there are currently no marketed products. Absynth's research focuses on the identification of new target antigens which are both essential to the bacterium and highly conserved. Absynth's lead programme targets *S. aureus*, a hospital "superbug" which causes thousands of deaths annually and which is becoming increasingly difficult to treat due to antibiotic resistance. Work at Absynth is in progress to combine and test lead *S. aureus* antigens for the selection of a candidate vaccine. *S. aureus* is a commensal microorganism carried by 30 per cent of the population which can successfully evade the immune system, so Absynth's approach is to identify antigens which are not normally exposed. Absynth is also working towards the development of vaccines against the pathogens *C. difficile* and *S. pyogenes*. We spoke to Dr Fiona Marston, Chief Executive of Absynth Biologics, to discuss the company's strategy and the wider vaccine field.

IP and Regulatory Strategy

"Our IP strategy is actively evolving, and we identify potentially patentable inventions through regular reviews of our research. Our initial patent filings were directed to compositions of matter, specifically the antigens on which our vaccines are based. At the next level, as our research has progressed, we have filed patent applications to combinations of antigens. At another level, we aim to protect engineered versions of the antigens, particularly those that give rise to unexpected results. Building up a portfolio in this way helps to maximise the duration of patent protection. In the future, we may also rely on supplementary protection certificates to further extend our protection.

"We protect the use of our vaccines in humans and animals, both companion animals and livestock. The latter is particularly important due to the problem of antibiotic resistance in agriculture, which has arisen through the routine use of antibiotics in cattle in certain countries. We have had much interest from other companies in developing vaccines to combat this problem.

"We are aware of the need to adjust our patent strategy according to the different approaches taken by different patent offices. The recent changes introduced by the USPTO which restrict the patenting of naturally-occurring products are a significant issue for small biotechnology firms, and one which we hope will be challenged by big pharma.

"Our vaccines are still in pre-clinical development but we are starting to plan our approach to clinical trials with the help of external advisors. A priority for us is making product development as time- and cost-efficient as possible, for example by using fast-track designation in the USA for anti-infective vaccines."

Changes in the vaccine field

"In recent years we have seen a lot of activity and product launches by the leaders in the field (GlaxoSmithKline, Merck, Pfizer and Sanofi), all of which have active vaccine development programmes. The large number of mergers and acquisitions (14 deals since 2005) indicates that the vaccine sector is very vibrant. However, the impact of anti-bacterial vaccines on antibiotic use and, therefore, resistance, is becoming increasingly recognised. The natural production of antibiotics by soil bacteria creates an environmental pressure leading to the development of resistance genes. In contrast, there is no evidence of such vaccine-stimulated resistance.

"I think that the focus on vaccines will continue to increase. There are lots of opportunities, both in the developed and developing world. For example, with an increasing elderly population, with people grouped in care homes and hospitals making it is easy to acquire infections, the need for anti-bacterial vaccines will increase. Treating infections in the elderly may be difficult due to the weaker immune system, but this is to be proven. At government level there is now recognition that prevention is better than cure. There will always be people who have concerns about vaccination, but provided that we can demonstrate the safety of new vaccines, I think that their use will continue to expand."

Future Developments

"The UK Government's drive towards prevention will increase the prominence of vaccines, although their importance needs to be brought into the spotlight in the same way as antibiotic resistance. Government support is also crucial for filling the gap in financing and progressing research programmes to the clinical stage, since prior to clinical trials it is very difficult to raise private funding. Absynth Biologics has received three grants from Innovate UK which have allowed us to advance our *S. aureus* programme and to raise more investment from the private sector, as well as enabling us to evaluate and develop our *C. difficile* pipeline. It is important that this type of government support continues.

"Over the next five to 10 years we will see the launch of new vaccines, both anti-viral and anti-bacterial. I think that a *C. difficile* vaccine will come onto the market. Current vaccines against *C. difficile* target its toxins, whereas at Absynth Biologics we aim to target the organism itself. There is therefore an opportunity to bring through a vaccine which is differentiated and potentially better than existing vaccines. With the increasing incidence of meningitis and tuberculosis, both of which are particularly challenging to treat, the increase in antibiotic resistance to gram-negative bacteria like *E. coli*, *Acinetobacter* and *Klebsiella,* there is a need for new vaccines to combat these diseases. There is therefore a need for new technology that will allow us to break through existing scientific barriers in order to develop new vaccines and treatments."

"The UK Government's drive towards prevention will increase the prominence of vaccines, although their importance needs to be brought into the spotlight in the same way as antibiotic resistance."

The annual number of patent families filed relating to vaccines research targeting bacterial antigens shows a gradual downward trend (Fig. 34). Over the period studied, the number of families has declined from a peak of 528 families in 2005 to just over 400 families by 2012.

While healthy humans are subject to the occasional bacterial or viral infection, serious fungal diseases most often affect those already with conditions affecting the immune system. As such, there may be less emphasis of the development of vaccines for these conditions and more of a focus on the treatment of the underlying condition. However, in animal husbandry dense populations of animals are prone to fungal infections and vaccines may represent a cost effective means of protection.

Not unexpectedly therefore, the IP landscape within the field of vaccines that target fungal infections comprises far fewer applications and families (Fig. 35). The number of patent families reveals a volatile pattern with the numbers rising and falling over the 10-year period from a low of six in 2004 and 2005 to 23 the following year. However, generally, the number of patent families appears to be on the rise.

The data shows that with seven patent families, the Moredun Research Institute, an organisation focussed on animal health, has been the most active organisation in this field.

While there are a number of common protozoal diseases associated with travelling, it is malaria that persists as the greatest problem. Most travellers are used to taking prophylactic drug-based therapies, but the side effects render these treatments suitable for short-term use only. So far, effective vaccines against malaria have proved elusive but there is no doubt that a vaccine-based therapy would represent the most suitable way of tackling the devastating effects of this disease across South America, Asia and Africa.

The number of patent families containing applications concerning protozoal antigens has gradually declined since 2004–2007 where the numbers peaked at 98 families in 2005 (Fig. 36). In 2012, the total number of patent families had fallen to 51.

Vaccines useful against viral infections have seen major success over the years. Thanks to vaccines, polio is virtually eradicated and rubella and mumps are now under control. However, there is still much research to be done as diseases such as influenza still represent a threat with current vaccines providing often unpredictable levels of protection.

The data shows that over a 10-year period, there have been a consistently high number of patent families containing applications relating to vaccines for viral diseases (Fig. 37).

Novartis, GlaxoSmithKline and the Harbin Veterinary Institute appear to be very active in this field, all having filed over 100 patent families in this area.

Vaccine innovation appears buoyant with both the private and public sectors investing significant resources towards the development of new and improved vaccines. Vaccines against bacterial infections remain the prime focus, but we are also now in a new era where vaccine technology and delivery methods are being exploited in the treatment and prevention of cancers. The ability to analyse the “antigen” profile of a cancer cell allows researchers to personalise vaccines for use in specific patients or populations. The success of vaccines is clear – it has been possible to eradicate a number of clinically important diseases and bring others under control. Further, through the application of proteomic and genomic analysis techniques, it has been possible to provide vaccines against some of the most difficult subjects. The data analysed in this report clearly suggests that there remains an appetite for innovation in this field but the recent ebola outbreak and the continuing problem of malaria show that there is much work to be done.

1 data point per patent family
Patent families entered by earliest priority date
N.B. Scales are different on each y axis

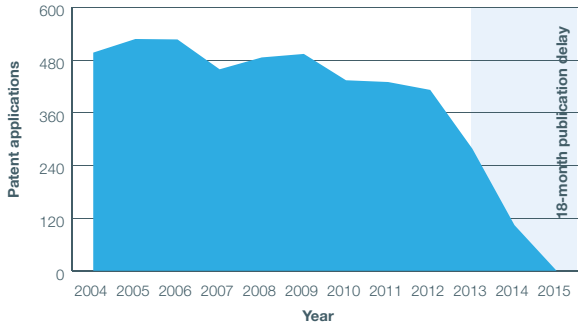


Fig. 34 Patent applications (families) relating to vaccine research targeting bacterial antigens

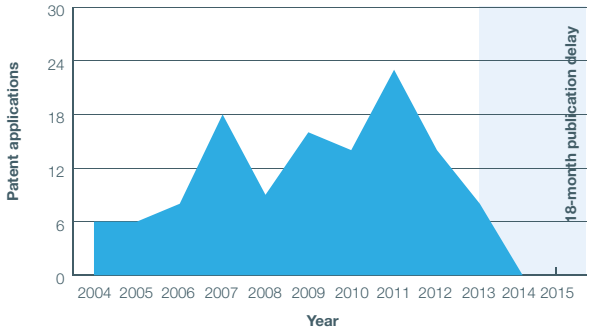


Fig. 35 Patent applications (families) relating to vaccine research targeting fungal antigens

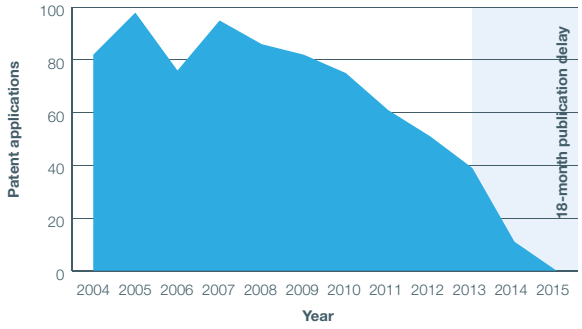


Fig. 36 Patent applications (families) relating to vaccine research targeting protozoal antigens

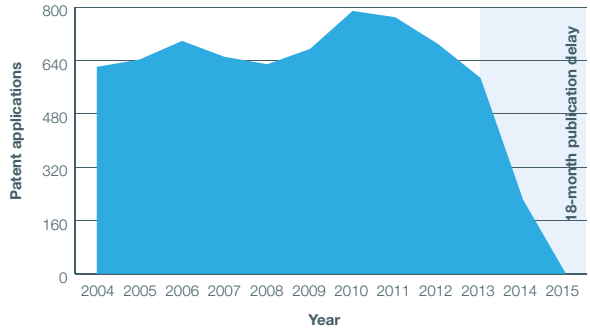


Fig. 37 Patent applications (families) relating to vaccine research targeting viral antigens

Methodology

The patent filing data analysed in this report was provided by RWS Information.

Patent landscaping was carried out for patent applications filed around the world between 1 January 2004 and February 2015 relating to three separate areas of technology: medicines for rare diseases, antibiotic use/formulations, and vaccines.

All searches were conducted on PatBase, with keyword strategies conducted through the title, abstract and claims fields.

The search criteria used to identify patents relevant to each area of technology were as follows:

Medicines for rare diseases:

- Disease names were taken from Orphanet's July 2014 'List of rare diseases and synonyms'
- Searches were limited to IPC or CPC A61K or A61P

Antibiotic use:

- Searches were conducted for known groups of antibiotics, as listed on Orthobullets and Wikipedia web pages
- Searches were limited to IPC or CPC A61
- Additionally, searches were conducted using terms for new/novel classes of antibiotic/anti-infective agents – searches were limited to IPC or CPC A61

Vaccines:

- For fungal, protozoal and viral vaccines, searches were conducted through IPC or CPC headings from A61K 39, grouped where appropriate for broad categories of vaccines, and individually
- For cancer vaccines, searches were conducted through the most pertinent CPC heading, together with a supplementary keyword search limited to IPC or CPC A61

Analysis on Top Filers in each technology type was run in order to make the data set manageable. Reliable analysis could not be run for data from 2013 and 2015 due to delay in publishing all patent filings. Some filing in this range may not be yet published.

Assignee ("Applicant") data has been cleaned and consolidated to include patent reassignments (where data is available). It does not include subsidiaries.

The data used in Fig. 1 was obtained using the PatBase Corporate Tree and includes data for all known subsidiaries of companies. The list of companies consists of the world's top 10 healthcare companies, according to *Scrip 100* 2014 (revenues for global drug makers).

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