Fighting antibiotic resistance

The importance of patent information when taking strategic action

PRV

Patent Landscape Report on: Antibiotic resistance
The Swedish Patent and Registration Office
By: Linus Plym Forshell, Maziar Soltani, Oscar Dieden, Margarita Linné and Rebecka Grunditz.
Photo: Shutterstock.
Date: April 2018

Patent Landscaping – important in the fight against antibiotic resistance

Sweden performs well in international ranking of innovation capacity and digitization. Growth is good and the employment rate is very high. At the same time, competition is stifling. If Sweden is to remain strong in a global market, we must accelerate. Sweden need to keep creating opportunities for continuous training and a strong knowledgebase in the workforce, utilize the potential of innovation and digitalization in business and society and ensure that Swedish companies and creators have good possibilities to work strategically with intellectual property, IP.

In order for Sweden to continue to be a knowledge economy at the forefront of which creativity, innovation and digitization are encouraged and transformed into welfare, the government has initiated a strategic work for IPR in which the Swedish Patent and Registration Office, PRV, plays an important role. The work aims to contribute to strengthened competitiveness, growth and new jobs.

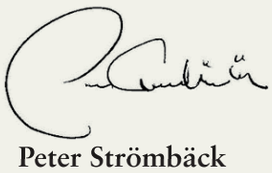
One area where Sweden today is internationally competitive is the Life Sciences. Sweden has a long history of successful research in this area and many internationally renowned pharma companies are the result of Swedish innovations.

One field within the Life Sciences where Sweden today holds a strong position is the field of Antibiotic resistance, ABR. We have a long history of working with the complex issues of ABR and we have some of the worlds most renowned experts and scientist in this field making Sweden a highly recognised actor on the international arena.

In the last decades the spread of antibiotic resistance, ABR, has become one of the biggest threats to human health globally. The severity of the issue has spurred both international and national action plans to fight ABR. In 2016 the Swedish government presented a national action plan, “Strategy to combat antibiotic resistance (S2016/02971/FS)”, with the overarching goal to preserve the possibility of effective treatment of bacterial infections in people and animals. Among others this plan states that the government expects that all relevant players of society including government agencies are to collaborate nationally and internationally to identify and bridge knowledge gaps.

As experts in intellectual property rights, IPR, PRV have the competence to search and analyse patent information from all fields of technology from all over the world. Patent information does not only contain technical information but also contain legal and business information. Therefore, patent information can also be a valuable source of information when taking strategic action in a project.

With this report we want to highlight an area where Sweden today is very competitive and has the capacity to grow. Also, the fight against ABR concerns us all and requires that all parts of society strive towards the same goal. Therefore, we wanted to do our part and contribute to this fight by giving examples of what is known about ABR from information found in patents. This way of presenting patent information is called “Patent Landscaping” and allows one to analyse a field of technology for strategic purposes.



Peter Strömbäck
Director General, Swedish Patent and Registration Office

About PRV

The Swedish Patent and Registration Office, PRV, is the authority for intellectual property. We constantly work with cutting edge ideas which enable us to strengthen Sweden's growth and competitiveness.

Our vision is to be the obvious center in Sweden for intellectual property. We also aim to be an internationally respected, viable customer-oriented agency.

PROMOTE GROWTH

Our main task is to promote growth and strengthen the country's capacity for innovation and competitiveness. By increasing knowledge and awareness we want entrepreneurs and others in the innovation community to understand that management of intellectual property is the key way to increase profitability. We achieve this through communication and education.

PRACTICE AREAS

Our mission covers such areas as supporting innovations through patent, design and trademark protection. We help people apply for a certificate of publication of a journal. Copyright issues also fall within our area of operation. Moreover, at PRV you apply for a certificate of publication.

SEARCH SERVICES

Detached from our official agency mission, we also offer and perform search services in patent, trademark and design for clients at a cost. You can use the processed information as a basis for strategic business decisions.

PROUD PCT AUTHORITY

We are proud to be a PCT authority for over 40 years. The acronym stands for Patent Cooperation Treaty, an international agreement that allows you to file a single application in one language and get an international filing date for your case.

Contents

Summary

Since the discovery of penicillin in 1928, antibiotics have been used extensively in health care, research and the agriculture sector. Antibiotics are used to treat bacterial infections and are an essential part of modern health care. However, bacteria can develop resistance to the antibiotic they are exposed to, making antibiotics less and less effective over time.

Antibiotic resistance (ABR) is not a new phenomenon but is as old as the antibiotics themselves (Davies J. et al., 2010). Today ABR is a global health problem, and unless actions are taken to check the spread of ABR, we could soon be facing a situation where the advancement of health care is set back more than 70 years.

Therefore, in 2015 the world health organisation (WHO) adopted a "Global action plan on antimicrobial resistance" (WHO, 2015) to adress this issue. Sweden, having a long history of working with the prevention of antibiotic resistance, in turn presented a national plan with the title "Strategy to combat antibiotic resistance" in 2016 (S2016/02971/FS). Today Sweden has one of the most favourable resistance situations in the world (Morel C. et al, 2016; Gelband H., 2015). However, no country is isolated from the ever increasing threat of ABR. The strategy to combat ABR will rely on the involvement of people from all areas of society, and will require time as well as the investment of financial resources. A successful global strategy will be the result of the strategic decisions, and coordinated, cooperative effort, between individual nations.

Analysing the information found in the patents and patent applications covering a certain area of technology can provide value when making these kinds of decisions.

As a national patent authority, the swedish patent and registration office PRV are experts in searching and analyzing patent documentation available in the different patent databases of the world. PRV is thus an actor of society with the knowledge and the competence to provide valuable patent information from any field of technology, including the field of antibiotics and antibiotic resistance.

Therefore, our contribution to the fight against antibiotic resistance is this report where we present an analysis on what is known in the area of antibiotic resistance based on information found in patent documents. For more details on how the searches for patent documentation was conducted, see section "Search methodology" on page 42.

PATENT INFORMATION ON ANTIBIOTIC RESISTANCE HISTORY

First, we analyzed the patent information in the area of antibiotic resistance. The data shows that patent applications describing the problem of antibiotic resistance date back to the early 1960´s, with an exponential increase in filed applications in the late 1990´s. These patent documents describe processes for propagating, maintaining or preserving microorganisms, methods for genetic engineering and measuring processes involving enzymes or microorganisms. Many documents also describe medical preparations such as antibacterial agents. The applicants of these documents come from various sectors such as major pharma companies as well as several Universities.

PATENTS AND PENICILLIN ANTIBIOTICS

Next, we analysed the class of penicillin antibiotics. The filing of patent documents describing penicillins started in the 40´s, when concentrated effort was made to mass-produce penicillins for the medical market. There was a stable level of applications from the 40´s until late 60´s, the "golden years" of antibiotic discovery, when most of todays antibiotics were discovered. During this timeperiod the applicants mostly consisted of a mix of major pharma companies such as Merck Sharp Dome, GlaxoSmithKline, Pfizer and Bristol Myers Squibb.

In 1969 there was an increase in patent applications mostly due to increased patenting activity from major pharma, particularly from GlaxoSmithKline. This increase lasted until the end of the 70´s when we see a reduction in the patent trend for the first time. This "peak" in filed patent documents occurred during a time period when no new antibiotic classes were discovered, but the field instead focused on modifying existing antibiotic molecules or designing new ones.

In the 90´s, after an almost decade long decrease, there was another shift in the penicillin discovery field resulting in an exponential increase in patent applications. This coincides with the increased use of high-throughput screening platforms to find new antibiotics. The data shows that this increase is partly caused by patent applications filed by different international Universities and Research Institutes but mostly by patent applications filed by smaller pharma companies and Universities in China. We can also see that these Chinese applications are targeted to the domestic market.

This high-throughput screening approach ultima-

tely failed, causing many of the major pharma companies to cancel their antibiotic R&D-programs (Lewis, 2013).

THE SUCCESS OF THE SMALL

From the group of lipopetide antibiotics, we highlight the story of the antibiotic daptomycin. Initially a promising new antibiotic, daptomycin was put on the shelf due to toxic side-effects. Today a huge success, both medically and financially, because of a clear-headed scientist at a small biotechnology firm called Cubist Pharmaceuticals. We also present the success story of a Croatian pharma company, Pliva, which developed and patented the antibiotic azithromycin which enabled this small local company to become a large global player in the antibiotics field.

BETTER DIAGNOSTICS TO FIGHT RESISTANCE

One key factor in the fight against antibiotic resistance is fast and accurate diagnostic methods. The diagnostic methods used today are often too slow and unspecific resulting in erroneous diagnosis and contributing to the development of ABR. Our analysis shows that the number of diagnostic method patent applications began increasing in the early 1970´s, and has exponentially increased during recent years. We speculate that this increase was caused by the failed attempts of finding new antibiotics in the 1990´s. Initially, a significant portion of these documents were filed in the US and it was not until in the 1990´s that we see applications from other countries such as Japan, Great Britain, France and Germany. In the 21´st century, Chinese applications began increasing exponentially in number. In 2015, there were twice as many patent applications filed in China alone, compared to the total number of applications filed in all of the other top 29 countries in this field taken together. However, as for the penicillins, a majority of these filed patent applications were only published in China suggesting that the domestic market is the priority for these innovations.

Sweden shows some activity in the diagnostics field, particularly during the timeperiod between late 80´s to early 21st century. One current example of a company with active patent applications is Astrego Diagnostics, whose patent applications describe a microfluidic device used for antibiotic susceptibility testing on bacteria.

Patents and the Patent system

A patent can be seen as a mutually beneficial contract between the inventor and the state. The inventor receives a time-limited monopoly of 20 years to produce, import and sell the patented technique on the market enhancing the chance to make profitable business.

In exchange, the inventor must make the invention publicly available. This way the public learns about the invention, what is protected, how it is made and how it works. By making the invention available to the public, other inventors can improve existing technology, driving technology development forward, and benefiting society in general.

THE PATENTING PROCESS

Patent applications are filed at a national patent office or with a patent organization such as the European patent office (EPO) or the World Intellectual property organisation (WIPO). Eighteen months after the application date the application becomes publicly available, irrespective of its current status (i.e. the application is granted, pending or rejected). From that moment on, the patent application can be searched and read by the public. However, the applicant has the option to withdraw the application anytime within 18 months from the application date, and thereby prevent the invention from becoming publicly known. Most patent applications are either granted or rejected within 2-3 years after the application date.

Patents are national rights, meaning that a patent only protects the invention in the country in which it has been filed and granted. It is possible to file the same patent application in multiple countries, but each national patent office has the right to decide whether the invention should be granted a patent in that particular country.

THE PATENTABILITY CRITERIAS

For a patent to be granted, the invention must be a technical solution to a problem and it needs to meet certain criteria for patentability. These criteria are novelty, inventive step and industrial applicability. In terms of novelty, the invention must be new on the day when the patent application was filed at the patent office. This means that up until this date the invention cannot have been presented, performed or made available in the public domain in any shape or form anywhere in the world. If novel, the invention must also differ essentially from already known technology, i.e. comprise an inventive step. This means that the invention may not be an obvious modification of already known technology. The third criteria, industrial applicability, entails that the invention must be applicable in an industrial setting. This means that the invention must work, have an technical effect, and must have the same outcome/result whenever the invention is performed.

When a patent application is granted the invention is protected for a maximum of 20 years (starting from the application date) with an exception for pharmacological agents and plant protection products which can get an extension of patent protection for up to 5 years. A patent enables the patent holder to prevent competitors from producing, selling and importing, into that market, what is protected by the patent.

If you want to learn more about patents and the patent system, you can find more information here: www.prv.se, www.wipo.int/pct/en or www.epo.org.

Patent information and patent landscaping

Patent information is the information found in patents and the associated databases. Patent information is available to the public, free of charge, in national and international patent databases.

These databases comprise all globally publicly available patent documents. Examples of such databases are the Swedish Patent database, Espacenet (maintained by the european patent organisation, EPO) and Patentscope (maintained by the world intellectual property organisation, WIPO).

Patent information can be used to answer technological questions such as how to solve a technical problem and whether anyone else has developed a similar product, method or device. It can also be used to elucidate the legal status (granted, pending, lapsed, revoked or expired) of a patent. This is essential information when one wants to sell a product on a specific market. If there is a granted patent or a pending patent application on the same market protecting the same technology you run the risk of infringing on this patent. The legal information can so be used to verify if there is "freedom to operate" in that market.

PATENT INFORMATION AS BUSINESS INFORMATION

Patent information contains not just technical and legal information but also business information. All patent documents must conform to internationally agreed rules on document structure, making it possible to search and analyze thousands of documents simultaneously using specific analytical tools and statistics. By analysing thousands of patent documents describing a specific technical field it becomes possible to answer questions such as,

- Is patenting in this field of technology increasing, decreasing or is it stable over time?
- Are there any sub-areas in this field of technology where players file more patents?
- Who are the major players in this field of technology?
- Where are these players operating in the world?
- Where are the markets?
- Which are the most cited patent documents in this field?
- Who are the most cited inventors in this field?
- Are there any collaborations between these players?
- What is the legal status of these players patent portfolio?

All this data is then presented visually as graphs, tables, diagrams and maps in a summarizing report together with a summarizing text. This analysis of an entire area of technology is called landscaping, and the summarizing report is therefore commonly known as a landscape report. Being an overview over an entire area of technology a landscape report have many different kinds of users. Most often, the user of a landscape report is a decision maker that needs to make strategic decisions. Therefore, politicians, company board members, the investors and the research managers in companies or research facilities are common users of a landscape report.

Landscape reports are provided by professional patent search agencies and patent office's such as the Swedish Patent Office. As mentioned above, the purpose of this landscape report is to give a brief overview of what is known regarding ABR in patent information, and by doing so, contributing to the increased awareness on this urgent topic.

From single-celled organism to consumed antibiotics

Almost 90 years ago humanity stumbled over what has become a prerequisite for modern health care. A common weapon in the world of microorganisms fighting for space and resources, a wonderdrug for humanity. However, this weapon turned out to be a double-edged sword and in our hands the blade has turned dull.

Bacteria is one of the oldest life form known today, and it is thought that life on earth began with a single-celled organism, like a bacteria. Earth back then was a rather uninhabitable place. Therefore, organisms who could survive the harsh environment had to be able to cope and adapt to the extreme conditions. Bacteria are adaptable, which is one of the reasons that bacteria can be found in all possible milieus on this planet. Even the most extreme milieus such as hydrothermal vents, cold seeps and rocks are habitats for bacteria.

Bacteria can survive extremes of temperature, acidity, alkalinity, salt concentration, oxygen levels, pressure, radiation and water supply. This adaptability is because bacteria can alter it´s genome quite easily. Genetic elements such as plasmids or transposons can transfer between bacteria (even between bacteria of different strains) through what is called horizontal gene transfer (HGT). If such an element contains a gene encoding a specific trait the recipient bacteria now aquired a new trait.

A LIFESAVING COINCIDENCE

In the world of microorganisms, antibiotics have been used in the battle for space and resources for millions of years (Wright G. D., 2007). For humans the timeline of antibiotics began in 1928 when Alexander Fleming discovered penicillin by chance. Fleming, a physician and biologist, had left some agar-plates with bacteria cultures out in his laboratory while he was away for a few days. When he returned, he noticed that on some of the plates, the bacteria hadn´t grown and seemed inhibited by mold contamination. Fleming realized that the mold released something which prevented the bacteria from growing on the agar-plates. This is how penicillin, the first antibiotic known to man, was discovered (Kingston W., 2000).

Bacteria also have a high rate of spontaneous mutation in its genome which can result in new traits, some of which might give a competitive advantage in that habitat. Having a relatively short reproduction time, bacteria with the most suitable genetic makeup can quickly reproduce (by binary fission) and colonize even a rapidly changing environment. These rapid adaptation and reproduction abilities explain why bacteria are so succesful in colonizing all possible environments on this planet.

THE GOOD BACTERIA IN OUR BODIES

Bacteria of many different strains also colonize the animal and human body, many of which exist in a symbiotic relationship with the host. For instance, the adult human body is estimated to harbour 0,2-0,3 kilograms of different strains of bacteria, most of which can be found in the gut and intestine where they help to digest food, enable the uptake of nutrients, defend against pathogenic bacteria but also contribute to the maturation and proliferation of our immunesystem (Sender R. et al., 2016; Gensollen T. et al., 2016; Matamoros S. et al., 2013).
We also carry a lot of bacteria on our skin which help protect us from pathogenic bacteria and other microbes such as different parasites and fungi (Kamada N. et al., 2013). Many of us have encountered the less pleasant side-effect associated with using antibiotics, namely diarrhoea. This side-effect is caused by the antibiotics killing not only the pathogenic bacteria but also the symbiotic bacteria in our gut. This offsets the balance between the symbiotic bacteria and the pathogenic bacteria in our gut, thus causing diarrhoea (Abt M. C. et al., 2016).

BACTERIAL COMPETITION AND THE SPREAD OF ANTIBIOTIC RESISTANCE

In the world of microbes there is a constant battle ongoing for resources and space. Therefore, most bacteria have developed elaborate systems to defend themselves against other microbes trying to outcompete them in a space. Once a bacteria retracts from an space other microbes will take over and colonize that same space (Hibbing M. E. et al., 2010).

External factors such as changes in temperature, humidity, nutrient supply, space, oxygen levels or the presence of a toxic chemical, such as antibiotics, affect the reproduction and survival of a bacteria in a space. These changes can favour one bacterial strain over another such that the bacteria best suited will survive in that space. As stated above, spontaneous mutations and horizontal gene transfer can also give one strain beneficial traits enabling survival in the new space.

Prolonged exposure to an external factor in the

environment can also accelerate bacterial genetic changes.

A typical example here is when bacteria are exposed to a toxic substance such as antibiotics. If the concentration is high enough the antibiotic will either stop the bacteria from reproducing or kill all bacteria sensitive to that antibiotic. However, due to high adaptivity of bacteria, bacteria can spontaneously acquire a mutation in its genome or "pick up" a genetic element by horizontal gene transfer which confers resistance to the otherwise toxic antibiotic. Thus, the bacteria are now resistant and survives the exposure of that antibiotic.

This resistant bacteria is now the only bacterial cell able to survive, reproduce and colonize this otherwise toxic environment. Due to the short bacterial reproduction time, this can occur in a matter of days or even hours. The duration of exposure and the concentration of the toxic substance are critical factors in resistance development. The longer time bacteria are exposed to a substance, the higher the risk they will become resistant to that substance. The dose of the antibiotic also matters. If the concentration is not high enough to prevent reproduction and/or quickly kill the target bacteria, there is increased risk that resistance will develop (Anderson D. I. et al., 2014).

Therefore, following every discovery of a new antibiotic, bacteria resistant to that drug have been identified shortly after. For instance, in 1940 bacteria resistant to penicillin were discovered (Davies J. et al., 2010). These resistant bacteria express penicillinase, an enzyme that degrades the penicillin molecule. As described previously, bacteria modify their genetic makeup through spontaneous mutations or through horizontal gene transfer (HGT) which also enables bacteria to develop resistance to an antibiotic.

HOW ANTIBIOTICS WORK

To understand how resistance arises, one has to understand the mechanisms for antibiotic toxicity in a cell. Different antibiotics cause toxicity through different mechanisms in the bacterial cell.

Many antibiotics function by binding cellular components and thereby blocking its function. Common targets for antibiotics in the bacterial cell are the ribosomes (responsible for producing proteins), enzymes facilitating replication and transcription of the bacterial genome or cell wall synthesis (Lewis K., 2013). By blocking the function of the ribosomes or blocking enzymes enabling transcription, the bacteria loses the capability to produce proteins which are necessary molecules for cell survival. By blocking enzymes enabling replication the bacterial cell cannot reproduce. An intact cell wall is a prerequisite for bacterial cellular integrity. The cell wall contributes to regulating cellular contents, what comes in and what goes out of the cell and maintaining the stable "inner milieu" of the cell required for cell survival. Thus, antibiotics blocking cell-wall synthesis hinders bacterial cells from maintaining that integrity, causing cell death.

THE DEFENCE AGAINST ANTIBIOTIC TOXICITY

As described above, bacteria fight a constant battle against other microorganisms for space and resources. One way of doing this is by releasing a toxic substance, such as an antibiotic. Not surprisingly, bacteria have therefore developed defence systems to protect themselves from competing microorganisms antibiotics (Lewis K., 2013).

In an environment with an antibiotic present, there is a natural selection for a bacterial cell to develop defence mechanisms against that antibiotic and become resistant. The expression of antibiotic degrading enzymes, increased activity and number of drug efflux pumps, decreased membrane penetration and mutations in antibiotic targets preventing the antibiotic to bind its target protein, are all common mechanisms of resistance.

PATENTING PENICILLINASE


Patented June 24, 1952 2,601,350

UNITED STATES PATENT OFFICE

Although penicillinase was a rude awakening for the antibiotic field, quite soon after its discovery areas for application of this enzyme opened up. For instance in patent application US2601350 a process is described where penicillinase is used for sterility control and for diagnosis of infected patients.

Other known resistance mechanisms are overproduction of target molecules to outnumber the antibiotic molecules, enzymatic modification of the antibiotic molecule to alter its function, and compensatory pathways serving as an alternative route to the one blocked by an antibiotic (Lewis K., 2013).

Some bacteria develop resistance to not only one but to several antibiotics. These bacteria are labelled multidrug-resistant (MDR), and are often called "superbugs". As the new classes of antibiotics started being used in the health care system, pathogenic MDR-bacteria were also being identified. MDR-bacteria commonly arise in environments with a constant exposure of different types of antibiotics, such as health care facilities. MDR bacteria are of particular concern since it is hard to find any functional antibiotics which can kill the pathogenic bacteria causing the infection.

Today, there are bacteria which are resistant to all known types of antibiotics. These are refered to

as pandrug-resistant (PDR) bacteria (Alekshun M. N., 2007; Magiorakos A. P. et al., 2012). MDR- and PDR- bacterial infections are not only a medical problem for the patient and the caregiver, but also pose an extra stress on the health care system since infections caused by MDR- and PDR- bacteria require more frequent and prolonged care. This adds a financial stress on the system and increases the risk for further spread of the MDR- and PDR- bacteria.

There are many different strains of MDR- bacteria in society today. Some of the more common ones are Vancomycin-resistant Enterococci (VRE), Methicillin-resistant Staphylococcus aureus (MRSA) and Extended-spectrum beta-lactamase (ESBLs) producing gram-negative bacteria. Also, the "ESKAPE" group comprising multidrug resistant *Enterococcus Faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and Enterobacter species are common (Alekshun M. N., 2007).

THE COST VERSUS THE BENEFIT OF ANTIBIOTIC RESISTANCE

For a bacterial cell to acquire a new gene and express the corresponding protein, energy is required which is a "cost" for the cell. Therefore it needs to be a "benefit" of doing so for the bacteria, such as expressing a protein that degrades an antibiotic molecule. Expressing an antibiotic resistance gene is only a benefit if the bacteria is growing in an environment where that antibiotic is present, thus giving it a competitive advantage over other bacteria not carrying this resistance gene. In an antibiotic-free environment there often is no "benefit" just a "cost" to carrying a resistance gene, which enables other non-resistant bacterias to outcompete the antibiotic resistant bacteria.

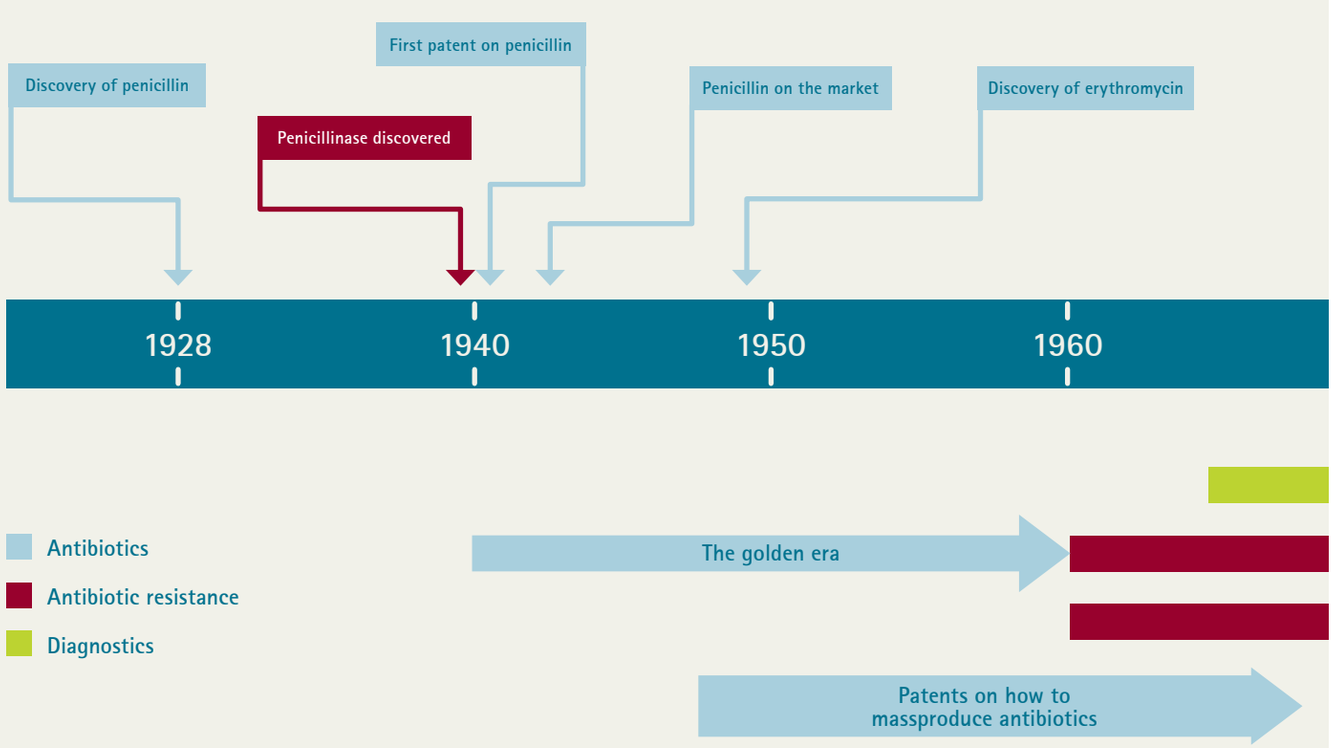
Interestingly, this benefit-cost relationship is not always true. Studies have shown that there are also cost-free resistance mutations such as compensatory mutations which make up for the resistance cost (Wright G. D., 2007, Anderson D. I. et al., 2011).

ANTIBIOTIC USE IN HEALTHCARE

Whatever the cost-benefit relationship, it is essential that we limit the use of antibiotics. Excessive use of antibiotics increases the risk for resistance to develop and spread between the interconnected environments of society (medical environment, agricultural environment, aquacultural environment, the pharmaceutical industry and the wider environment) (Anderson D. I. et al., 2014).

Antibiotics are used in many different areas of society. Besides the obvious use of antibiotics in healthcare, antibiotics are also extensivley used in the agricultural and scientific areas. The major problem in the healthcare area contributing to antibiotic resistance is the overuse and incorrect use of antibiotics. Overuse is more common in countries where antibiotics are sold over the counter, prescription free, where the caretaker is able to selfadminis-

Significant events in the history of antibiotics and antibiotic resistance.



ter and regulate the use themselves (Laxminarayan R. et al., 2013; O´Neill J. 2014). Not aware of what is causing their illness, people self-administer antibiotics for infections where antibiotics are ineffective (e.g. viral infections).

However, even in countries where the caregiver is in control of the access to antibiotics, incorrect use of antibiotics is common. Patients stop taking the antibiotic when they start feeling better thinking the infection is gone. The problem is that by not following the prescribed regimen, the concentration of the antibiotic in the patient's body will not be high enough for long enough to kill all the infectious bacteria. Thus, there might still be some bacteria left in the body, now exposed to suboptimal concentrations of the antibiotic enabling the development of resistance (see the reasoning above). It is also common that antibiotics are incorrectly prescribed due to lack of knowledge, personal financial gain but also because of old and slow diagnostic methods (you will find a discussion on diagnostic methods below).

ANTIBIOTIC USE IN AGRICULTURE

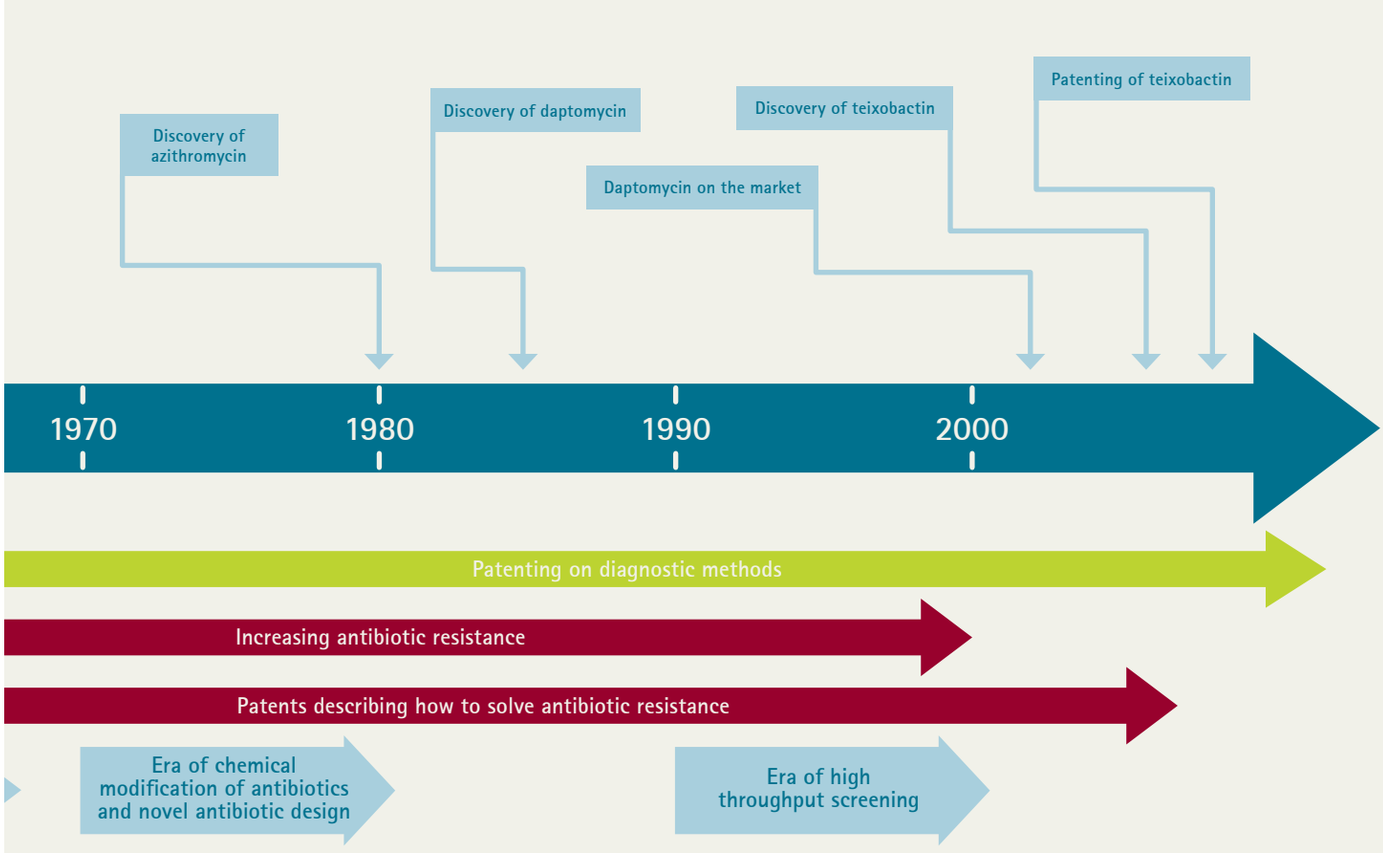
Another area of heavy antibiotic use is the agriculture sector. Today a major portion of the produced antibiotics in the world is used in animal farming. Antibiotics are used in the agricultural sector to treat bacterial infections in the animals, but also as a preventative measure. One problem with animal husbandry is that due to the "industrial scale" of today's farms, where hundreds or even thousands of animals live in a confined area, infectious diseases are common and easily spread between individuals. A sick animal is not productive and will not give the same yield, if any. Therefore, in many

SWEDEN, A PIONEER IN ANIMAL HEALTH CARE

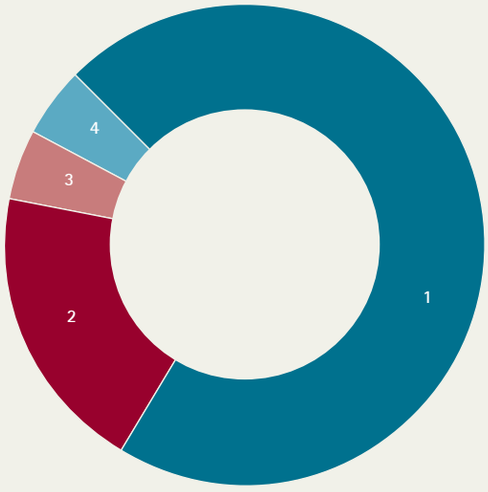
Sweden is one of a few countries in the world which does not allow the distribution of antibiotics to healthy animals, and since 1986 it has been forbidden in Sweden to give antibiotics to animals for growth promoting purposes (Wierup M., 2001). Also, in the 1970´s preventative health programs for farm animals were established to increase the general health of the animals and so minimize the risk of animals acquiring an infection, which would require antibiotic treatment. For instance, many of the reasons that infections occur in these millieus are avoidable by:

– better planning of the animal handling;
– better layout of the animal housing and
– improved animal hygiene.

These programs have been very successful and has allowed Sweden to keep one of the healthiest animal industries in the world (Wierup M., 2001; Benfalk C. et al., 2000). In 2006 EU also banned the use of antibiotics for growth promoting purposes in animals. Unfortunately, many other countries continue to use enormous amounts of antibiotics in their agricultural industry, contributing to the development and spread of antibiotic resistance (Gelband H. et al., 2015).



TEVA PHARMACEUTICAL AREAS OF PATENTING



The diagram shows the relative distribution of technology for Teva's patents.
1. Medical preparations (including medical preparations of special physical form).
2. Organic chemistry and peptides.
3. Medical and Veterinary science .
4. Analysis, gene technology and biocides.

countries of the world healthy animals are given antibiotics in the fodder as a preventative measure, protecting the animals from contracting a bacterial infection.

Also, one commonly exploited side-effect of providing antibiotics to healthy animals is an increased growth rate. Quicker growth means shorter time before an animal is ready for slaughter. Thus, more animals can be "cycled through" the farm in a shorter period of time, generating more revenue. This creates an incentive for the farmer to continue provide antibiotics to healthy animals (Gelband H. et al., 2015; Grave K. et al., 2014).

As explained above this is a perfect setup for antibiotic resistance to develop and spread. These resistant bacteria can transfer to humans working on the farm, or spread via the food products produced, enabling the spread from the original source into the living environment of humans (Gelband H. et al., 2015; EFSA, ECDC, 2015).

THE PHARMA INDUSTRY AND ANTIBIOTIC RESISTANCE

The producers of antibiotics, the pharma industry, are also a contributing factor to the spread of antibiotic resistance. One problem is the accidental and sometimes intentional release of antibiotics from production plants. Needless to say, the release of antibiotics directly into the environment enables resistance to build in nearby waters and land from which it can easily spread to other environments (Anderson D. I. et al., 2014; Larsson D. G. et al., 2014).

However, a bigger issue contributing to this problem is how pharma gets a return on their investments. As stated above, today the patent system only allows protection for a maximum of 20 years (for some drugs 25 years is possible). Commonly, the first 10-15 years of patent protection is spent on basic research, clinical testing and drug development. Thus, before the drug is finally approved for use by the regulatory authorities and so can be sold on the market, there is only 5-10 years left of the patent (i.e. exclusivity on the market). This means 5-10 years to make a return on that investment. To compensate for this "delay to market" effect it becomes important to sell as much as possible in the years left of protection. Also, after the patent on a drug has expired competitors are free to sell copies (generics) of the same drug on that market. Now there are multiple manufacturers of the same drug competing with lower prices. All these manufacturers then need to sell even more of the drug to get a return on their investment. This adds to the flooding of the market with cheap antibiotics, further contributing to development of resistance (Horowitz J. B. et al., 2004).

Clearly, the pharmacompanies need to be on board with tighter regulation on the use of antibiotics. Therefore, we need to figure out how to optimize the risk/reward so that there will be a financial incentive for pharma to develop and sell new antibiotics, while getting a fair return on their investments without the return being directly related to the volume sold of that antibiotic.

Perhaps one way is to further extend the protection a patent offers. However, the complexity of antibiotic resistance and then especially multi-resistance may prevent that from being a viable solution (Spellberg B. et al., 2007; Horowitz J. B. et al., 2004).

ANTIBIOTIC RESISTANCE REQUIRES GLOBAL ACTION

We need to reduce the amount of consumed antibiotics on a global scale, particularly in the developed world. In fact, one major problem is that while we in the western world over-consume antibiotics, and therefore need to reduce our consumption, some countries in the 3rd world need to increase their consumption for medical purposes. Today, many of the poorest people who need access to antibiotics do not get them (Laxminarayan R et. al., 2013).

For humanity to continue to benefit from this bacterial natural defence system, we need to change the way we use antibiotics today to reduce the spread of antibiotic resistance. As it is a global problem, we need to take action together. It doesn´t matter if a few countries have tight national regu-

lations on antibiotic use if there are other countries that do not regulate in this area. All parts of society need to work together against this common goal, nationally and internationally (Laxminarayan R et. al., 2013).

USING PATENT INFORMATION TO FIGHT ANTIBIOTIC RESISTANCE

The Swedish patent and registration office PRV handles all applications for patent protection related to the Swedish market. PRV is also a PCT-authority and handles patent applications filed through the PCT-system. PRV is an expert at searching for patent information, and also performs specially tailored consultancy services according to clients needs.

As explained above, information found in patents can complement other information when making strategic decisions in a project. Many times, patent information is the only source of information on a specific technology, making patent information an essential part in any major decision-making process.

We performed a number of searches in patent databases in the technical fields of antibiotics, antibiotic resistance and diagnostic tools for detection of antibiotic resistant bacteria. In this report, we present data from some of these searches. The aim of this report is to show the richness of information found in patent documentation and to highlight the value of patent information when making strategic decisions. It is our hope that this report, in its own way, will contribute to the fight against antibiotic resistance.

INNOVATION IN GENERIC PHARMACEUTICAL COMPANIES

Teva, one of the worlds largest pharmaceutical companies is a global dominant, especially in the field of generic drugs. Among the generic products Teva produce and sell there are many antibiotics. Examples are amoxicillin, azithromycin, ciprofloxacin, clarithromycin, clindamycin, doxycycline and penicillin V (TEVA product catalogue 2016/2017). However, Teva also have their own research and development. For instance, when analyzing the patent documentation on Teva one can see that many of their patent applications concerns different physical forms of the drug molecules produced (see diagram page 12). Thus, even if the drug molecule in itself can not be patented anymore, improvements in how it is formulated and delivered to the patient seems to be one area where Teva´s R&D is focused.

GLOBAL AND NATIONAL ACTION PLANS TO COMBAT ANTIBIOTIC RESISTANCE

In 2015 WHO adopted a "Global action plan on antimicrobial resistance" that presents five objectives to fight AMR. A coordinated "one health" approach, that encompasses everyone, and every area of society, is essential for managing this crisis. This plan also highlights the need for multisectoral national action plans to combat AMR (WHO, 2015). Sweden, having a long history of working with prevention of antibiotic resistance, presented a "Strategy to combat antibiotic resistance" in 2016 (S2016/02971/FS, 2016).

This strategy comprises an overarching goal and seven strategic objectives. The overarching goal is "to preserve the possibility of effective treatment of bacterial infections in people and animals". The fourth of these seven objectives are "increased knowledge for preventing and managing bacterial infections and antibiotic resistance with new methods". It is stated here that the government expects research to be carried out in the areas of antibiotic resistance, basic bacterial infection mechanisms, as well as outlining how new strategies and other knowledge can best be implemented in relevant activities, and implementing strategies to bridge the gap between basic research and the commercialisation of research findings. Also, it is stated that universities and other education institutions, government agencies, health and medical care institutions and the industry are to collaborate at national level, as well as within the EU and at international level, to identify and bridge knowledge gaps.

Antibiotics and antibiotic resistance – two sides of the same coin

Antibiotic resistance has been a problem as long as antibiotics have been used. Looking at the patent information this problem was not completely realized until the 90´s. Patenting in the field is increasing but the question is if current efforts are enough.

Antibiotic resistance is not a new problem. Alexander Fleming discovered early on that bacteria treated with penicillin can develop resistance to the antibiotic. This was later confirmed in experiments performed by the two researchers E.P. Abraham and E. Chain (Abraham E. P. et al., 1940). In the 1960´s (see timearrow) resistance to antibiotics was becoming a bigger and bigger problem. By then most of the known antibiotics had already been discovered and were being used extensively which enabled the rise of antibiotic resistance (Davies J. et al., 2010). Interestingly, as can be seen in figure 1, patent applications describing antibiotic resistance were filed starting in the early 1960´s.

PATENTS ON ANTIBIOTIC RESISTANCE

In the 1960´s and 1970´s there was a low and steady stream of patent applications, not exceeding more than 5 applications per year. However, beginning in the 1980´s patent applications increased, and from the late 90´s and onward there has been an exponential increase in applications in this field of technology. Perhaps one reason for this is that in the 1960´s and 1970´s, during and right after the golden era of antibiotic discovery, there were a lot of alternative antibiotics to use if resistance occurred, so no one was focusing on techniques to solve the problem of resistance. Also, in the ensuing decades, more effort was put into biochemically modifying known antibiotics or using high-throughput technology to develop new antibiotics (Davies J. et al., 2010). Perhaps the exponential increase in patent documents in the 1990´s and onward is because it took until the beginning of this decade to realize that current attempts to solve this issue were ineffective.

When analysing the documents filed during this time period one can see several different areas of technology represented. Some documents relate to processes for propagating, maintaining or preserving microorganisms. Other documents focuses on genetic engineering and measuring processes involving enzymes or microorganisms. Many documents also relate to medical preparations. In the middle of the 1990´s a significant increase can be seen for documents describing antibacterial agents specifically (figure 2).

MARKETS AND ANTIBIOTIC RESISTANCE

When analysing where the possible markets are for these inventions (figure 3) it is clear that the North American (especially the US), Chinese, Japanese, Australian, South Korean and the Indian markets dominate.

PATENTING TREND IN THE FIELD OF ANTIBIOTIC RESISTANCE

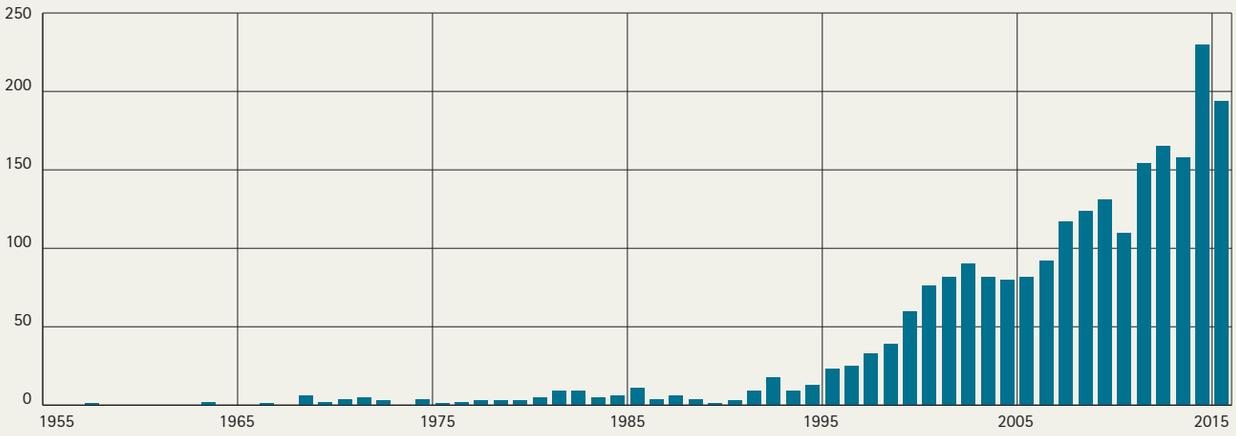


Fig. 1. The figure shows the total amount of patent documents filed between 1955-2015 presenting inventions on how to solve antibiotic resistance.

TECHNOLOGY PATENTING TREND IN THE FIELD OF ANTIBIOTIC RESISTANCE

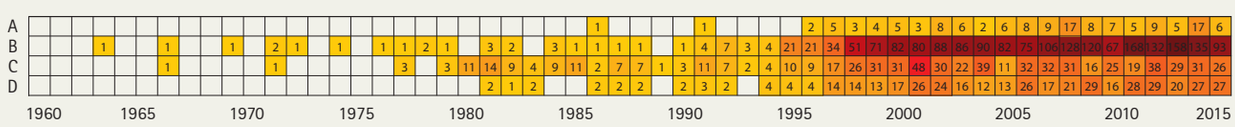


Fig 2. The figure shows the number of patent documents filed in each area of technology in the field of antibiotic resistance between the years 1960-2015.
A low number of filed patents is represented by bright yellow colours as higher numbers of patents are represented by darker red colours.

A. Biocides (e.g. antimicrobial compounds).
B. Medical preparations (e.g. antibiotics and antibacterial agents).
C. Microorganisms and genetic engineering.
D. Analysis.

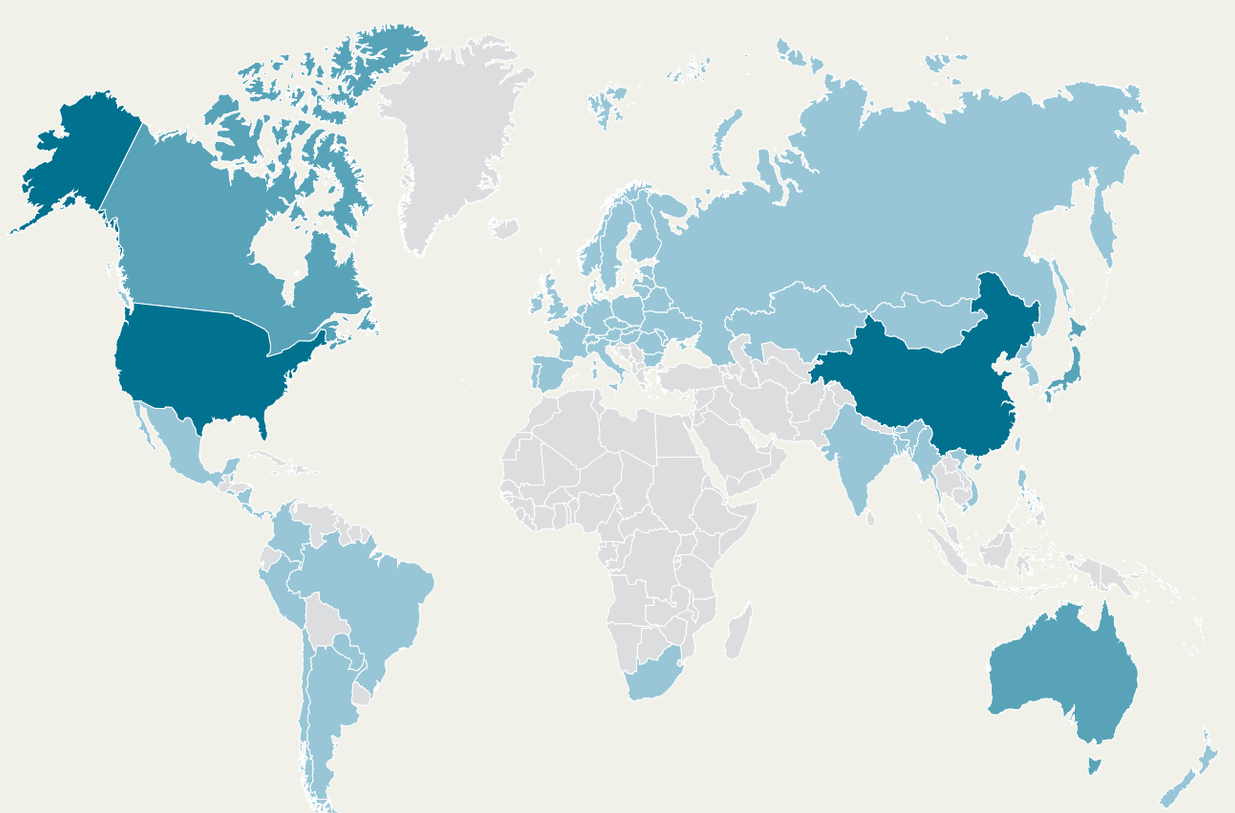


Fig 3. The figure shows markets for the technology concerning antibiotic resistance. A darker blue colour represents a higher activity as grey colour represents no activity.

MAJOR PLAYERS IN THE FIELD OF ANTIBIOTIC RESISTANCE

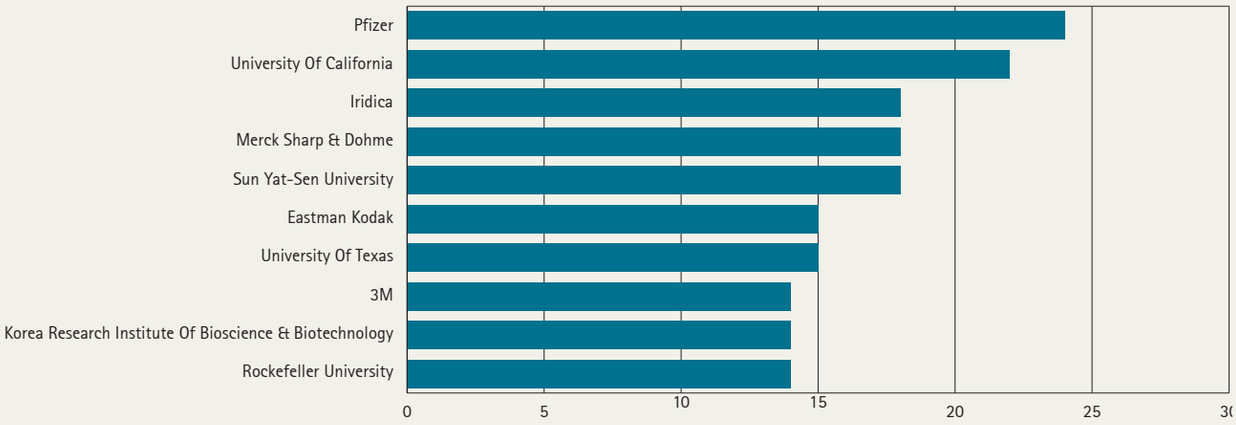


Fig 4. The figure shows the top 10 players with the highest number of patents within the field of antibiotic resistance.

MOST CITED PLAYERS IN THE FIELD OF ANTIBIOTIC RESISTANCE

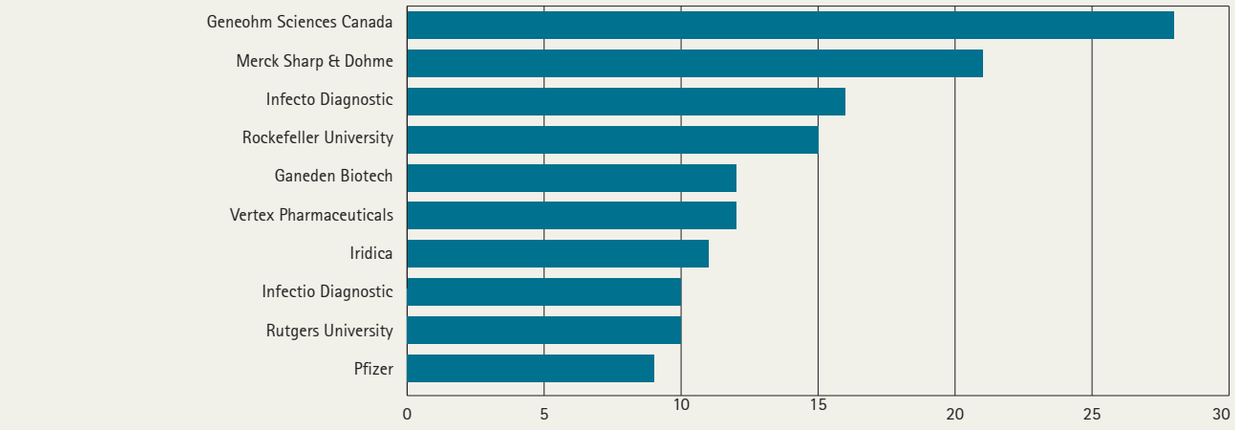


Fig 5. The figure shows the 10 most cited players within the field of antibiotic resistance.

Many European and South American markets such as the German, Spanish, Austrian, Danish, British, Russian, Brazilian, Mexican and Argentinean markets are also quite active. Africa, the Middle East (with the exception of South Africa and Israel) and South-East Asia do not seem to be particularly active markets. However, these markets represent some of the poorer countries in the world. These countries are often not profitable markets since they cannot afford the latest antibiotic treatments or diagnostic tools, but instead have to rely on older and cheaper antibiotics and diagnostic systems (Kariuki S. et al., 2015; Laxminarayan R. et al., 2013).

TOP PLAYERS IN ANTIBIOTIC RESISTANCE

When analysing the applicants holding the most patent applications in this field (figure 4) we can see that it is a mix of applicants from different sectors. Major pharma companies such as Pfizer, Merck Sharp & Dome and Iridica (now Abbott) are represented here. Universities, such as UCLA, Sun Yat-Sen University and University of Texas, are also represented. Analyzing the sub-area of technology that these applicants operate in one can for instance see that Pfizer and UCLA have applications mainly focused on medical preparations while applicants such as Iridica and Geneohm Sciences Canada have applications mainly focused on methods for diagnosis or for determining the presence of microorganisms (data not shown).

It appears that Geneohm Sciences Canada have technology interesting to other applicants since they are the highest cited applicant (figure 5). Geneohm Sciences Canada patent portfolio contains patent documents describing the use of advanced molecular technologies, such as PCR, for detecting different bacteria and antibiotic resistance genes.

Calculations from a report supported by the UK government and the Welcome Trust, estimate that if we fail in reducing the spread of antibiotic resistance by the year 2050, as many as 10 million people will die from antibiotic resistant infections, every year. In addition to the human cost, this could also cause financial losses of up to 100 trillion US dollars. (O´Neill, 2014).

Old antibiotics and new resistance

Most of the antibiotics still in use today were discovered in the "golden era" from the 1940´s to the 1960´s. Since research and development of new antibiotics is difficult and hard to make profitable major pharma now focus on other more lucrative areas. Although new antibiotics are urgently needed patenting on known antibiotics such as penicillin are increasing. Especially in China.

Since the discovery of the first antibiotic penicillin in 1928 more than 20 different classes of antibiotics have been discovered and marketed (Coates A. RM. et al., 2011). Most of these antibiotics were discovered between 1940 – 1960 in the "golden era" of antibiotics. These antibiotics were, like penicillin, isolated from its natural source. In fact, a majority of the antibiotics still in use today were originally isolated from different bacteria or fungi (Lewis K., 2013; Wright G. D., 2007). However, this source for novel antibiotics slowly came to an end. At the same time, antibiotic resistance was becoming an increasing problem.

Therefore, in the 1970´s and 1980´s the pharma industry focused on chemically modifying the molecules of already existing antibiotics, producing analogues, but also tried to design new molecules (Wright G. D., 2007; Davies J. et al., 2010).

In the 90´s the genomes of several bacteria were sequenced. This spured pharma to use another approach of developing novel antibiotics. Methodology allowing rapid screening of a large amount of samples in parallell using automation equipment (also known as high-throughput screening) was used to screen drug candidates against genomically identified targets to find molecules that could be used as antibiotics (see timearrow, pages 10-11). Unfortunatelly this did not result in any new antibiotics. Instead, this expensive failure led to many pharmaceutical companies discontinuing their research and development programs in the antibiotic field (Davies J. et al., 2010; Payne D. J. et al., 2007).

CLASSIFICATION OF ANTIBIOTICS

Antibiotics are classified based on their chemical structure, mechanism of action, or activity spectrum (target bacteria) (Kadam S. S. et al., 2013). Antibiotics are either bacteriostatic or bacteriocidal in its effect. Bacteriostatic antibiotics do not kill the bacteria but stop it from proliferating, leaving it to the immunesystem to clear out the pathogenic bacteria. Bacteriocidal antibiotics on the other hand kill the targeted bacteria.

Antibiotics utilize one of three common mechanisms of action, as described above. Antibiotics either target bacterial ribosomes (responsible for producing proteins), enzymes facilitating replication and transcripiton of the bacterial genome or cell wall synthesis mechanisms (Lewis K., 2013).

THE SPECTRUM OF ANTIBIOTICS

Antibiotics are also divided into "narrow-spectrum" and "broad-spectrum" antibiotics. The spectrum indicates how specific an antibiotic is in its antibacterial effect. Narrow-spectrum antibiotics are only functional against specific families of bacteria, whereas broad-spectrum antibiotics have effect on different types of bacteria such as gram-positive and gram-negative bacteria. Thus, broad-spectrum antibiotics are more useful since they can be used for many different types of bacterial infections. For example, broad-spectrum antibiotics are often prescribed when a doctor does not have enough information to make a proper diagnosis. Commonly, if a doctor suspects a patient has a bacterial infection, and before the doctor has any test-results in hand, he/she will prescribe a broad-spectrum antibiotic to increase the likelihood that an efficient treatment is started promptly reducing the bacterias chance to grow and spread in the body. This is a major problem contributing to antibiotic resistance (Laxminarayan R. et al., 2013).

Since broad-spectrum antibiotics are effective against many different bacterial infections it is important to use them sparsely. Thus, once the doctor has a diagnosis and knows what strain of bacteria is causing the infection they should change antibiotics from a broad-spectrum to a narrow-spectrum antibiotic, when possible. This is particularly important from a resistance perspective since a more specific antibiotic (narrow-spectrum) leads to less resistance development (Lewis K., 2013).

NEW ANTIBIOTICS ARE EXPENSIVE

Many challenges lie ahead. For us to continue to have functional antibiotics in the future several things must change. We need to develop new antibiotics at a much higher rate compared to the past decades. The "low hanging fruit" which was "picked" in the 1940-1960´s are losing their effect one by one due to resistance and we urgently need new antibiotics to replace them (Coates A. RM. et al., 2011).

Unfortunately, as history has shown, innovation and discovery in the antibiotic field is especially challenging and therefore discourages investments

In 1928 Alexander Fleming discovered penicillin. Did you know that the mold which contaminated Flemings bacteria culture, and which was later identified as a strain of Penicillum notatum, most likely came from a laboratory in the same building as Flemings. This laboratory housed a large collection of unique molds, including the strain that contaminated Flemings bacteria cultures. It is thought that spores of this mold had spread throughout the building and contaminated Flemings bacteria cultures. (Kingston 2000)

BACTERIAL CELL STRUCTURES COMPLICATES ANTIBIOTIC DESIGN

Antibiotic molecules are chemically very complex structures posing extra challenges for their synthesis. Even if an antibiotic is successfully synthesized it might not be possible to get it inside the bacteria, a prerequisite to stop the proliferation or kill the target bacteria (Davies J. et al., 2010; Lewis K., 2013). To get a molecule inside a bacteria it needs to pass the bacterial envelope. The envelope provides structural support and regulates what molecules come in and which goes out. It also serves protection from the physical, mechanical and chemical strains of the surroundings.
The envelope comprises an inner cell membrane and an outer cell wall. Bacteria are divided into two different groups based on their envelope physiology, gram-positive or gram-negative bacteria. The difference between these two groups is that gram-positive bacteria only have one cell membrane, whereas gram-negative bacteria have two (Silhavy T. J. et al., 2010). Therefore, it is especially difficult to synthesize new antibiotic molecules that can be used against gram-negative bacteria (Lewis K., 2013).

in much-needed research. The molecules themselves are complex. They are hard to synthesize and are often difficult to deliver into the bacteria, which is necessary for the anti-bacterial effect.

It usually takes 12-15 years for a new medical product to reach the market. These are expensive years making it hard to attain profitability within the normal 20 years of patent protection (see above). Only 1,5 - 3,5% of new promising antibiotics make it to the market, so for every new marketable drug there are many more which failed along the way thus necessitating a substantial return on the few successes (O´Neill et al., 2015). Even if a new antibiotic makes it to the market it is not a given that it will sell or be effective for very long.

Older, still functionable/effective antibiotics still on the market are usually cheaper, so the higher pricing of the new antibiotic negatively impacts major sales. For drugs where the patent protection on the original molecule has expired there are often many generics of the same drug, perhaps with lower prices, further reducing the chance of return on the investment (Bhardwaj R. et al., 2013).

The uncertainty of resistance is also a factor. It is hard to predict when resistance will develop against a new antibiotic. Thus, the manufacturer does not know for how long their new antibiotic will be functional. As explained above, resistance often occurs when an antibiotic is overused. Therefore, there will likely be some restrictions on the use of this newly developed antibiotic to prevent or at least delay resistance development. That restriction could stretch long enough for the patent to expire on the new antibiotic, further reducing the return on investment (O´Neill et al., 2015).

What further complicates things is that resistance against an antibiotic does not necessarily need to be a result of overuse of that specific new antibiotic but can be a result of overuse of another, older, antibiotic. Therefore, the unpredictable factors of resistance make it even harder to get a return on investment.

NOVEL STRATEGIES FOR NEW ANTIBIOTICS

Something needs to change in the process of antibiotic research and development to encourage pharma to start focusing on the antibiotic field again.

THE RISK/REWARD BALANCE

One key change is to create a risk/reward balance such that even with the high risk there is a financial incentive to pursue antibiotic research. Importantly the financial return for R&D on novel antibiotics needs to be disconnected from volumes sold and instead be connected to the value it brings to society (Laxminarayan R. et al., 2013; O´Neill et al., 2015).

PREDICTABLE MARKET AND FOCUSED FUNDING

Some suggestions on how to support development of novel antibiotics is to create a predictable market for antibiotics to sustain commercial investment in R&D, focus funding into early-stage research to tackle AMR and interventions to support efficient drug development through centralised public platforms for clinical trials (O´Neill et al., 2015).

NEW AND OLD DISCOVERY PLATFORMS

There are also the more technical aspects of future antibiotic research. Although the discovery of penicillin was pure luck, the rest of the antibiotics discovered in the 40´s - 60´s were the result of purpose driven structured research. By setting up a regulated process, a platform, for a systematic screen, numerous bacteria were tested for their capacity to produce usable antibiotics. We still profit from the results of this platform today. However, this platform finally stopped providing new molecules. As described above, the new platform tested in the 90´s, based on high-throughput screening of drug candidates, failed to contribute to todays new antibiotics. Therefore, new discovery platforms also need to be developed. There are many different suggestions to novel platforms, all with their benefits and drawbacks (Lewis K., 2013).

Another suggestion is to revive the “old platform”, which was so successful in the 1940´s – 1960´s, since we have not yet screened all potential antibiotic-producing bacteria. This involves taking bacteria from their habitat in nature and culturing (growing) them in the artificial environment of the laboratory.

As demonstrated with the penicillin-producing fungi, the major problem with this platform is how

to get a microbe to grow in the laboratory. In order to screen for new antibiotics in this old platform, do research and produce these antibiotics, it is absolutely necessary to be able to culture the bacteria or fungi in a laboratory setting. The trick here is to mimic the growth-conditions in nature such that the necessary nutrients and growth promoters are present at adequate concentrations while minimizing the presence of growth-inhibiting molecules.

Today 99% of all bacteria are unculturable because we do not understand the nutrients and growth promoters necessary to culture them in a laboratory setting. If we can figure out how to culture these bacteria we could also screen them for novel antibiotics as we did in the 1940´s.

PENICILLIN – FROM DISCOVERY TO CONSUMED ANTIBIOTIC

In 1928 Alexander Fleming discovered penicillin for which he was awarded the Nobel Prize in 1945. Although celebrated for the discovery, Fleming was not able to make any significant medical use of his discovery. Fleming never managed to stabilize and purify penicillin, which is necessary in order to test the medical use of a molecule. Instead it was two other researchers, Howard Florey and Ernst Chain who proved the medical potential of Flemings discovery. First, Florey and Chain managed to stabilize and purify the active molecule of penicillin.

Then in 1940 they performed a series of experiments first on mice and finally on critically ill patients which proved the medical potential of penicillin (Kingston W., 2000; Chain E. et al., 1940). For this work, they shared the Nobel prize with Fleming in 1945.

The "patent story" of penicillin did not start with Fleming. Flemings contribution was the discovery, which he published in a scientific article in 1929 (Fleming A., 1929). Instead it was Florey and Chains work which laid the ground for the ensuing patents.

In addition to stabilizing and purifying the penicillin molecule, there was also a problem with culturing the penicillin producing mold on a scale large enough to get a good yield of the molecule. They needed to produce enough of the penicillin mold to perform more clinical tests on humans and, if possible, to make it a marketable drug.

After moving to the US, the US government provided Florey the funding and assistance to develop the fermentation process, in order increase the production of penicillin. The US government engaged the drug industry to help Florey develop processes for large- scale production of penicillin. Two of these companies Merck (also known as MSD) and Squibb (now Bristol-Myers Squibb) played a major role in this development.
A third drug company, Pfizer, was also recruited to help in this work and their contribution of submerged-fermentation enabled significant production volumes of penicillin. Several more companies got involved in the production and by 1944 the production yield of penicillin had increased more than 7000 times. This successful increase in penicillin production meant there was enough penicillin to provide soldiers fighting in World War II with this new "wonder drug" (Kingston W., 2000).

INNOVATIVE CULTURING OF BACTERIA GIVE NEW ANTIBIOTIC

Recently a group of researchers presented a new device, the iChip, for culturing previously unculturable bacteria. By using the iChip they discovered a new antibiotic called teixobactin (Ling L. L. et al., 2015). The iChip allows culturing bacteria in their natural environment, in the soil. By starting the bacteria culture in the soil, using the iChip, the bacteria can be acclimatized and later transferred into a laboratory setting allowing for expansion of the bacteria culture. Teixobactin has shown promise in all tests run so far. According to the patent information Novobiotic Pharmaceuticals have filed a patent application for teixobactin and its use as an antibiotic (patent application WO2014089053).

MARKETING OF NEW ANTIBIOTICS

After the successful campaign to make penicillin a marketable drug, several analogues of the penicillin molecule were developed and introduced on the market. Examples of these are penicillin V, ampicillin, methicillin, carbenicillin, cloxacillin, flucloxacillin, piperacillin, ticarcillin, mezlocillin, oxacillin, dicloxacillin, nafcillin, azlocillin and amoxicillin. Today amoxicillin is one of the most sold antibiotics in the world and penicillins as a group are the most consumed antibiotics worldwide (Gelband H. et al., 2015).

PATENTING THE PENICILLINS

All penicillins belongs to the class of β-lactam antibiotics. The antibiotics in this class share a specific chemical structure, a beta-lactam ring. As can be seen in figure 6 the first patent documents that discuss compositions containing a molecule from the penicillin group were filed in the early 1940´s. In the beginning, only a few documents were filed per year. However, in 1944 something happened and a substantial increase in filed documents can be seen. A closer analysis of these documents show that most of them describe methods on how to optimize culture conditions to maximize the yield as well as how to isolate the produced penicillin from these cultures (data not shown).

From the 1940´s until late 1960´s the number of patent applications stays on a low and rather stable level (figure 6). It seems as if at this time there was

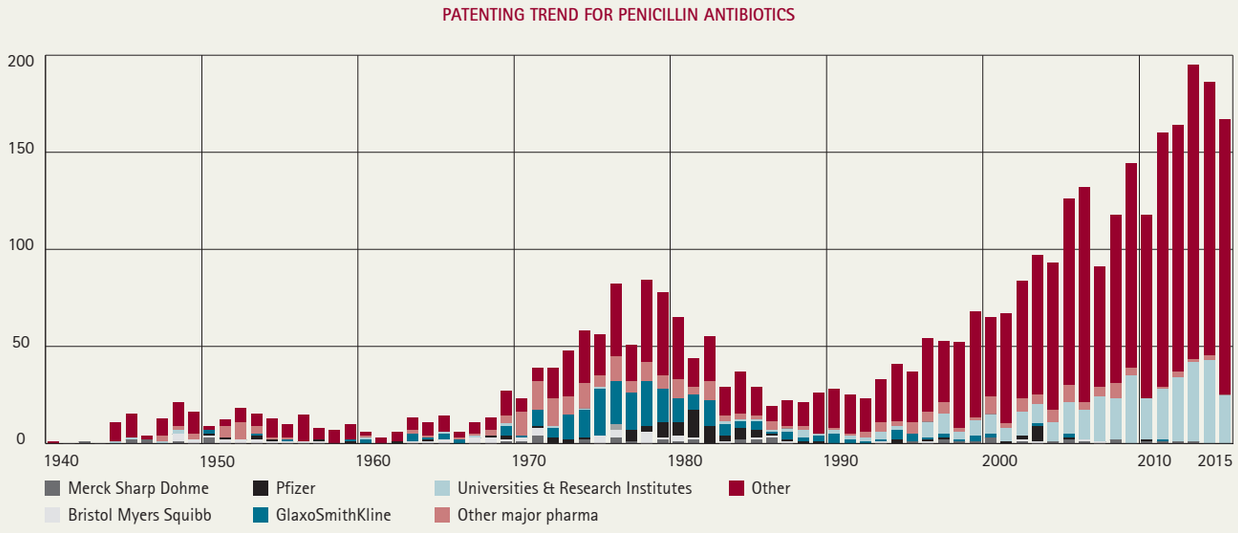


Fig 6. The figure shows the total amount of patent documents filed from 1940-2015 describing medical compositions comprising a penicillin molecule ("Major Pharma" as defined in Jurney C. 2016).

no company that "dominated" the penicillin field. Rather we see a mix of different companies here.

PRODUCING SYNTHETIC PENICILLINS

Once the problem of how to massproduce penicillin was solved in the 1940´s, focus shifted toward making a synthetic process for producing penicillin.

There are many advantages to chemically synthesizing a molecule compared to isolating it from its natural source. For instance, isolating a synthesized molecule is often easier and less time-consuming than isolating the molecule from its natural source. Also, chemical synthesis can be controlled on a very detailed level enabling a more stable and repetitive process. Chemical synthesis also allows for modification of the synthesized molecule enabling the chemists to add extra features to the molecule.

Initial attempts to chemically synthesize penicillin in the 1940´s were unsuccessful.

However, in the late 1950´s a scientist finally succeeded to make a synthetic copy of the natural penicillin molecule. In 1959 a variety of synthetic penicillin molecules were introduced into the market and increased the industry for synthetic penicillins. Ernst Chain, now working for the Beecham group, and two other researchers, John C. Sheehan and Kenneth R. Henery-Logan played key roles in advancing these methods (Kingston W., 2000; Sheehan J. C. et al., 1959; Sheehan J. C., 1967; US3159617).

The British pharma company Beecham and the US pharma-company Bristol-Myers had a huge success marketing the synthetic penicillin's (Kingston W., 2000). Beecham became a major pharma company due to this success and later mergered with SmithKline Beckman to become SmithKline Beecham. They later merged with Glaxo Wellcome to become GlaxoSmithKline (GSK), currently one of the largest pharma companies in the world.

Bristol-Myers merged with Squibb in 1989 to become Bristol-Myers Squibb (BMS) also one of the worlds largest pharma companies today.

THE ERA OF CHEMICAL MODIFICATION AND NOVEL DESIGN

The next significant increase of patent applications seen starts in 1969 (figure 6). This increase lasts until the end of the 1970´s when we see a reduction in the patent trend for the first time.

GlaxoSmithKline became a major player in the field at the beginning of the 1970´s and filed almost 25% of the total amount of patent applications several years in a row. However, this trend ended about a decade and a half later (figure 6).

The first decrease of filed patent documents on penicillins started in the early 1980´s and lasted almost a decade (figure 6). This decrease coincides with the end of the previous "golden era" and "the era of chemical modification and designing of new molecules". At the same time, antibiotic resistance had become a serious problem, further detering pharma from investing money and time into antibiotic R&D (see above). As shown in figure 6, this decrease was because several major pharma companies (such as GSK and Pfizer) reduced their filing of patent applications.

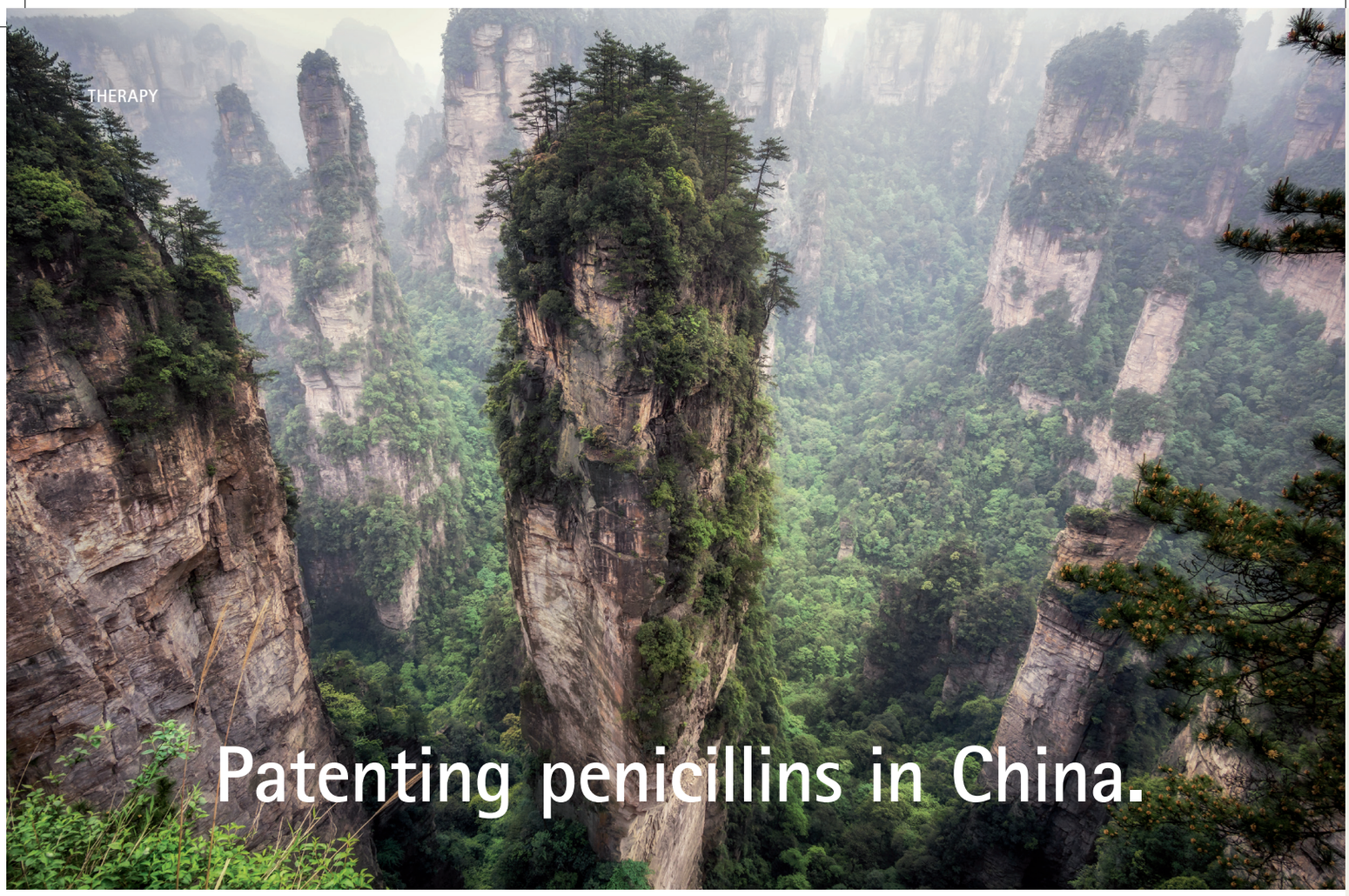
Interestingly the peak in patent documents from 1969-1985 occurred when no new antibiotic classes were discovered, but the field instead focused on modifying existing molecules and designing new ones (Davies J. et al., 2010; Wright G. D., 2007).

Modifying existing molecules was a response to the increasing threat of antibiotic resistance. By modifying existing antibiotic molecules, the aim was to circumvent the resistance mechanism bacteria had developed and make the antibiotics functional again (Wright G. D., 2007).

THE EXIT OF BIG PHARMA

From the 1990´s onward, we see a new exponential increase of patents documents describing penicillins. As explained above, the failed efforts using high-throughput technology to find new antibiotics resulted in that major pharma companies cancelled their antibiotic R&D-programs. This is reflected in figure 6 where major pharmaceutical companies now constitute a rather small part of the otherwise exponential increase. Instead other institutions such as Universities and Research Institutes make up a significant part of the increase seen in figure 6.

However, this does not fully explain the exponential increase we see here. For example, entities presented in figure 6 as "other" represents well over half of all these patent documents.



Patenting penicillins in China.

To answer this question we looked at where many of these patent documents first were filed and later published. Interestingly, we found that China is one of the major countries for patenting on penicillins, especially from the beginning of the 21st century and onwards (figure 7).

When looking at the patent information from China, we do not see any major pharmaceutical companies dominating (figure 8). Instead there seem to be many smaller pharmaceutical companies as well as some Universities, each filing roughly the same number of patent documents. The Chinese pharmaceutical industry is considered to be very fragmented which could explain what we see here (ITA, 2016).

CHINA'S NEED FOR PENICILLINS

China has a large population that continues to rapidly increase. Therefore, there is a continuous increase in the need for basics such as food and pharmaceuticals. The quality of life is also improving, and therefore the demand for more expensive produce and meat is increasing. In fact, China is currently the largest meat consuming country in the world as well as one of the world's largest producers of meat. Unfortunately, from the perspective of combating antibiotic resistance, the Chinese agricultural industry uses a lot of antibiotics and is allowed to use antibiotics for growth promoting purposes (Collignon P. et al., 2015; Khrisnasamy V. et al., 2015).

China also has a large pharma industry for generic drugs. As explained above, when a patent expires on a profitable drug the market often gets flooded with cheaper copies (generics) of that drug. At the point when prices on the drug fall, and return on the investment is at its lowest, manufacturing commonly moves abroad to places where manufacturing costs also are lower. One of these places is China (Ni J. et al., 2017). One explanation for the intensive rate of Chinese patenting in the field of penicillins over the last 10-15 years, is the presence of a large domestic need for antibiotics combined with the fact that China is a major producer of generic antibiotics. Although they primarily produce generics, these pharma companies also must be innovative and develop their products and processes in order to be competitive on the market. This might then spur research and innovation of better manufacturing processes, new formulations or new uses of the produced drug which could be patent protected.

The system set out by the Chinese government to spur innovation and patenting through different incentives is most likely also a contributing factor here (The Economist, 2010).

Interestingly, when looking at these patent documents first filed in China we see that they are, with a few exeptions, published only in China. This suggests that the market for these inventions is China (figure 9).

GEOGRAPHIC PATENTING TREND FOR COMPOSITIONS COMPRISING PENICILLIN MOLECULES

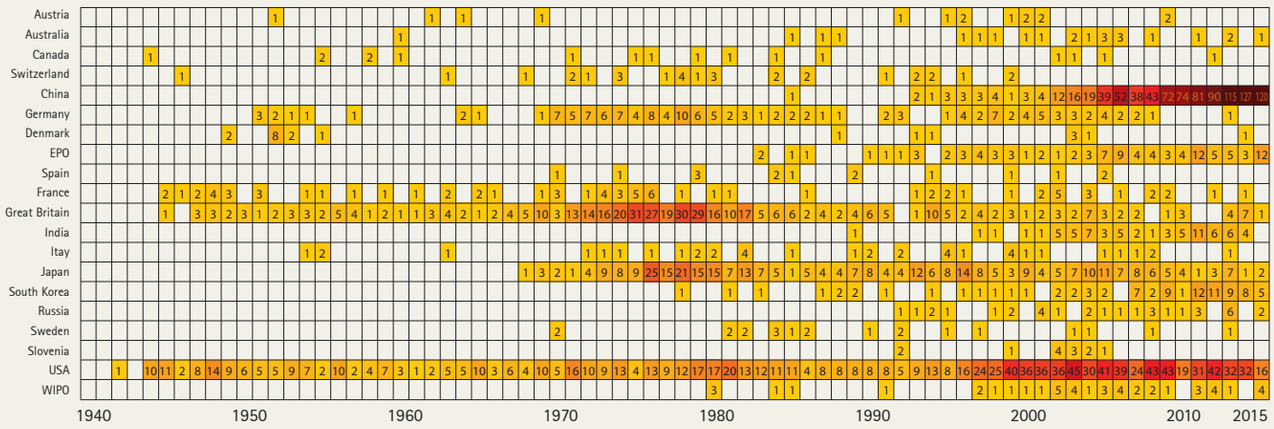


Fig 7. The figure shows where in the world patent documents describing medical compositions comprising a penicillin molecule where published between the years 1940-2015. Note that "EPO" and "WIPO" do not refer to actual countries but to the European patent organisation and the World intellectual property organisation respectively". A low number of filed patents is represented by bright yellow colours as higher numbers of patents are represented by darker red colours.

MAJOR CHINESE PLAYERS IN THE FIELD OF PENICILLIN ANTIBIOTICS

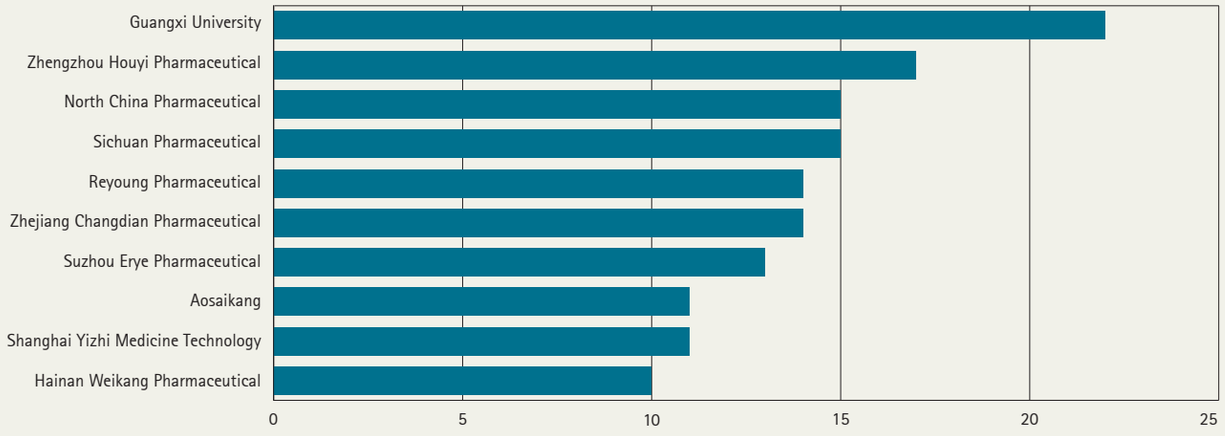


Fig 8. The figure shows the 10 most active applicants in China that have filed patent applications describing medical compositions comprising a penicillin molecule.

CHINESE PATENTS FOR THE CHINESE MARKET

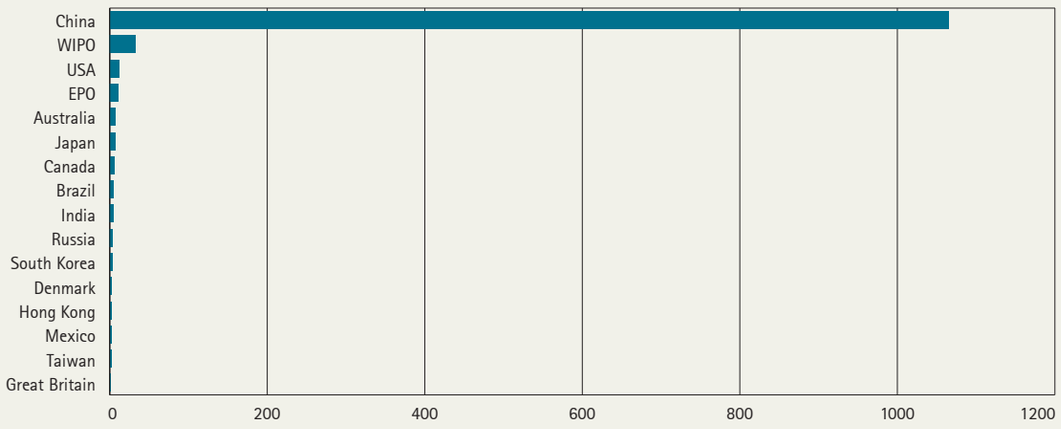


Fig 9. The figure presents markets and competitors location for compositions comprising a penicillin molecule for patent documents first filed in China.
Note that "EPO" and "WIPO" do not refer to actual countries but to the European patent organisation and the World intellectual property organisation respectively.

The success story of daptomycin

The story about daptomycin presented here below shows how a new approach can turn an unsuccesful project into a medical triumph and a financial gold mine. It makes you wonder, are there more "shelved projects" out there harbouring new antibiotics?

The lipopetides comprise several antibiotic families such as the polymyxins, amphomycins and echinocandins. Another member of this class, the daptomycins, were discovered first in the 1980´s when scientists identified and analyzed the bacterial strain *Streptomyces roseosporus*, isolated from soil samples collected at the base of a dormant volcano, Mount Arat, in Turkey.

A scientist at Eli Lilly realised the antibiotic potential of daptomycin and initiated the development of daptomycin into a usable drug. However, due to serious adverse effects in some of the volunteers during the clinical trials, Eli Lilly suspended further trials and put the antibiotic ”on the shelf” (Pirri G. et al., 2009; Eisenstein B. I. et al., 2010). Luckily, Richard Baltz, who had been working on the daptomycin program at Eli Lilly, met with Dr. Tally, a representative for a small biotechnology firm called Cubist Pharmaceuticals, at a scientific meeting in the late 1990´s.

Dr. Tally knew about the shutdown of the ”daptomycin-program” at Eli Lilly and asked Baltz if he would be interrested in taking the chair as Vice president of molecular biology at Cubist instead (Eisenstein B. I. et al., 2010). Richard Baltz did not take the offer but did give a presentation on the ”daptomycin-program” for Dr. Tally and his colleagues. It is said that after this presentation Dr. Tally decided that the daptomycin-program was worth developing and he therefore started negotiating with Eli Lilly for a license on daptomycin.

In 1997 Cubist and Eli Lilly agreed on the terms for a license on daptomycin. Later Cubist also hired Richard Baltz. Scientists at Cubist started to develop derivatives of daptomycin and to investigate the reasons for the adverse effects of daptomycin that caused Eli Lilly to cancel its program. The problem of the adverse effects was finally solved and in 1998 Cubist filed a patent application concerning methods for administering daptomycin in order to minimize adverse effects.

A patent was granted by the Unites States Patent and Trademark Office in 2005 (US6852689 B2). In 2003 daptomycin for injection (Cubicin) was approved by the United States Food and Drug Administration (USFDA) and Cubicin was taken to the market. Cubicin has been a financial success enabling Cubist to grow and become a major player in the antibiotic field (Eisenstein B. I. et al., 2010).

In 2014 Merck aquired Cubist in a strategic move to enter the market of drugs combating superbugs (Merck, 2014). Today daptomycin is used to treat complicated skin infections caused by gram-positive bacteria such as *Staphylococcus aureus, Streptococcus pyogenes and Enterococcus faecalis*. Daptomycin is a key antibioitic in fighting superbugs like Methicilin-resistant isolates of *Staphylococcus aureus*, also known as MRSA (Gonzalez-Ruiz A. et al., 2016). MRSA is a variant of the common Staphylococcus aureus bacteria that is resistant to methicillin and other penicillins commonly used to treat Staphylococcus infections.

MRSA is spread by contact between humans but can also spread between animals and humans. Many people in the population are healthy carriers of MRSA-bacteria.

Although these “carriers” are asymptomatic they can spread MRSA, and whenever that happens, there is always a risk that it will cause a serious infection in the recipient. For a sick person, or a person with an otherwise weakened immune system, a MRSA infection is very serious. Not surprisingly, MRSA is a big problem especially in healthcare settings and it is estimated that hundreds of thousands of people die every year from MRSA infections (Sangvik M. et al., 2011; Laxminarayan R. et al., 2013).

As can be seen in figure 10, patent documents related to lipopeptide antibiotics and specifically to daptomycin quickly increased in number from the end of the 90´s into the 21st century. During this period, daptomycin was becoming widely used, revenue from daptomycin increased significantly, and contributed to Mercks strong position on the market (Eisenstein B. I. et al., 2010).

Interestingly, it is not “major pharma”, such as Merck, that are behind this increase in filed patent documents. Instead it is smaller pharma, Universities and Research institutes that have filed most of these patent documents (figure 11).

Antibiotics are used for preventing and for treating ongoing infections in humans and animals. However, antibiotics are also used as a growth promoter in animal farming. Therefore, today more antibiotics are used for animals than for the entire human population. Unfortunately, the antibiotics used in animal farming are often the same as the ones used for humans. This is a major factor contributing to the spread of antibiotic resistance.

(Gelband, 2015)

PATENTING TREND FOR LIPOPEPTIDE ANTIBIOTICS

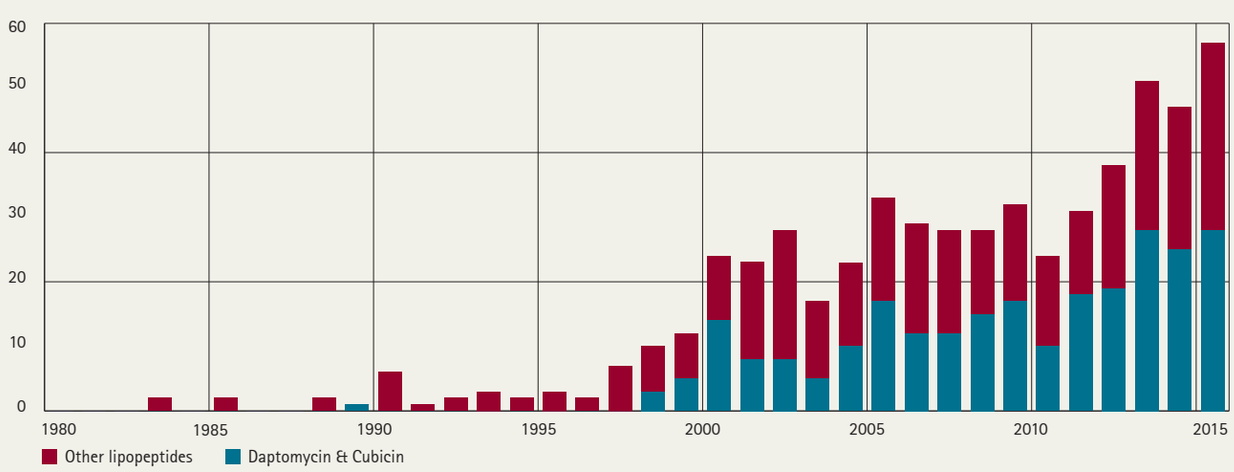


Fig 10. The figure shows the total amount of patent documents from 1980-2015 describing medical compositions comprising a lipopeptide antibiotic such as daptomycin.

THE PATENTING TREND OF MAJOR PLAYERS IN THE FIELD OF LIPOPEPTIDE ANTIBIOTICS

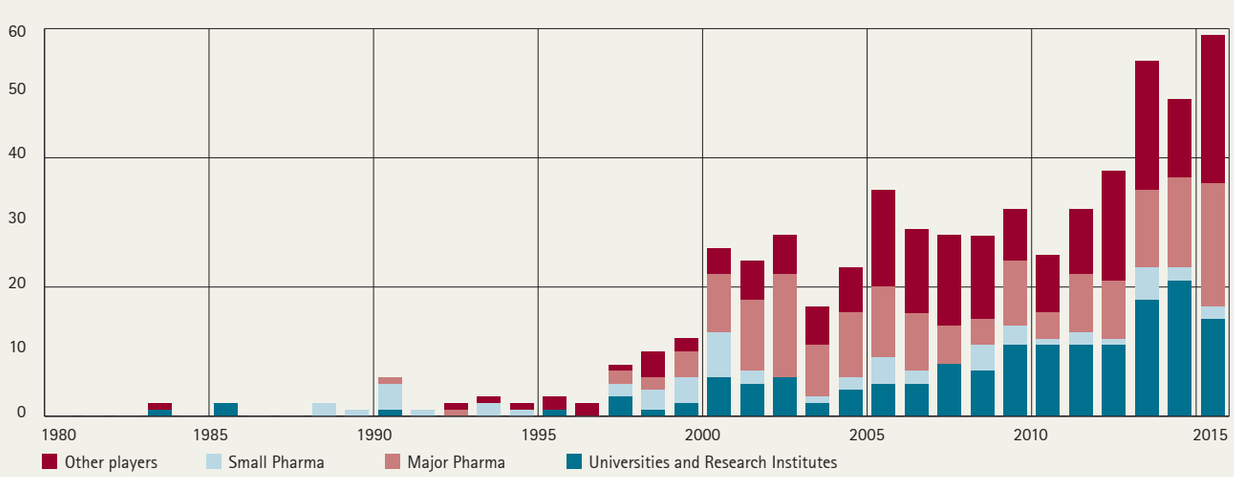


Fig 11: The figure shows major players responsible for filing patent documents from 1980-2015 describing medical compositions comprising a lipopeptide antibiotic. For a definition of "Major Pharma" see reference Jurney C. 2016.

Pliva, from small to big by smart patenting

Here below we tell the story of how a small pharma company became a significant player in the field of antibiotics by strategically using their patented technology.

Another class of antibiotics discovered during the golden era is the macrolides (see page 10-11). All the antibiotics belonging to this class are chemical modifications of the first macrolide, erythromycin, discovered in 1949.

Macrolides function by inhibiting protein synthesis and are used against both gram-positive and gram-negative bacteria, they are broad-spectrum antibiotics. The class of macrolides comprises many different antibiotics, and between 2000 and 2010, it was one of the most used antibiotic classes in the world. In 2009 macrolides were the most sold class of antibiotics for animal use (Seiple I. B. et al., 2016; Gelband H. et al., 2015).

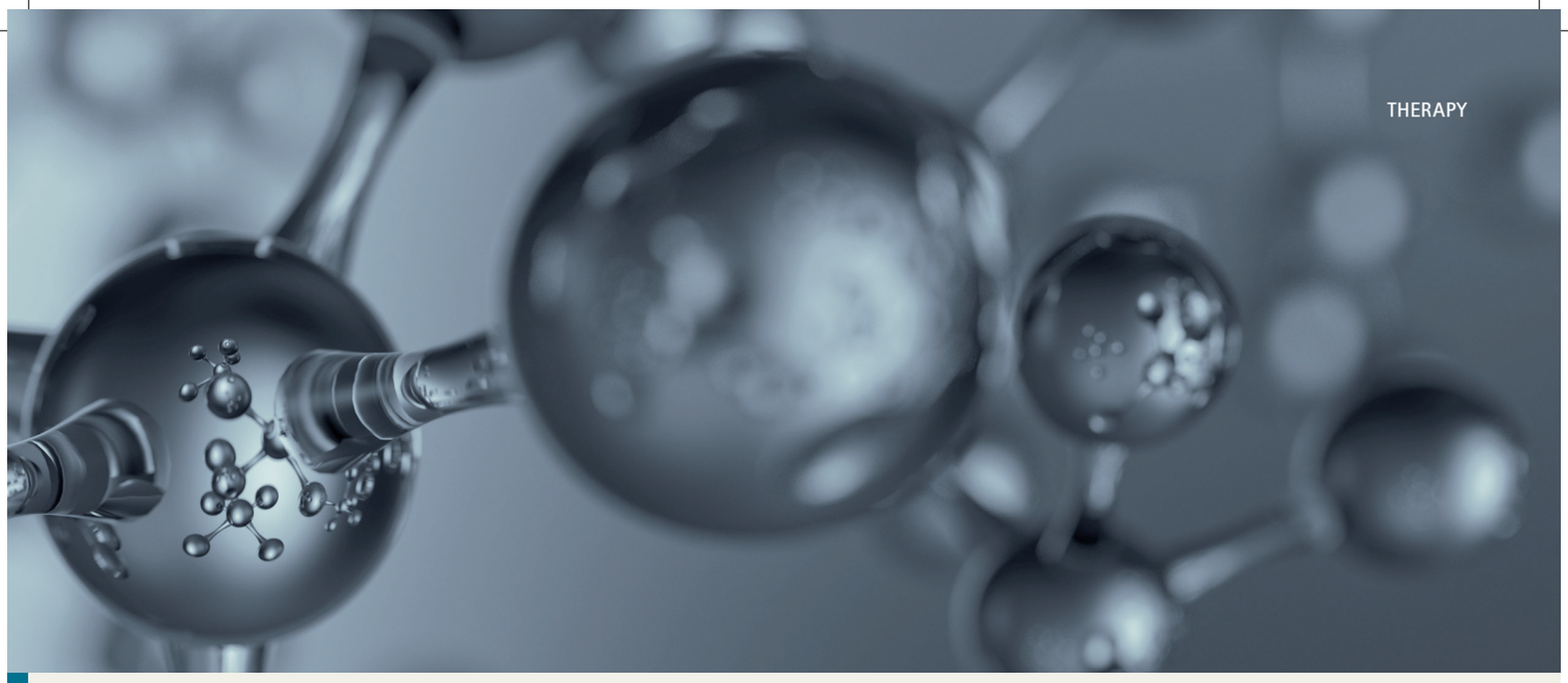
In 1980, azithromycin, a macrolide antibiotic, was synthesized from erythromycin for the first time by the Croatian pharmaceutical company Pliva (Yesterday, Today, Tomorrow, PLIVA). Realizing the antibiotic potential of azithromycin, Pliva filed a patent application for azithromycin in 1979 in former Yugoslavia (Application number YU76879A). At that time, Pliva was a small pharmaceutical company and did not have the financial strength to commercialize their new antibiotic globally.

However, Pliva did manage to receive patent protection for azithromycin in many more countries of the world, including in the US. In 1991 azithromycin was approved by the USFDA for medical use. Some years earlier Pliva had signed a licensing agreement with Pfizer for selling azithromycin on the american and western european markets. Pfizer had found Plivas patents after searching the United States Patent and Trademarks office (USPTO) database and realized its market potential. By teaming up with Pfizer, Pliva could now reach many more markets with their drug and increase their profit. Azithromycin quickly became one of the best-selling antibiotics worldwide (WIPO, Azithromycin).

In 2010, together with penicillins, macrolides were one of the most prescribed class of antibiotics, in the US. The most prescribed antibiotic of all was azithromycin (Hicks L. A. et al., 2013). The fincancial success of azithromycin enabled Pliva to expand their business into new markets and grow as a pharmaceutical company. In 2008 Pliva became a member of the Teva group, one of the world's largest generic pharmaceutical companies.

When analyzing the data for patent documents related to the macrolide family, we see that the first patent documents mentioning this class of antibiotics start to appear in the 50´s (figure 12). At first published patent documents appear at a steady and low rate. However, we see that in the end of the 60´s the amount of published documents describing macrolides increases rapidly. This trend continues well into the first decade of the 21st century where we see, for the first time, a decrease in filed patent documents.

Pliva is one of the top 10 of companies who have filed patent documents describing macrolides. Of these 10 companies Pliva has the 6th largest macrolide patent portfolio of granted patents with a total of 20 patents currently in force (figure 13). Although Pliva is still a main player in the macrolide field, Pfizer is the dominating company here with the largest patent portfolio and with the highest number of granted patents.



PATENTING TREND FOR MACROLIDE ANTIBIOTICS

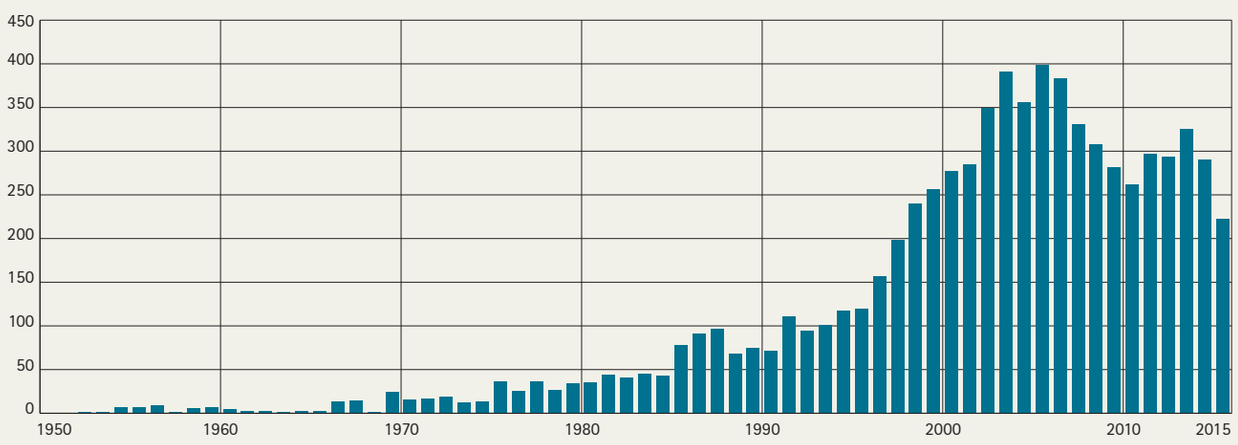


Fig 12. The figure shows the total amount of patent documents from 1950-2015 describing medical compositions comprising a macrolide antibiotic.

LEGAL STATUS FOR THE TOP 10 PLAYERS IN THE FIELD OF MACROLIDE ANTIBIOTICS

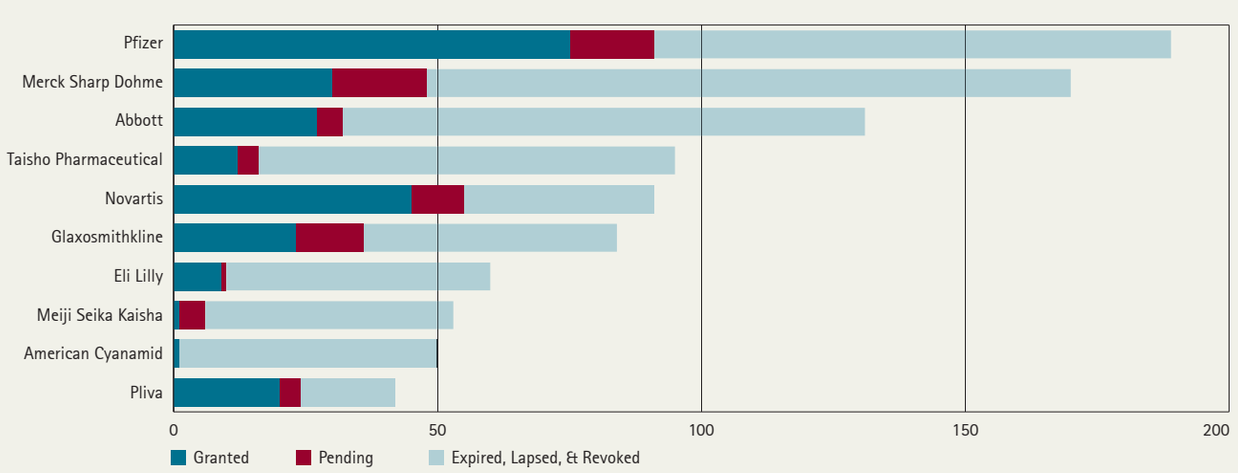


Fig 13. The figure shows the top 10 players patent portfolios and its current legal status in the technology area of compositions comprising a macrolide family member. Note that "Granted" means that the patent is in force. "Pending" means the that the patent application has not yet been determined on (rejected or granted). "Expired, revoked and lapsed" means that the patent is not in force.

Diagnostics driving antibiotic resistance

Better diagnostic methods are urgently needed in the fight against antibiotic resistance. Today we rely on methods developed in the 1950´s which are to slow and unspecific and therefore contribute to the spread of resistance. Newer methods are available but they are either too expensive, too advanced, too complicated and are often not specific or sensitive enough.

In order to maintain the quality of today's medical care, it is necessary to develop new therapies for treating resistant bacterial infections. A key factor in the fight against antibiotic resistance is cheaper and faster diagnostic methods. Diagnostic methods used in the clinic today are often too slow and unspecific for doctors to quickly determine if their patients have a bacterial infection and would benefit from an antibiotic treatment.

With currently available diagnostic methods it often takes 24-48 hours before the doctor knows if bacteria are causing the infection, and then an additional 24 hours before it is known which antibiotic will be most effective against that strain of bacteria. Meanwhile, the doctor must try to identify what is causing the patients infection based on the patients medical history, observed symptoms and the doctors medical experience. If this "empirical diagnosis" results in the conclusion that a bacterial infection cannot be ruled out, a broad-spectrum antibiotic is prescribed as a safety measure.

There are several problems with this approach. Often a patient´s infection is not caused by bacteria, but by a virus, against which antibiotics have no effect. Even if the infection is indeed caused by bacteria, it is not necessarily sensitive to the antibiotic prescribed even if it is broad-spectrum.

Therefore, it is common that patients are subjected to unnecessary treatment or are treated with the wrong drug for several days. Since broad-spectrum antibiotics are functional against many different types of bacteria side effects are common. This not only results in unnecessary suffering for the patient but also contributes to the development of antibiotic resistance (O´Neill J. et al., 2015).

THE NEED FOR CHEAP, FAST AND RELIABLE METHODS

Many of the diagnostic methods in use today were developed in the 1950s and involve the relatively slow process of culturing bacteria (O´Neill J. et al., 2015).

Today, there are diagnostic technologies available that can identify if disease-causing bacteria are present in a sample, and also determine if the bacteria is resistant or sensitive to certain antibiotics. However, the problem is that there is not one complete method which shows sufficient sensitivity and

PATENTING TREND FOR DIAGNOSTIC METHODS ON BACTERIAL INFECTION

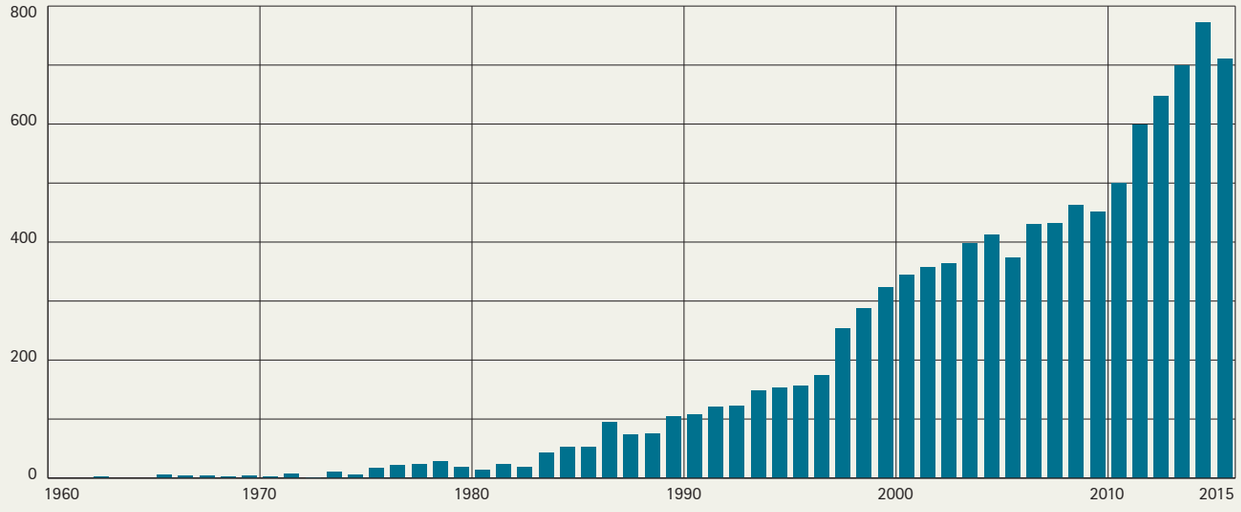


Fig 14. The figure shows the total amount of filed patent documents between 1960-2015 describing diagnostic methods for bacterial infection.

specificity and can quickly answer all the questions in the same assay. The many different technologies available today come with their pros and cons but also lack standardization, making it hard to use these technologies in a clinical setting.

These technologies are also often costly, require advanced equipment and complicated machinery as well as highly trained professionals. This is a problem particularly when implementing new diagnostic technologies in less developed countries (Morel C. et al., 2016; Goossens H. et al., 2013).

Thus, there is a huge need for diagnostic methods that are cheap and can deliver quick and reliable diagnostic results.

THE OPTIMAL DIAGNOSTIC METHOD

According to a report published by the WHO in 2015 (O´Neill J. et al., 2015), such a method should optimally be able to deliver 4 answers:

- Is the infection caused by bacteria?
- If bacterial, what type of bacteria is causing the infection?
- Are the infection-causing bacteria resistant to available antibiotics?
- Are the infection-causing bacteria susceptible to any existing drugs?

Even if a method could only answer the first question, but give reliable results quick enough so that the doctor can make a diagnosis in “real-time” and avoid prescribing antibiotics for viral infections, it would be a significant improvement. For the US-market it is estimated that up to two-thirds of the treatments for respiratory infections, where antibiotics are prescribed, are ineffective because it is not an infection or the infection is caused by a virus against which antibiotics have no effect. This equals to 27 million courses of antibiotics wasted per year in the US alone (O´Neill J. et al., 2015).

PATENTING ON DIAGNOSTIC METHODS INCREASE

The patent information in the field of diagnostic methods for identifying bacteria shows that there has been an almost exponential growth of patent documents from the beginning in the 1970´s until today (figure 14). As discussed above, in the 1990´s big pharma left the antibiotics field after their attempts of synthesizing novel antibiotics had failed. It is possible that the realization that the antibiotic resistance problem could not be resolved by simply producing new antibiotics, but that a better stewardship of existing antibiotics was necessary, initiated this increased interest in diagnostic methods.

Analyzing where this increase in patent documents originated, we see that a significant portion of these documents were filed in the US. Not until in the 1990´s do we see a significant filing of documents in other countries such as Japan, Great Britain, France and Germany (figure 15).

One interesting observation is that Chinese patent applications first began appearing in the beginning of the 21st century and have since increased exponentially. As for the analysis of the penicillins discussed above, even in the field of diagnostics it seems as if the documents that were first filed in China were also published there, and only there (figure 16).

GEOGRAPHIC PATENTING TREND FOR DIAGNOSTIC METHODS ON BACTERIAL INFECTION

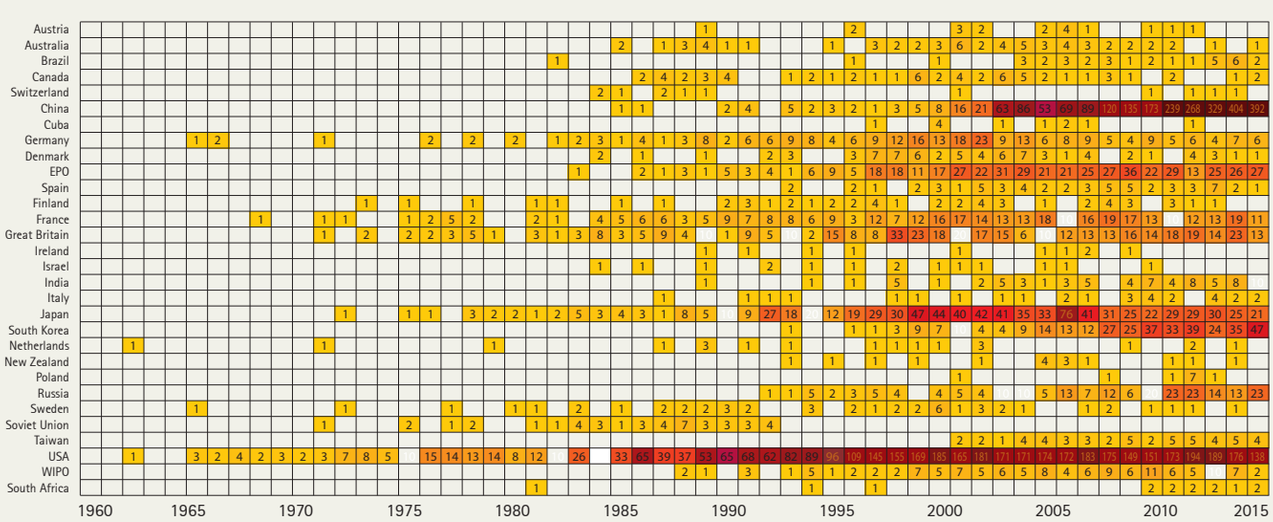


Fig 15. The figure shows the geographic patenting trend between 1960-2015 on diagnostic methods for bacterial infection. Note that "EPO" and "WIPO" do not refer to actual countries but to the European patent organisation and the World intellectual property organisation respectively". A low number of filed patents is represented by bright yellow colours as higher numbers of patents are represented by darker red colours.

PATENTS ON DIAGNOSTIC METHODS IN SWEDEN

Patent applications on diagnostics have also been filed in Finland and Sweden since the 1960´s -1970´s. When looking closer at the Swedish patent documents one can see that these are spread out between 1965 and 2014 with a concentration of filed documents between the late 80´s to early 21st century (figure 17). The major applicants here are the pharmaceutical companies Astra and Pfizer followed by Alfa Laval (figure 18). When analyzing the legal status of these patent documents we can see that out of 30 applicants, only 9 have at least one granted patent, and two more applicants have at least one pending patent application (figure 18).

This coincides with the age of these applicant's patent portfolios showing that with the exemption of one company, Astrego Diagnostics, the average age of these applicant's portfolios are 12 years or older (figure 19). Considering that a patent is granted for 20 years, this implies that most of these applicant´s patent portfolios are "middle-aged".

Astrego Diagnostics two applications describes a microfluidic device used for antibiotic susceptibility testing on bacteria. By placing the bacteria in channels of the microfluidic device and exposing the bacteria to different antibiotics one can select for antibiotics having an effect on the bacteria. Although these applications were first filed in Sweden, these are now applications pending decision in the US and Japan (US2017137861A1 and JP2017520262A1).

Astrego Diagnostics have recently developed a method using a microfluidic chip to trap and analyze bacteria from urine samples (qUTI). The method is reported to be both rapid and accurate and provides antibiotic susceptibility information (Astrego product information). Another applicant seen in figure 18, EMPE Diagnostics, has a pending patent application describing a device for analysing samples comprising amplified nucleic acids. The device can be used for the detection of antibiotic resistant bacteria (WO2017142467 A1).

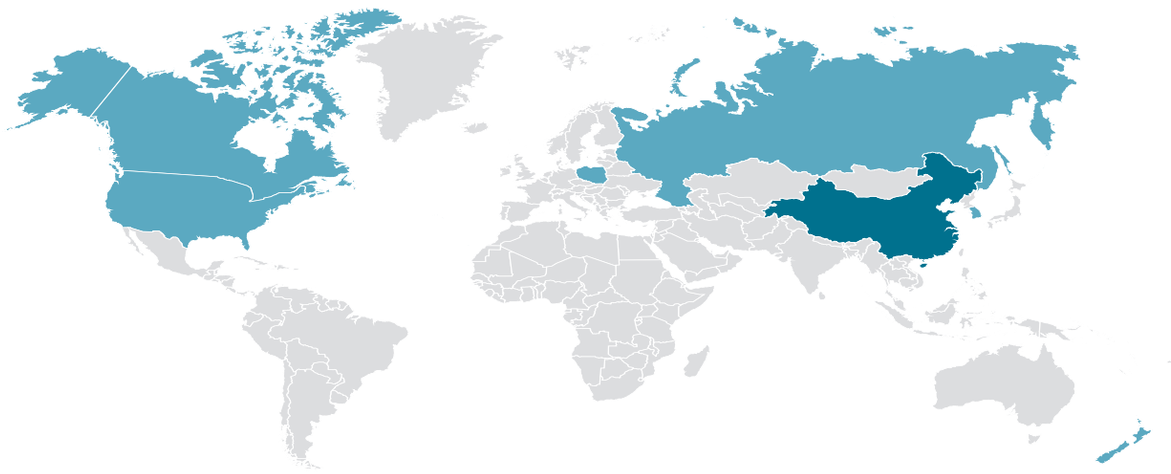


Fig 16. The figure shows where in the world patents on diagnostic methods, that were originally filed in China, later were published. A darker blue colour represents a higher activity as grey colour represents no activity.

SWEDISH PATENTING TREND FOR DIAGNOSTIC METHODS ON BACTERIAL INFECTION

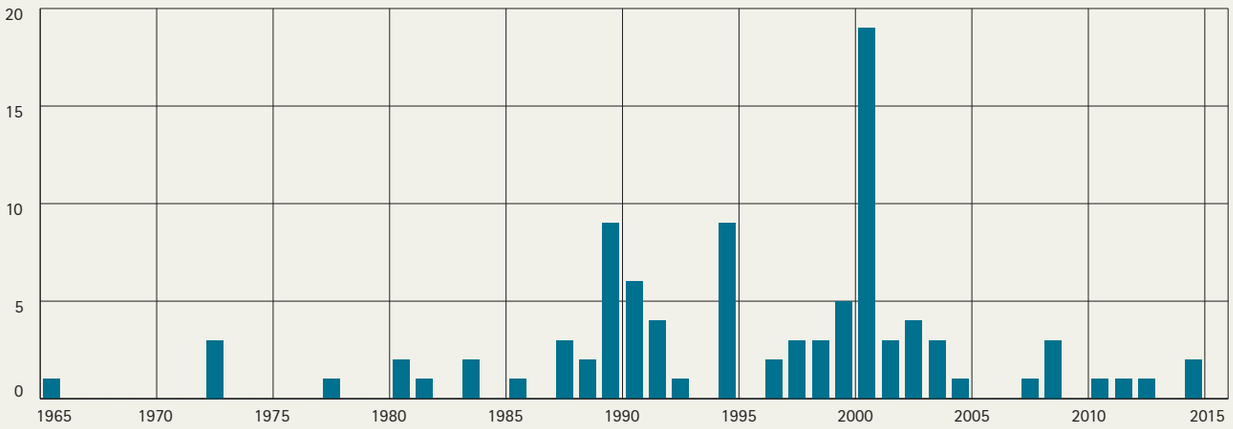


Fig 17. The figure shows the total amount of filed patent documents in Sweden between 1965-2015 describing diagnostic methods for bacterial infection.

LEGAL STATUS FOR THE TOP 30 SWEDISH PLAYERS

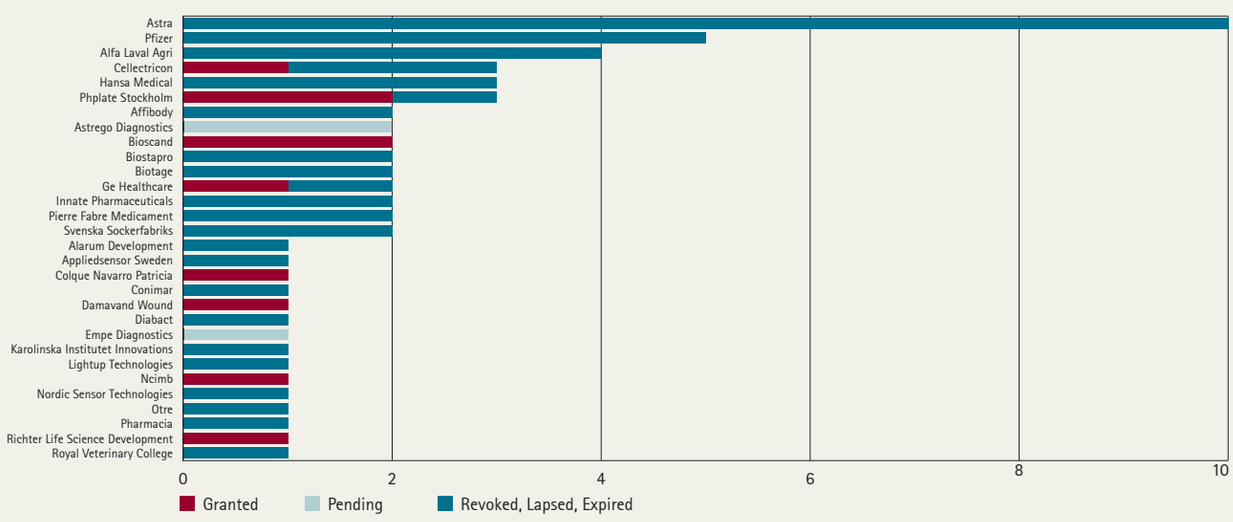


Fig 18. The figure shows the top 30 swedish players patent portfolio and its current legal status within the area of diagnostic methods on bacterial infection. Note that Granted (green colour) means that the patent is in force. Pending (yellow colour) means the that the patent application has not yet been determined on (rejected or granted). Expired, revoked and lapsed (red colour) means that the patent is not in force.

PATENT PORTFOLIO SIZE AND MEDIAN AGE FOR THE TOP 15 SWEDISH PLAYERS

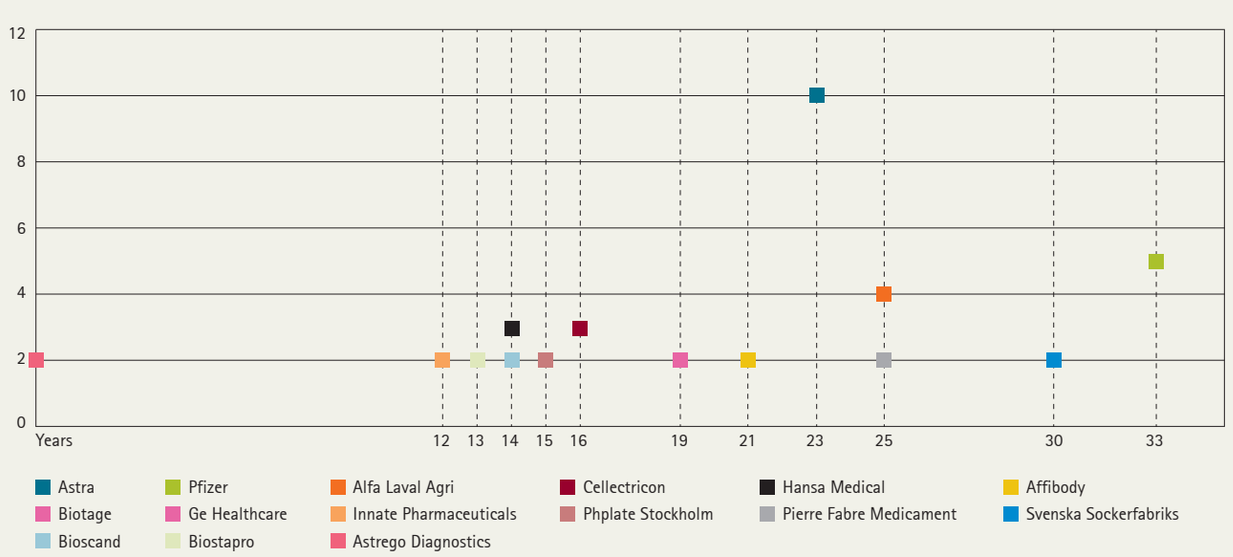


Fig 19. The figure shows the size and median age of the patent portfolio for the top 15 swedish players in the field of diagnostic methods on bacterial infection.

In conclusion

Information found in patents can give not just a deeper understanding of a technology but also provide business information. This information can be valuable when making strategic decisions in a project.

Common questions answered by patent information is for instance:

- Is patenting in this field of technology increasing, decreasing or maintaining over time?
- Are there any sub-areas in this field of technology where players file more patents?
- Who are the major players in this field of technology?
- Where are these players operating in the world?
- Where are the markets?
- Which are the most cited patent documents/ applicants in this field?
- What is the legal status of these players patent portfolio?

PATENT INFORMATION IN THE FIELD OF ANTIBIOTIC RESISTANCE

In this report we present data from 5 patent information searches from the area of antibiotic resistance. The searches covered different aspects of antibiotics and antibiotic resistance.

From the search on antibiotic resistance we present data showing that:
Patents have been filed in this area of technology since the 1960´s. From the start of 1990´s we see a lasting exponential increase in patent applications indicating a significant increase of activity in this field. When looking into detail what specific areas of technology these documents relate to we can see that some documents relate to processes for propagating, maintaining or preserving microorganisms. Other documents focus on genetic engineering and measuring processes involving enzymes or microorganisms. Many documents relate to medical preparations and since the middle of the 90´s a significant increase can be seen for documents describing antibacterial agents specifically. The major players in this filed are for instance major pharma companies such as Pfizer, Merck Sharp & Dome, Iridica (now Abbott), several Universities, such as UCLA, Sun Yat-Sen University, University of Texas and Rockefeller University. We also see other "non-pharma" companies such as Eastman Kodak and 3M. The markets for these inventions is especially North America, China, Japan, Australia, South Korea, India and some of the EU-countries. The most cited actor in this field is Geneohm Sciences Canada which patent portfolio contains patent documents describing the use of advanced molecular technologies, such as PCR, for detecting different bacteria and antibiotic resistance genes.

PATENT INFORMATION ON PENICILLINS

From the search on pencillin family members we present data showing that:

Patents have been filed in this area of technology since the 1940´s. From 1969 until the end of the 1970´s there is a temporary increase of filed patent applications which fall back to lower levels until the 1990´s when a lasting exponential increase in patent applications is seen. We show that major pharma lie behind the increase in filings between 1969 to the end of 1970s while the exponential increase starting

in the 1990´s an onward show a high degree of applicants from different Universities and Research institutions. However, further analysis show that most applications during this timeperiod are patent applications filed in China. The data also suggest that patent applications first filed in China concerns inventions targeted to the Chinese market.

PATENT INFORMATION ON DAPTOMYCIN

From the search on lipopeptides we highlight data from a specific antibitoic, daptomycin, showing an exponential increase of filed patent application from late 1990´s an onward. In general the applicants behind a majority of the filed patent applications on lipopeptides are shown to be Universitites and Research institutions as well as smaller pharma companies.

PATENT INFORMATION ON MACROLIDES

The search on the class of macrolides show that patent applications was filed already in the 1950´s. After a period of stable levels of filings in the end of the 1960´s we see the start of an exponential increase in filed applications in this field. Top applicants in this area are major pharma companies such as Pfizer, Merck Sharp Dome, Abbott and Novartis. Interestingly, of the top 10 largest applicants we can see a small Croatian pharma company, Pliva, which were the first to patent the antibiotic azithromycin. The legal status of the 10 major applicants show that Pliva place itself in 6th place with a total number of 20 granted patents currently in force.

PATENT INFORMATION ON DIAGNOSTIC MEHODS

In the area of diagnostics we show that also here there is an exponential increase in filed patent applications from the start in the 1970´s. Most of the earlier patent filings originate from the US, Japan and some European countries as China is responsible for a majority of the applications filed in the last 10 years (2005-2015). Again we can see that patent applications first filed in China are mainly targeted to the Chinese market. Finland and Sweden show activity in this area and for Sweden the most active period seen is between late 1980´s to early 21st century. The analysis of the top applicants from Sweden shows a mix of major pharma companies and smaller diagnostic companies. Most of these applicants patent portfolios are not in force (lapsed, revoked or expired). A few applicants do have some live patents (granted and in force or pending). One of these is Astrego Diagnostics with two pending patent applications.Analysing the size and age of the top 15 applicants portfolios we see that Astrego Diagnostics separates from the rest with a portfolio with an average age of 0 years as all other applicants portfolios is at least on average 12 years or older.

THE ROAD AHEAD

Ever since the beginning, with the use of Penicillin, antibiotics have played an essential role in health care. Unfortunately, with the use of antibiotics comes the problem of resistance. The overuse of antibiotics today has led to antibiotic resistance, a global problem threatening modern health care. The time to act is now. The question is how we can continue using antibiotics in the future, without creating a post-antibiotic world in which antibiotics are no longer effective. The many different parts of society, all over the world, need to be involved working together to find a solution to this problem. What we do next, who will do what, where the financial support will come from and how we optimally organize this work, are some of the important issues at hand. Although it took us a long time to realize the gravity of this threat, recent efforts, nationally and globally, have been taken to counteract the spread of antibiotic resistance. Also, new antibiotics and diagnostic methods are on their way. Let´s just hope our efforts are not too little and too late.

Meet the experts – interview with Malin Grape, Anders Blank and Patriq Fagerstedt

Support for businesses to combat antimicrobial resistance

WHAT IS YOUR BACKGROUND AND WHAT ARE YOU UP TO THESE DAYS?

I have master's degree in pharmacy and a PhD in medicine with a specialisation in clinical microbiology. I have been a pharmacy manager, consultant on pharmaceutical distribution in Switzerland and international coordinator for the Public Health Agency of Sweden. Right now, I head their Unit for antibiotics and infection control.

HOW DO YOU AND YOUR ORGANISATION ARTICULATE THE ISSUES ASSOCIATED WITH ANTIBIOTIC USE AND RESISTANCE?

The Public Health Agency receives more assignments and assumes greater responsibility in this area than any other authority within the human sector. We work primarily at the national level in cooperation with regional Collaboration to Combat Antimicrobial Resistance (STRAMA) groups. We take a multifaceted approach. We monitor antibiotic use and resistance, as well as healthcareassociated infections, and we provide evidence-based support for health care providers and other authorities within the human sector. We partner with the Swedish Board of Agriculture to chair the national coordina-ting mechanism for multisectorial work against AMR. The group consists of 25 governmental agencies and other stakeholders.

WHAT ARE THE BENEFITS OF THE KIND OF REPORT THAT PRV HAS COMPILED?

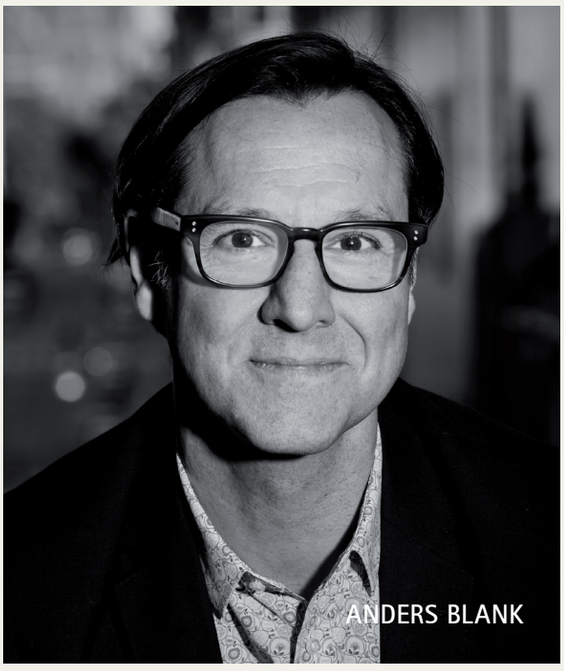
Personally, I learned a great deal by reading the report, but research funders probably have the most to gain. It also shows that many agencies and organisation are interested in promoting the work to counteract AMR even if it is outside the scope of their primary tasks. The international community would profit by reading it as well.


MALIN GRAPE

IS THERE ANYTHING IN THE REPORT THAT YOU CAN APPLY DIRECTLY TO THE WORK YOU DO?

The Government recently instructed us to explore new incentives for businesses to combat antimicrobial resistance. We are looking at push and pull mechanisms, along with other compensation models. The issues are quite complex, and companies don't always know where to start. Hopefully the report will point them in the right direction.

New incentive models for developing antibiotics


ANDERS BLANK

WHAT IS YOUR BACKGROUND AND WHAT ARE YOU UP TO THESE DAYS?

I have an MBA from the Stockholm School of Economics. I held various positions at the Ministry of Health and Social Affairs from 1993 to 2004. I have been with the Swedish Association of the Pharmaceutical lndustry (LIF) since 2005 and administrative director since 2011.

HOW DO YOU AND YOUR ORGANISATION ARTICULATE THE ISSUES ASSOCIATED WITH ANTIBIOTIC USE AND RESISTANCE?

Our goal is to address the challenges that our members have identified. Above all, we need to deal with the dysfunctionality of current incentive models for discovering and developing new antibiotics. Pharmaceutical companies make money when drugs are sold, but new antibiotics tend to remain on the shelves. In collaboration with our members, we have proposed a different model, which the Government has instructed the Public Health Agency of Sweden and the Swedish Dental and Pharmaceutical Benefits Agency to evaluate.

In response to new academic studies of emissions in lndia and elsewhere, the industry increasingly focuses on environmental impact issues, particularly those related to antibiotic manufacture.

Going much further back, we have long monitored and supported public efforts to minimise erroneous and unnecessary use of antibiotics.

We work closely with other European and international colleagues and organisations.

WHAT ARE THE BENEFITS OF THE KIND OF REPORT THAT PRV HAS COMPILED?

You can't confront the challenges of the future unless you are fully acquainted with the past. Patent perceptions add another dimension to analyses that are based strictly on the medications that have been approved or launched.

The report should be able to teach us about previous development efforts that were abandoned or that never generated marketable products. We have every reason to believe that same of these initiatives can be restarted, or at least inspire researchers to try fresh approaches.

IS THERE ANYTHING IN THE REPORT THAT YOU CAN APPLY DIRECTLY TO THE WORK YOU DO?

It gives us an opportunity to contribute new data and insights when speaking with our colleagues around the world.

International research projects benefit from patent history

WHAT IS YOUR BACKGROUND AND WHAT ARE YOU UP TO THESE DAYS?

I have a degree in microbiology and chemistry, as well as a PhD in neuroscience from Karolinska Institutet in Stockholm. I conducted research on the way that neural networks in the brain and spinal cord, as well as sensory impressions, control and affect movement. At Astra Zeneca, I researched drugs to alleviate chronic pain. For the past four years, I have been an administrative assistant at the Swedish Research Council. My tasks include financing, public policy and international collaboration to combat antimicrobial resistance. I am also in charge of the National Research Programme in the field with the Research Council as coordinator.

HOW DO YOU AND YOUR ORGANISATION ARTICULATE THE ISSUES ASSOCIATED WITH ANTIBIOTIC USE AND RESISTANCE?

In 2017, the Government instructed us, along with other funders, to draw up a 10-year national programme for coordination of antimicrobial resistance research. We will be cobbling together an agenda to identify knowledge gaps in priority areas of research.

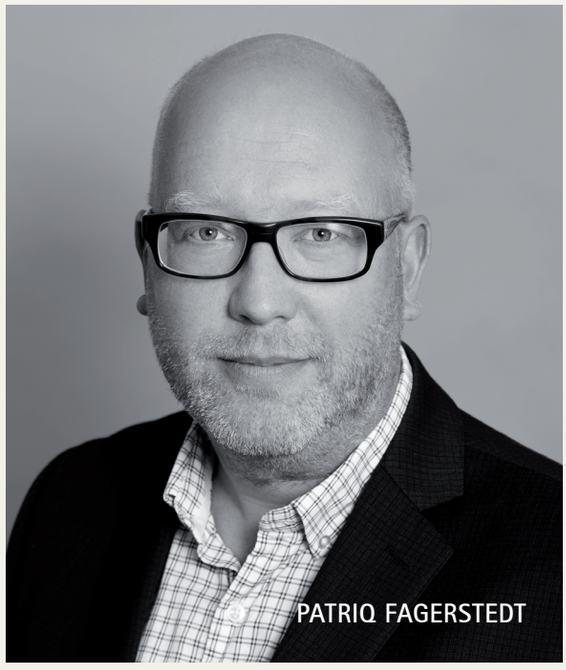
The Council represents Sweden in the international Joint Programming lnitiative on Antimicrobial Resistance (JPIAMR). Moreover, five of our employees host their office.

In addition to funding and support issues, JPIAMR coordinates research policy, analyses of various needs and joint priorities. The initiative published a strategic research agenda (SRA) in 2014 and is working on an updated version that is due out in 2018 or 2019.

The Council also has the task of analysing various research projects on antimicrobial resistance and other subjects, as well as reporting to the Government as a basis for future policy.

WHAT ARE THE BENEFITS OF THE KIND OF REPORT THAT PRV HAS COMPILED?

An historical overview of antibiotic patents is particularly valuable for its ability to shed light on shifting dynamics among different drug categories, organisations and countries. Given the vast need for new drugs, we must understand underlying trends and impulses so as to maximise support for innovation. The report is also important for the information it contains about the opportunities, challenges and competitive factors that Swedish researchers and companies face when they eye the development of new antibiotics.


PATRIQ FAGERSTEDT

IS THERE ANYTHING IN THE REPORT THAT YOU CAN APPLY DIRECTLY TO THE WORK YOU DO?

The report can provide a fundamental analysis of patent history that will prove useful in our own examinations and as a point of reference in our effort to combat antimicrobial resistance. The fact that it was written in English and presents patent information from a global point of view will make it more available to other countries as well. lf we take the time to disseminate the report abroad, our international colleagues and partners will have the chance to benefit from its insights.

Sammanfattning

Sedan penicillinets upptäckt 1928 har antibiotika i stor omfattning använts inom sjukvården, forskningen och jordbruket. Antibiotika används för att behandla bakterieinfektioner och har stor betydelse inom dagens sjukvård. Bakterier kan emellertid utveckla resistens mot antibiotika som de exponeras för, vilket gör att antibiotikan med tiden blir mindre och mindre effektiv.

Antibiotikaresistens (ABR) är inte något nytt fenomen, den har funnits lika länge som antibiotikan (Davies J. m.fl., 2010). Idag är ABR ett globalt hälsoproblem och om åtgärder inte vidtas för att förhindra spridningen av den kan vi snart hamna i en situation där klockan vrids 70 år tillbaka i tiden inom sjukvården. För att motverka detta antog Världshälsoorganisationen (WHO) år 2015 en ”Global handlingsplan mot antimikrobiell resistens” (WHO 2015). Sverige, som länge har arbetat med att förebygga antibiotikaresistens, lade i sin tur år 2016 fram en nationell handlingsplan kallad ”Strategi för arbetet mot antibiotikaresistens” (S2016/02971/FS). Idag har Sverige en av de mest gynnsamma situationerna i världen när det gäller resistens (Morel C. m.fl., 2016; Gelbrand H., 2015). Inget land är emellertid förskonat från den ständigt ökande risken för ABR.

Strategin för arbetet mot ABR bygger på att personer från alla samhällssektorer involveras. Den kommer att kräva tid och ekonomiska resurser. En framgångsrik global strategi bygger på strategiska beslut och samordnade insatser och samarbete mellan enskilda länder.

Att analysera den information som finns i patent och patentansökningar inom ett visst teknikområde kan vara av värde när den här typen av beslut ska fattas.

Som nationell patentmyndighet är det svenska Patent- och registreringsverket (PRV) experter på att söka efter och analysera patenthandlingar som finns i olika patentdatabaser runt om i världen. PRV är således en samhällsaktör som har kunskap och kompetens som krävs för att tillhandahålla värdefull patentinformation från olika teknikområden, däribland antibiotika och antibiotikaresistens.

Den här rapporten är därför vårt bidrag till arbetet mot antibiotikaresistens. Vi presenterar här en analys av vad som är känt inom området antibiotikaresistens på grundval av information som finns i patenthandlingar.

PATENTINFORMATION ÖVER HISTORIKEN OM ANTIBIOTIKARESISTENS

Till att börja med analyserade vid patentinformationen inom området antibiotikaresistens. Data visar att patentansökningar som beskriver problemet med antibiotikaresistens sträcker sig tillbaka till början av 1960-talet och att ansökningarna ökade exponentiellt i slutet av 1990-talet. Dessa patenthandlingar beskriver processer för att föröka, bibehålla eller bevara mikroorganismer, gentekniska metoder och mätningsprocesser som innefattar enzymer eller mikroorganismer. Många handlingar beskriver också medicinska preparat som antibakteriella medel. Sökandena kom från olika sektorer som större läkemedelsföretag och universitet.

PATENT OCH PENICILLINER

Därefter analyserade vi antibiotikaklassen penicillin. Patentansökningar som beskrev penicilliner började göras på 1940-talet, när koncentrerade insatser gjordes för att massproducera dessa för den medicinska marknaden. Antalet ansökningar låg på en stabil nivå från 1940-talet och fram till slutet av 1960-talet, vilket var antibiotikaupptäckternas ”gyllene tid” då de flesta av dagens antibiotika upptäcktes.

Under den här perioden utgjordes sökandena främst av större läkemedelsförtag som Merck Sharp Dome, GlaxoSmithKline, Pfizer och Bristor Myers Squibb.

1969 ökade antalet patentansökningar, främst på grund av en ökad patentverksamhet hos större läkemedelsföretag, i synnerhet GlaxoSmithKline. Ökningen fortsatte fram till slutet av 1970-talet då vi ser en minskning i patenttrenden för första gången. ”Toppen” när det gäller patentansökningar nåddes under en period då inga nya antibiotikaklasser upptäcktes. Fokus låg då i stället på att förändra befintliga antibiotikamolekyler eller skapa nya sådana.

Efter en nedgångsperiod på nästan ett decennium, skedde det på 1990-talet åter förändringar inom penicillinområdet som ledde till en exponentiell ökning av antalet patentansökningar. Den sammanfaller med den ökade användningen av masscreeningplattformar för att få fram ny antibiotika.

Data visar att ökningen delvis berodde på ansökningar från olika internationella universitet och forskningsinstitut, men främst på ansökningar från mindre läkemedelsföretag och universitet i Kina. Vi kan också se att dessa kinesiska ansökningar är inriktade på den inhemska marknaden.

Det visade sig så småningom att masscreeningmetoden inte fungerade, vilket gjorde att många större läkemedelsföretag upphörde med sina FoU-program rörande antibiotika (Lewis, 2013).

Med ett ökat användande av antibiotika ökar även antibiotikaresistensen (ABR). Idag är ABR ett växande hot mot vår hälsa. Därför måste representanter från alla delar av världen och alla delar av samhället arbeta tillsammans för att reducera spridningen av ABR. Som ett patentverk besitter PRV kunskapen och expertisen att söka och att analysera informationen i patent. Patentinformation är en av de mest kompletta, korrekta och uppdaterade teknikinformation som är allmänt tillgänglig. Med denna rapport hoppas vi att kunna bidra till ökad medvetenhet om utmaningarna med ABR och att visa på värdet av patentinformation när man tar strategiska beslut.

FRAMGÅNG FÖR DE SMÅ

När det gäller antibiotikagruppen lipopeptider, beskriver vi daptomycinets historia. Efter att först ha betraktats som ett lovande nytt antibiotikum, lades daptomycinet på hyllan på grund av toxiska biverkningar. I dag är daptomycinet en stor succé, såväl medicinskt som ekonomiskt, tack vare en klarsynt forskare på det lilla biomedicinföretaget Cubist Pharmaceuticals. Vi beskriver även framgångssagan med det kroatiska läkemedelsföretaget Pliva, som utvecklade och patenterade antibiotikumet azitromycin, vilket förvandlade detta lilla lokala företag till en stor global aktör inom antibiotikaområdet.

BÄTTRE DIAGNOSTIK I KAMPEN MOT RESISTENS

En viktig faktor när det gäller arbetet mot antibiotikaresistens är snabba och exakta diagnostikmetoder. De diagnostikmetoder som används idag är ofta alltför långsamma och ospecifika, vilket leder till felaktiga diagnoser och bidrar till utvecklingen av ABR. Vår analys visar att antalet patentansökningar rörande diagnostikmetoder började öka i början av 1970-talet och att de har ökat exponentiellt på senare år. Det är möjligt att denna ökning berodde på de misslyckade försöken med att få fram nya antibiotika på 1990-talet. Till att börja med gjordes en stor del av dessa ansökningar i USA och det är först på 1990-talet som vi ser ansökningar från andra länder som Japan, Storbritannien, Frankrike och Tyskland.

På 2000-talet började antalet kinesiska ansökningar öka exponentiellt. År 2015 gjordes dubbelt så många patentansökningar i Kina som i alla de 29 största länderna inom detta område tillsammans. På samma sätt som för penicillinerna publicerades emellertid merparten av ansökningarna enbart i Kina, vilket tyder på att dessa innovationer främst är inriktade på den inhemska marknaden.

Sverige uppvisar viss aktivitet inom diagnostikområdet, särskilt från slutet av 1980-talet och fram till början av 2000-talet. Ett aktuellt exempel på ett företag med aktiva patentansökningar är Astrego Diagnostics, vars ansökningar beskriver ett mikrofluidsystem som används för att testa bakteriers antibiotikakänslighet.

Search methodology

Several purpose searches were conducted to extract the information found in publicly available patents and patent applications. Both the searches and the analyses were performed using the commercial tool Orbit Intelligence (Questel).

Five different technology searches and related analyses were conducted. For every search, relevant classes and keywords were identified and combined to achieve the best search result. Some searches were performed only using keywords. Keywords were appropiately truncated to compensate for different spellings, plural forms and synonyms. Depending on the situation different keywords were searched for in different parts of the documents (e.g. title, abstract, claims or description) as a measure to identify relevant material for the following analysis. For each area of technology multiple searches were conducted to identify the best search query before final analysis.

ANTIBIOTIC RESISTANCE: The first search was executed to find documents describing the problem itself, antibiotic resistance. This search was conducted by combining keywords such as: multiresistant, resistant, antibiotic, bacteria and germ. Total patent families analyzed: 2389.

PENICILLIN ANTIBIOTICS: This search was executed to find documents describing the medical use of a member of the penicillin class. This search was conducted by combining keywords such as: penicillin, methicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin, ampicillin, amoxicillin, amoxycillin, carbenicillin and composition, formulation, pharma, medicine, tablet, powder, liquid, aerosol, solution or ester. Classes used for this search were, A61K31 (IPC) and A61P31 (IPC). Total patent families analyzed: 3800.

LIPOPEPTIDE ANTIBIOTICS: This search was executed to find documents describing the medical use of some members of the lipopeptide class of antibiotics. This search was conducted by combining keywords such as: daptomycin, cubicin, surfactin or lipopeptide combined with words such as antibiotic, composition, drug or formulation. Classes used for this search were, A61K (IPC) and A61P (IPC). Total patent families analyzed: 593.

MACROLIDE ANTIBIOTICS: This search was executed to find documents describing the medical use of some members of the macrolide class of antibiotics. This search was conducted by combining keywords such as: macrolide, erythromycin, azithromycin or clarithromycin. Classes used for this search were, A61K (IPC) and A61P (IPC). Total patent families analyzed: 7593.

DIAGNOSTIC METHODS: This search was executed to find documents describing methods of diagnosing bacterial infection or detection of bacteria. This search was conducted by combining keywords such as: diagnose, detect, determine, identify, antibiotic, resistant, multi-resistant, pan-resistant, microbe, bacteria, MRSA, VRE, ESBL, VRSA, CRE or VISA. Classes used for this search were, C12Q (IPC) and G01N (IPC). Total patent families analyzed: 11058.

Glossary

MICROBE/MICROORGANISM: an organism too small to see with the naked eye. Example are bacteria, archaea, fungi, protists and viruses.

BACTERIA: one-celled organism which belongs to the domain of prokaryotic microorganisms. One of the first life forms on earth. Bacteria thrives in all habitats and multiply by binary fission.

GRAM-POSITIVE/GRAM-NEGATIVE BACTERIA: Bacteria are divided into two different groups based on their envelope physiology, gram-positive or gram-negative bacteria. The bacterial envelope comprises an inner cell membrane and an outer cell wall. The difference is that gram-positive bacteria have one cell membrane as gram-negative bacteria have two.

ANTIBIOTIC: type of antimicrobial drug used for treating infections caused by bacteria. Also used for preventing a bacterial infection.

BACTERIOSTATIC: the effect of an antibiotic on a target bacterium which entail that the antibiotic does not necessarly kill the bacteria but prevent it from reproducing.

BACTERIOCIDAL: the effect of an antibiotic on a target bacterium which entail that the antibiotic kill the bacteria.

ANTIBIOTIC RESISTANCE: a state where an antibiotic no longer causes a bacteriostatic or bacteriocidal effect on the target bacteria. Bacteria often acquire resistance through spontaneous mutations or through horizontal gene transfer.

BROAD-SPECTRUM ANTIBIOTICS: antibiotics which can be used to treat both gram-positive and gram-negative bacteria.

NARROW-SPECTRUM ANTIBIOTICS: antibiotics which can be used to treat either gram-positive or gram-negative bacteria.

GENERIC DRUG: a pharmaceutical drug equivalent to a brand-name product in all aspects. Generic drugs become available after the patent on the original drug expired on a market. These types of drugs are commonly produced by competing pharma companies resulting in lowered prices for the original brand-name product and the generics.

GENOME: the genetic material (DNA) of an organism.

TRANSPOSON: genetic element such as DNA which can change position within a genome.

PLASMID: a small DNA molecule within the cell physically separated from the chromosomal DNA. Plasmids can replicate independently from other DNA in the cell.

HORIZONTAL GENE TRANSFER (HGT): movement of genetic material (such as transposons and plasmids) between cells. Antibiotic-resistance is commonly spread through HGT when plasmids or transposons carrying a gene coding for resistance is transferred from one bacterial cell to another.

DNA: the chemical structure comprising the genetic information in an organism. The genetic information is chemically encoded by nucleotides. Nucleotides are built up of a sugar molecule and a phosphate group connected to either one of four nitrogen-containing nucleobases called adenine (A), cytosine (C), thymine (T) and Guanine (G). The order in which these nucleotides occur in a stretch of DNA is called the nucleotide sequence. A nucleotide sequence which encodes a protein is called a gene. The nucleotide sequence determines what protein is produced in a process called translation.

BACTERIAL BINARY FISSON: the process of reproduction where one bacteria divide into two bacterias.

REPLICATION: the process responsible for duplicating a cells genome (DNA-molecule). When a bacteria reproduce, by binary fission, the replication process enables that the two “daughter bacteria” each receive an identical copy of the parental DNA.

TRANSCRIPTION: the first step of gene expression where a segment of DNA is copied into a messenger RNA (mRNA) molecule which in turn can be decoded into a protein by a process called translation.

TRANSLATION: the process where the mRNA-molecule sequence is decoded and translated into a functional protein by the assembly of a long chain of aminoacids. Translation is facilitated by a large molecular complex called the ribosome.

SYMBIOSIS: two different organisms living in a close long-term biological interaction.

Reference list

Abraham E. P. et al., 1940. An enzyme from bacteria able to destroy penicillin, Nature, 837

Abt M. C. et al., 2016. Clostridium difficile colitis: pathogenesis and host defence, Nature Reviews Microbiology, 14, 609-620

Alekshun M. N., 2007. Molecular Mechanisms of Antibacterial Multidrug Resistance, Cell, 128, 1037-1050

Anderson D. I. et al., 2011. Persistence of antibiotic resistance in bacterial populations, FEMS Microbiol Rev, 35, 901-911

Anderson D. I. et al., 2014. Microbiological effects of sublethal levels of antibiotics, Nature Reviews Microbiology, 12, 465-479

Astrego product information, https://astrego.se/solution/

Benfalk C. et al., 2000. På väg mot världens renaste kor, Jordbrukstekniska institutet, 264, 1-30

Bhardwaj R. et al., 2013. The impact of patent linkage on marketing of generic drugs, J Intellect. Propert. Rights, 18, 316-322

Chain E. et al., 1940. Penicillin as a chemotherapeutic agent, Lancet, 226-228

Coates A. RM. et al., 2011. Novel classes of antibiotics or more of the same?, Br J Pharmacol., 163, 184-194

Collignon P. et al., 2015. China, what antibiotics and what volumes are used in food production animals?, Antimicrob. Resist. Infect. Control, 4, 1-3

Davies J. et al., 2010. Origins and evolution of antibiotic resistance, Microbiol and Mol. Biol. Reviews, 74, 3, 417-433

EFSA, ECDC, 2015. EU Summary Report: antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food 2103, EFSA Journal 13, 4036

Eisenstein B. I. et al., 2010. Daptomycin: From the Mountain to the Clinic, with Essential Help from Francis Tally, MD, Clin. Infect. Dis., 50, 10-15

Fleming A., 1929. On the antibacterial action of cultures of a penicillum, with special reference to their use in the isolation of B. Influenzae. British J. Experiment. Pathol. 226-236

Gelband H. et al., 2015. The state of the worlds antibiotics 2015, Center for disease dynamics, Economics & Policy, 1-84

Gensollen T. et al., 2016. How colonization by microbiota in early life shapes the immune system, Science, 352, 539-543

Gonzalez-Ruiz A. et al., 2016. Daptomycin: an evidence-based review of its role in the treatment of Gram-positive infections, Infection and Drug Resistance, 9, 47-58

Goossens H. et al., 2013. Strategic Research agenda: Joint Programming Initiative on Antimicrobial Resistance, JPIAMR, 1-71

Grave K. et al., 2014. Sales of veterinary antimicrobial agents in 26 EU/EAA countries in 2012, Fourth ESVAC report, EMA, 1-128

Hibbing M. E. et al., 2010. Bacterial competition: surviving and thriving in the microbial jungle, Nat. Rev. Microbiol. 8, 15-25

Hicks L. A. et al., 2013. U.S. Outpatient Antibiotic Prescribing, 2010, NEJM, 368, 1461-1462

Horowitz J. B. et al., 2004. How property rights and patents affect antibiotic resistance, Health Econ, 13, 575-583

ITA, 2016. 2016 Top Markets Report Pharmaceuticals Country Case Study: China, 1-5 JP2017520262A1

https://worldwide.espacenet.com/searchResults?submitted=true&locale=en_EP&DB=EPODOC&ST=singleline&query=JP2017520262&Submit=Search

Jurney C. 2016 Global 2000: The World´s Largest Drug and Biotech Companies, FORBES, May 27

Kadam S. S. et al., 2013, Principles of Medicinal Chemistry, 1, Pragati Books Pvt. Ltd, 1-470

Kamada N. et al., 2013. Role of the gut microbiota in immunity and inflammatory disease, Nature Reviews Immunology, 13, 321-335

Kariuki S. et al., 2015. Antimicrobial resistance and management of invasive Salmonella disease, Vaccine, 33, 21-29

Khrisnasamy V. et al., 2015. Antimicrobial use in Chinese swine and broiler poultry production, Antimicrob. Resist. Infect. Control, 4, 1-9

Kingston W., 2000. Antibiotics, invention and innovation, Research Policy, 29, 679-710

Larsson D. G. et al., 2014. Pollution from drug manufacturing: review and perspectives, Phil. Trans. R. Soc. B 369:20130571

Laxminarayan R. et al., 2013. Antibiotic resistance—the need for global solutions, The Lancet Infect Dis, 13, 1057-1098

Lewis K., 2013. Platforms for antibiotic discovery, Nature Reviews, Drug Discovery, 12, 371-387

Ling L. L. et al., 2015. A new antibiotic kills pathogens without detectable resistance, Nature, 517, 455-459

Magiorakos A. P. et al., 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance, Clin Microbiol Infect, 18, 268-281

Matamoros S. et al., 2013. Development of intestinal microbiota in infants and its impact on health, Trend in Microbiology, 21, 167-173

Merck, 2014. Press Release: Merck to Acquire Cubist Pharmaceuticals for 102$ Per Share in Cash, Business Wire, Dec 8

Morel C. et al, 2016. Ensuring innovation in diagnostics for bacterial infection: Implications for policy; WHO, 1-338

Morel C. et al., 2016. Ensuring innovation in diagnostics for bacterial infection: Implications for policy, WHO, 44, 1-321

Nathan C. etl al., 2014, Antibiotic resistance- Problems, Progress, and Prospects, In: N Engl J Med, Vol: 371, 1761-1763

Ni J. et al., 2017. Obstacles and opportunities in Chinese pharmaceutical innovation, Globalization and Health, 13, 1-9

O´Neill J. 2014. Antimicrobial resistance: Tackling a crisis for the health and wealth of nations, The review on antimicrobial resistance, 1-20

O´Neill J. et al., 2015. Securing new drugs for future generations: The pipeline of antibiotics, Review on Antimicrobial Resistance, 1-82

O´Neill J. et al., 2015, Rapid diagnostics: Stopping unnecessary use of antibiotics, Review on Antimicrobial Resistance, 1-39

O´Neill et al., 2016. Tackling drug-resistant infections globally: Final report and recommendations, Review on Antimicrobial Resistance, 1-81

Payne D. J. et al., 2007. Drugs for bad bugs: confronting the challenges of antibacterial discovery, Nat Rev Drug Discov., 6, 29-40

Pirri G. et al., 2009. Lipopeptides as anti-infectives: a practical perspective, Cent. Eur. J. Biol. 4, 258-273

S2016/02971/FS, 2016. Swedish strategy to combat antibiotic resistance, 1-24

Sangvik M. et al., 2011. Age- and Gender-Associated Staphylococcus aureus spa Types Found among Nasal Carriers in a General Population: the Tromsø Staph and Skin Study, J Clin. Microbiol. 49, 4213-4218

Seiple I. B. et al., 2016. A platform for the discovery of new macrolide antibiotics, Nature, 533, 338-345

Sender R. et al., 2016. Revised Estimates for the Number of Human and Bacteria Cells in the Body, PLOS Biology, 14, 1-14

Sheehan J. C. et al., 1959. The total synthesis of Penicillin V, J. Am. Chem. Soc. 81, 3089-3094

Sheehan J. C., 1967. The chemistry of synthetic and semisynthetic penicillins, Annal. New York Acad Sci. 216-222

Silhavy T. J. et al., 2010. The Bacterial Cell Envelope, Cold Spring Harb Perspect Biol, 2, a000414

Spellberg B. et al., 2007. Societal Costs Versus Savings from Wild-Card Patent Extension Legislation to Spur Critically Needed Antibiotic Development, Infection, 35, 167-174

TEVA product catalogue 2016/2017

The Economist, 2010. Innovation in China, Patents, yes; ideas, maybe http://www.economist.com/node/17257940

US2017137861 A1 https://worldwide.espacenet.com/searchResults?submitted=true&locale=en_EP&DB=EPODOC&ST=singleline&query=US2017137861+&Submit=Search

US3159617, https://worldwide.espacenet.com/searchResults?submitted=true&locale=en_EP&DB=EPODOC&ST=singleline&query=US3159617

US6852689 B2, https://worldwide.espacenet.com/searchResults?submitted=true&locale=en_EP&DB=EPODOC&ST=singleline&query=US6852689&Submit=Search

WHO, 2015. Global action plan on antimicrobial resistance, 1-28

WHO-infographic AMR, http://www.who.int/drugresistance/publications/infographic-antimicrobial-resistance-20140430.pdf?ua=1

Wierup M., 2001. The Swedish Experience of the 1986 Year Ban of Antimicrobial Growth Promoters, with Special Reference to Animal Health, Disease Prevention, Productivity, and Usage of Antimicrobials, Microbial Drug Resistance, 7, 183-190

WIPO, Azithromycin: A world best-selling Antibiotic, http://www.wipo.int/ipadvantage/en/details.jsp?id=906

WO2014089053, https://worldwide.espacenet.com/searchResults?ST=singleline&locale=en_EP&submitted=true&DB=&query=WO2014089053

WO2017142467 A1, https://worldwide.espacenet.com/searchResults?submitted=true&locale=en_EP&DB=EPODOC&ST=singleline&query=WO2017142467&Submit=SearchWHO-infographic AMR

Wright G. D., 2007. The antibiotic resistome: the nexus of chemical and genetic diversity, Nature Reviews Microbiology, 5, 175-187

Yesterday,Today, Tomorrow, PLIVA, 1-20 http://www.pliva.com/img/themes/pcfrontend/brosure/en/03/03_YesterdayTodayTomorrow.pdf

YU76879A https://worldwide.espacenet.com/searchResults?submitted=true&locale=en_EP&DB=EPODOC&ST=singleline&query=YU76879A&Submit=Search

PRV