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PATENTS, ANTIBIOTICS, AND AUTARKY IN SPAIN

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SUMMARY

PATENTS, ANTIBIOTICS, AND AUTARKY IN SPAIN

Patents on antibiotics were introduced in Spain in 1949. Preliminary research reveals diversification in the types of antibiotics: patents relating to penicillin were followed by those relating to streptomycin, erythromycin and tetracycline. There was also diversification in the firms that applied for patents: while Merck & Co. Incorporated and Schenley Industries Inc. were the main partners with Spanish antibiotics manufacturers in the late 1940s, this industrial space also included many others, such as Eli Lilly & Company, Abbott Laboratories, Chas. Pfizer & Co. Incorporated, and American Cyanamid Company in the mid-1970s. The introduction of these drugs in Spain adds new elements to a re-evaluation of the autarkic politics of the early years of the Franco dictatorship.

Introduction

The first part of this work centres on identifying the first antibiotic patents introduced to Spain between 1948 and 1965. To do this, 110 antibiotic patent applications registered during this period at the Oficina Española de Patentes y Marcas (OEPM, the Spanish Patent and Brand Office) have been analysed. Patents construct both chronologies and biographies: the procedures contained in patents evoke a living history; antibiotics undergoing permanent change. The sec-

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ond part of this work is dedicated to looking at new scientific, industrial and also political practices that occurred in Spain during the 1950s and 1960s, and the introduction of these patents, specifically those related to streptomycin.

Speaking about patents puts us squarely in the sphere of the protection, normalisation and standardisation of knowledge. The principal objective of patents is to encourage innovation by temporarily protecting the innovator (for twenty years according to Spanish legislation), by preventing others from exploiting the innovation without the express permission of the patent's owner. The patent limits use of the knowledge exclusively to the proprietor, and only this person can cede or authorise its exploitation through the concession of licenses. Thus, the patent becomes one of the principal forms of technological appropriation and, as such, is a useful source for studying the circulation of techniques, processes and machines.

Therefore, delving deeply into the content of these documents enables us to gain a better understanding of how antibiotic production practices were introduced into autarkic Spain, how the appropriation of technologies occurred, who participated in this and what the political and economic consequences were¹.

In spite of the abundant historiography that exists on the history of antibiotics, we lack a chronology: of their identification and isolation, their production, and their clinical use. The history of penicillin, its successes and failures and the public expectations it generated, is the most well-known².

At the end of the Second World War, the expansion of penicillin benefited from policies of international co-operation in the post-war framework organised by the United Nations Relief and Rehabilitation Agency (UNRRA) and later by the World Health Organization (WHO), which established manufacturing plants from Eastern Europe to India and Italy³. The story of the successes and failures of penicillin has overshadowed other antibiotics, which played a part

in scientific, medical and industrial history in the second half of the twentieth century.

As a consequence of General Franco's dictatorship, Spain remained outside these policies of international co-operation. This could be one of the reasons why penicillin patents, when they arrived in Spain, came accompanied by patents for other antibiotics, the therapeutic activities of which had been proven and industrial production was in the developmental phase at least. The documentation consulted on patents portrays a scenario where penicillin occupies a space shared with other antibiotics: streptomycin, erythromycin and tetracycline⁴. The first patent applications for penicillin date to 1948; by 1949, applications related to streptomycin and erythromycin were already appearing⁵.

The information shows an ongoing presence of patents for these antibiotics in Spain during the period studied. Along with a desire to protect antibiotic manufacturing processes, these documents suggest key points for understanding the strategies of applicant companies, most of which were foreign.

The patent regulations for the period studied is that contained in the Estatuto de Propiedad Industrial (Statute of Industrial Property) of 1929. In this Statute, a patent is defined as the certificate awarded by the State in which the right to exclusively employ and utilise an invention for a maximum period of twenty years is recognised. The inventions must be original and have the potential for industrial results or products, that is, they must have a practical application. A matter that is clearly expressed in the Statute, and which is relevant in the case of antibiotics, is the prohibition on patenting products; it is only possible to protect procedures⁶.

In 1948, Franco's government declared the manufacture of penicillin of 'national interest' and the process for its production in Spain began. In June 1949, the government decided to permit production, under the strict control of the state, by two companies: CEPA (the

Compañía Española de Penicilinas y Antibióticos) and Antibióticos S.A.⁷. Thus a new industrial and clinical space for penicillin was opened in a country the government of which had authorised the construction of a market to license patents⁸.

Involved in the creation of this duopoly and the consequent arrival of, first, the patents and later, the contracts for the transfer of technology, was the existence of trained and informed doctors who argued for clinical necessities that up until then had been resolved through the black market⁹, and the presence of some chemical and pharmaceutical laboratories associated with the Spanish industrial bank, Banco Urquijo, which had benefited from the dismantling of German industry as a result of the Bretton Woods agreements of 1944: Productos Químicos S. A., registered in Madrid and property of Schering, was acquired by the Consorcio Químico Español; and Química Comercial y Farmacéutica S. A., property of Bayer and registered in Barcelona, was awarded to Productos Químicos Sintéticos¹⁰.

In this sense, the Instituto de Farmacología Española (IFE, Spanish Pharmacology Institute) is of particular interest. Created in 1950 by Banco Urquijo, it was a research centre directly promoted by CEPA. They shared space and personnel as well as research interests. These common interests can clearly be seen in the patents applied for by the Instituto de Farmacología Española, S. L. (Fundación Marqués de Urquijo) at the Spanish patents office between 1953 and 1964 regarding procedures to obtain derivatives of penicillin and tetracycline¹¹. This institute served CEPA well, with many of the products that were the subjects of patents later being commercialised by the company¹².

Chronologies

The chronology put together from the patent applications kept in the OEP archive show the bureaucratic-political entry of these drugs (Chart 1). Antibiotic production was one of the sectors the State gam-

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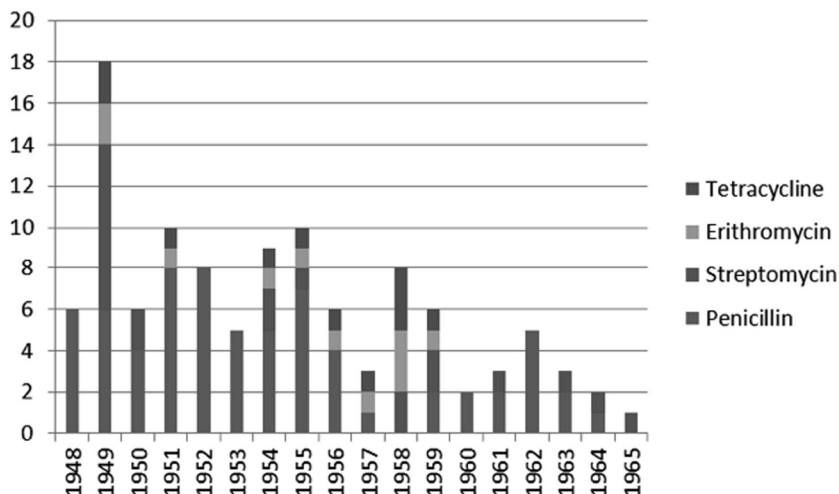


Chart 1 - Patent Applications by Year, 1948–1965

Source: Adapted from data at the OEPM Archive

bled on. As such, this chronology not only shows a willingness to protect certain procedures and methods of production as intellectual and industrial property, but also suggests some practices that contradict the autarkic discourse that monopolised this era. The arrival of antibiotic patents demonstrates the need that existed for contact with the outside world, stimulated in large part by the lack of technical, economic and industrial capabilities in Spain¹³.

Compared to the other years studied, a striking number of applications were made in 1949. Patents were requested to protect procedures related to penicillin, streptomycin and erythromycin. This information should be interpreted in relation to the history of Spain itself, it being the year the State formally created the political space for the production of penicillin. Thus it makes sense that, between 1948 and 1965, seventy per cent of applications correspond to patents relating to penicillin: manufacturing processes, different types

of presentation, salts, ointments, injections. In the same time period, applications associated with streptomycin represent twenty per cent of the total, with erythromycin ten per cent, and with tetracycline, barely one per cent.

Penicillin occupied a large space, but it was not alone (Charts 2 and 4.1); it rapidly had to share the stage with, above all, streptomycin, starting in 1949, and later erythromycin (starting principally from 1954, although in 1949 there were already patent applications to protect its methods of production). The fact that penicillin shared this space with other antibiotics suggests, above all, the limitations of penicillin itself and its inability to cure all infections. The resistance of some micro-organisms to penicillin encouraged the search for, and development of, new antibiotics: firstly streptomycin, which turned out to be effective against tuberculosis, among other infections, and later, other antibiotics.

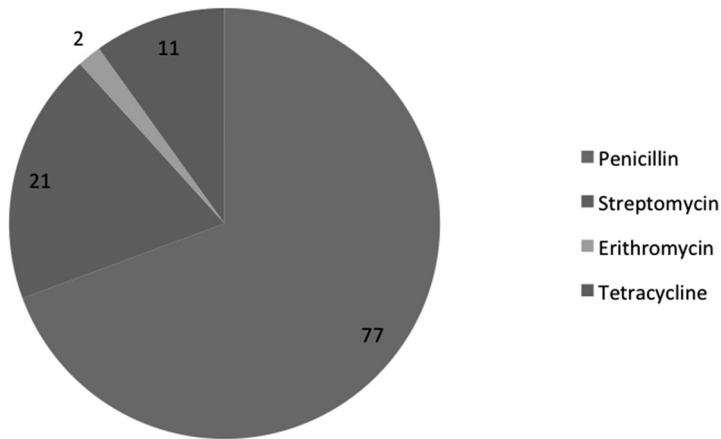


Chart 2. Patent Applications by Type of Antibiotic, 1948–1965
Source: Adapted from data at the OEPM Archive

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So, it could be argued that, from at least 1948, Spain participated in the expectations engendered by penicillin. Principally foreign companies, although also some Spanish ones, were motivated to take the precaution of protecting their methods of production, given the therapeutic triumphs of this new drug, which quickly had an impact on the lowering of infant mortality and the rise in life expectancy (Table 1)¹⁴.

	PENICILLIN	STREPTOMYCIN	ERYTHROMYCIN	TETRACYCLINE
A/S. APOTHEKERNES LABORATORIUM FOR SPECIALPRAEPARATER	1	0	0	0
ABBOTT LABORATORIES	0	0	3	0
ABILGAARD-ELLING, KNUD	2	0	0	0
ALONSO SAMANIEGO, MIGUEL ANGEL	0	1	0	0
AMERICAN HOME PRODUCTS CORPORATION	1	0	0	0
ANTIBIÓTICOS, S.A.	3	2	0	1
BASSAS GRAU, ENRIQUE	2	0	0	0
BEECHAM GROUP LIMITED	1	0	0	0
BRISTOL LABORATORIES INCORPORATED	3	0	0	0
CARL REITER, RUDOLF	1	0	0	0
CHAS PFIZER & COMPANY, INCORPORATED	0	0	0	1
CHEMIE GRÜNENTHAL, G.M.B.H.	1	0	0	0
COMMERCIAL SOLVENTS CORPORATION	1	0	0	0
DOCTOR ANDREU, S. A.	0	0	1	0
DURÁN MARTÍ, JUAN	0	1	0	0
E.F.E.Y.N.S.A	2	0	0	0
ELI LILLY AND COMPANY	2	0	5	0
FARBENFABRIKEN BAYER, A.G.	2	0	0	0
FARMACEUTICI ITALIA, S.A.	2	0	0	0
FOLCH VIDAL, CONRADO	0	1	0	0
GEWERKSCHAFT - RHEINPREUSSEN	1	0	0	0
GLAXO LABORATORIES, LIMITED	4	0	0	0
IMPERIAL CHEMICAL INDUSTRIES, LIMITED	1	0	0	0

INSTITUTO DE BIOLOGÍA Y SUE- ROTERAPIA, S.A.	1	0	0	0
INSTITUTO DE FARMACOLOGÍA ESPAÑOLA, SOCIEDAD LIMITADA (FUNDACIÓN MARQUÉS DE URQUIJO)	7	0	0	0
KABI, AKTIEBOLAGET	1	0	0	0
LABORATORIOS VIGONCAL, S.A.	1	0	0	0
LEO-INDUSTRIE CHIMICHE FARMACEUTICHE, SOCIETÀ PER AZIONI	1	0	0	0
LEPETIT, S. P. A.	2	0	0	0
LES LABORATOIRES FRANÇAIS DE CHIMIOTHERAPIE	3	0	0	0
LØVENS KEMISKE FABRIK VED A. KONGSTED	10	0	0	0
MERCK & CO., INCORPORATED	4	11	0	0
NOVO TERAPUTISK LABORATO- RIUM, A/S.	2	0	0	0
PIERREL, S.P.A.	0	0	1	0
ROBERT MESTRE, JOSÉ	1	1	0	0
ROUSSEL-UCLAF	1	0	0	0
SCHENLEY INDUSTRIES, INC.	5	4	1	0
SCHENLEY INDUSTRIES, INC.	5	4	1	0
SOCIÉTÉ DES USINES CHIMIQUES RHÔNE-POULENC	1	0	0	0
THE MARCELLE FLEISCHMANN FOUNDATION INCORPORATED	1	0	0	0
UNIÓN QUIMICA DEL NORTE DE ESPAÑA, S.A.	2	0	0	0
WYETH INCORPORATED	1	0	0	0

Table 1. Companies Applying for Patents by Antibiotic, 1948–1965

Source: OEPM Archive

Biographies

The procedures contained in the patents evoke a living history of antibiotics. Although on occasion a few changes and modifications make a patent obsolete and necessitate the writing of a new one, patents also construct biographies.

The procedures registered in Spain relating to the production of streptomycin are a good example. They illustrate processes where practices and techniques circulated from certain spaces, and disciplines, to others. In the history of streptomycin, the work space of Selman A. Waksman and changes in the field of soil microbiology, as well as the intersecting interests of the industry that supported and financed the investigation – Merck – and the clinical trials developed at the Mayo Clinic were of major importance. The work done in each of these places, as well as the interaction and circulation of knowledge that was produced between them, was highly significant.

The Agricultural Experiment Station in New Jersey was where Waksman spent a large part of his life studying fungi, actinomycetes and other soil micro-organisms. It was here that he analysed a considerable variety of soils and organic materials, and made cultures to see what inhibited the growth of colonies of pathogenic germs.

Firstly, he demonstrated the activity of streptomycin in the laboratory. From test tubes he moved on to *in vivo* studies with chicken and mouse embryos. This change of scale brought about new challenges: technical problems with the cultures had to be resolved and it was necessary to find adequate means to produce enough quantities of purified antibiotic.

In 1944, Selman Waksman, Albert Shatz and Elizabeth Bugie published an article in which they included a table of the concentrations of streptomycin necessary to stop the growth of different organisms, among them the tubercle bacillus. In 1945, it was William H. Feldman and H. Corvin Hirshaw, at the Mayo Clinic, who proved the activity of streptomycin against tuberculosis in guinea pigs, demonstrating its therapeutic activity. By 1946, the pilot plant of Merck was providing small quantities of streptomycin to groups of doctors for clinical trials and to the Army Medical Corp. At the beginning of 1947, streptomycin was already being distributed commercially. The numerous improvements that were introduced up to the 1950s in

the large-scale production of this antibiotic led to its sale price being reduced, just as had been the case with penicillin¹⁵.

Within a decade, ten antibiotics were isolated and described at the Agricultural Experiment Station in New Jersey, three of which had clinical importance: actinomycin¹⁶, streptomycin¹⁷ and neomycin¹⁸. As had happened with penicillin¹⁹, by the time the first patents to protect processes related to streptomycin were solicited in Spain, books by Spanish authors that included the work of Waksman were already circulating²⁰.

An interpretation of the procedures included in the streptomycin patents registered in Spain forms a trajectory, a life where techniques and practices from very distinct origins converged. Patents sought to improve fermentation under conditions of submerged aeration to give continuity to the fermentation process, which was very often interrupted. As such, on the one hand the *Actinomyces griseus* were strengthened with ultraviolet radiation and, on the other, the components and culturing conditions were constantly altered. The use of the electronic microscope allowed the substance responsible for cellular destruction and, as such, responsible also for the interruption in the fermentation process, to be seen. This instrument helped to isolate the resistant strains of *Actinomyces* with which to cultivate immune strains capable of producing streptomycin. While the introduction of improvements in fermentation procedures was added to this first group of patents, there was a second group that explored new methods that increased production²¹.

Nevertheless, the rapid growth of the organisms did not produce a comparable increase in antibacterial activity. It was this situation that led Waksman and Schatz to request a patent that distinguished between the 'activity factor' and the 'growth factor' in the preparation process of streptomycin²². Effectiveness was the priority, as growth was not useful unless accompanied by activity. As such, the need to secure mutant strains that were resistant, strong and efficient, organised and favoured the development of the research.

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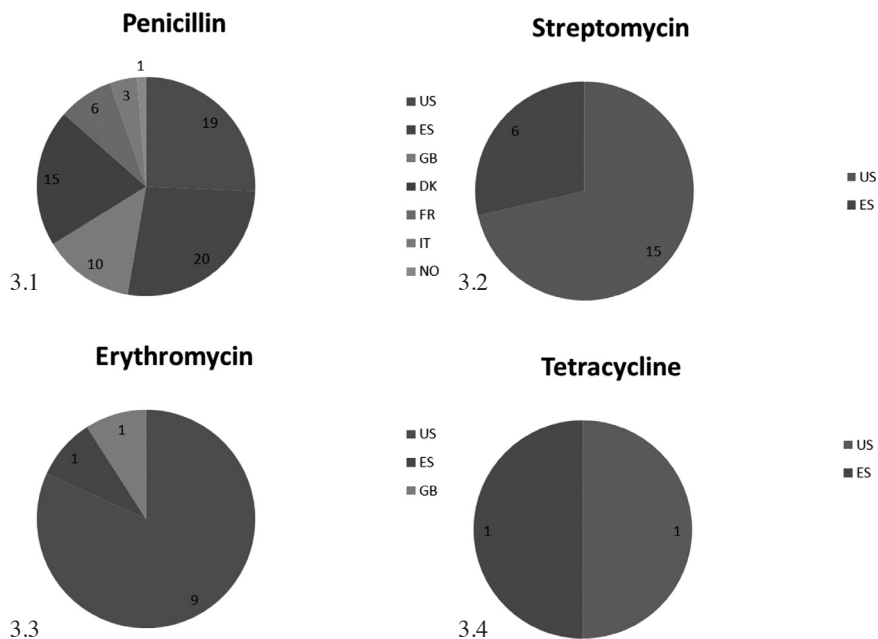


Chart 3. Patent Applications by Country and Type of Antibiotic, 1948–1965
Source: Adapted from data at the OEPM Archive

This journey, expressed here in an apparently simple and linear form, was not simple at all. The different patent applications and their content, the specific object of protection, evoke failures more than successes. Dissatisfaction with the results obtained was what energised research and drove the registering of new patents. The resistance of some micro-organisms to attack by the antibiotics available aroused, on one side, concerns – social resistance – but over time, this strengthened the development of new antibiotics and improvements in the manufacturing methods of penicillin. It is this context of concern and uncertainty, of good intentions and the need for improvement, which explains the sustainability of requests associated with penicillin and the other antibiotics during the time studied²³.

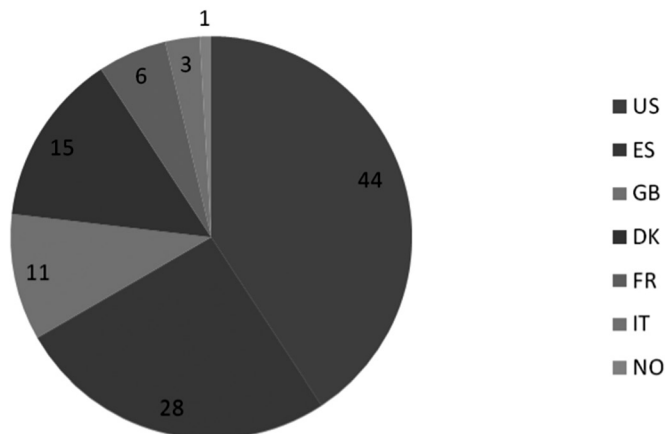


Chart 4. Patent Applications by Country, 1948–1965

Source: Adapted from data at the OEPM Archive

These factors, activity and growth, were the same factors used in placing these antibiotics on the market. Once the therapeutic strength of the drug was resolved, first in the laboratory and later in clinical practice, the next issue to be considered was how to improve techniques to make it strong and resistant in the market. To the factors of activity and growth were added others: production yield and costs.

Markets

In this sense, the patent applied for by Merck at the OEPM on 2 March 1949 and granted 23 May the same year, ‘Un procedimiento de recuperación de estreptomina de soluciones de la misma’ (A procedure to recover streptomycin from solutions of streptomycin), is doubly interesting²⁴. In the first place, the patent was solicited to protect a procedure that had been perfected to recover streptomycin,

which could provide not only extra economic profitability but also greater efficiency. Additionally, this is the patent listed in the agreement that Merck and CEPA signed in 1951, enabling the Spanish firm to manufacture streptomycin in Spain²⁵.

At the time this patent was written, streptomycin was already being industrially produced. The patents applied for by Merck (in February to April of 1949 alone, this company applied for the protection of ten different procedures) and by Schenley give an idea of the research interests and various developments they were carrying out related to this antibiotic²⁶.

The specific invention this patent offered was a new, perfected procedure to recover streptomycin from cultures using ion-exchange resins, which absorbed the antibiotic where it had been produced in the cultures due to the propagation of the micro-organism *Streptomyces griseus*. Until then, activated charcoal, an expensive non-reusable material with low, slow absorption capacity, had been used to recover streptomycin. These disadvantages multiplied when working with relatively large quantities. Resins, in addition to being reusable, enabled the recovery of streptomycin to be carried out at least fifteen times faster than activated charcoal; also, the streptomycin obtained in this manner was fairly pure and did not need intermediate purification to crystallise.

The efficiency of these processes also had a clear effect on the costs of the installations and even their physical aspect, and as such on production costs as well. The introduction of this innovation to the process and the subsequent improvement in production times allowed the use of lower-capacity equipment, as the recovery operation was much faster and less costly.

Activity and growth factors, the profitability of the processes, and production and output costs were of concern to the laboratories attempting to make their products competitive in the market, but there were also worries regarding the policies and strategies of the companies and governments.

Spain was a market with business possibilities. The experience of Merck and the agreement signed with CEPA to set up a penicillin production plant in Aranjuez demonstrate this: results gathered in reports were higher than estimated²⁷. This, along with the constant patent applications requested to protect processes related to the production of streptomycin, give the impression the American company had a clear interest in being in the Spanish market (Chart 4.2; Table 1). Preserved documentation on the contacts between CEPA and Merck suggest the supposed obstacles to entry by foreign companies, resulting from Spain's autarkic policies, were not so significant. The people in charge of the Spanish company were the ones who had to work hard to obtain information from Merck for the production of streptomycin in Spain. Merck was interested in producing streptomycin in Spain, just as it had penicillin, but not at any price. In a document attached to a copy of the contract signed with Merck sent to the General Director of the Ministry of Industry in 1951, Antonio Robert, Executive Director of CEPA, said expressly: 'the Compañía Española de la Penicilina y Antibióticos S.A. has secured, after many months of negotiations, the willingness of Merck & Co. to collaborate in the manufacturing of streptomycin and dihydrostreptomycin in Spain²⁸.

It is interesting that it was Antonio Robert who contradicted, in practice, the autarkic discourse. An industrial engineer, he was the General Director of Industry from 1945 to 1947 and one of the main defenders of autarkic politics. In his book, *Un problema nacional: la industrialización necesaria (A National Problem. The Necessary Industrialisation)*, he said that industrialisation, essential for development, could only be achieved by the substitution of large-scale importation, the protection of national production and the co-ordination of economic policy by a central institution²⁹. However, it appears the actual situation in Spain convinced him otherwise and, some years later, in *Perspectivas de la Economía española (Perspectives on the*

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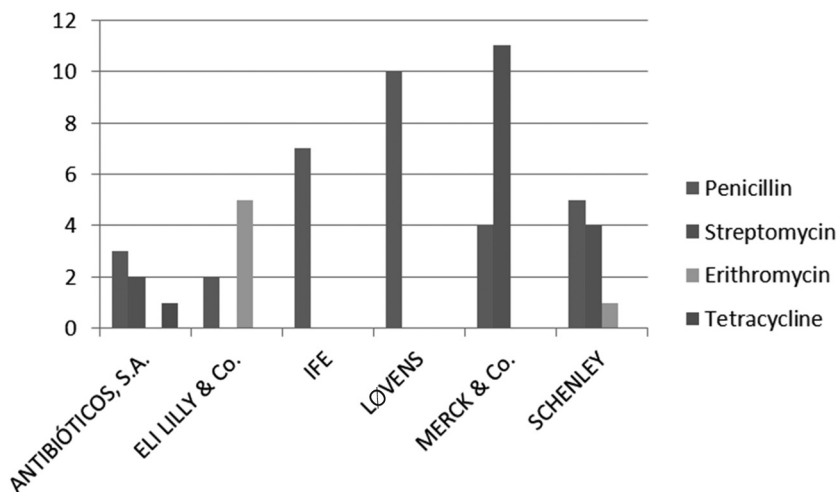


Chart 5. Patent Applications by Company and Type of Antibiotic, 1948–1965
Source: Adapted from data at the OEPM Archive

Spanish Economy), he lamented the loss of time and effort that resulted from trying to invent, with fewer resources, that which others had already developed³⁰.

The contract that CEPA signed with Merck had two parts. In the first, the American pharmaceutical committed to sending the documentation necessary to present the Ministry of Industry with a complete project for the factory – investments to be made, machinery it was necessary to import, estimated price of the product; and the second part centred on the contract for technical collaboration. Merck did not want to divulge secrets for the manufacturing of penicillin until receiving a clear commitment from the government and knowledge of what responsibilities Spain would take on. This coincides with the idea that often – and contrary to what had been established by law – the content of patents was not always enough to reproduce the actual processes³¹. To set up the factory and for it to function prop-

erly later on, it was necessary for technicians from CEPA to travel to the Merck installations. One of these trips was made in June 1964 by José María Rubio, head of the production department. He visited the antibiotic factories that Merck had in Stonewall (Virginia) and Cherokee (Pennsylvania), and according to Rubio in an interview published in *Noticias* – a monthly publication of the Company – the main objective of the trip was to ‘discuss with the bosses and technicians various matters about the manufacturing of streptomycin and penicillin...useful for our factory in Aranjuez’³².

Returning to the content, the contract made good business sense for Merck. The contract to produce streptomycin involved expanding the Aranjuez factory, doubling the production of penicillin – demand was outstripping supply – and having a reserve capacity for fermentation equal to six million doses of penicillin³³. The Merck experts estimated a minimum streptomycin production of three million one-gram doses per year, which meant – and this is one of the key points in the text that Robert sent to the Ministry of Industry – a saving for the Spanish State of around one million dollars in imports and, thus, in currency. In exchange, Merck committed to supplying CEPA with the initial subcultures and nutrients to produce streptomycin, to provide a description of production processes, to indicate the necessary materials, technicians and equipment, and to allow CEPA technicians to attend their factories. What this meant for the Spanish company in economic terms was five payments of \$50,000 to the American company for information on constructing the installation and implementing the process, plus seven per cent of the streptomycin sold during a period of fifteen years.

Also important was the possibility of patentable innovations and licenses that might arise during these fifteen years as a result of the new contractual relationship and, above all, from the new installation. Both companies agreed to mutually offer each other licenses, which were non-exclusive and exempt from rights, to use and manufacture streptomycin in their respective plants, as well as to sell it.

The inauguration in Aranjuez in September 1954 of the CEPA installations to produce streptomycin was recorded in the press and in NO-DO (the Spanish Cinematic Newsreel Service) as a major national event³⁴. Taking the statements made ten years later by José María Rubio, the differences between these installations and the American ones came down to size, in line with the market that each had to service, and to Spain's lesser experience. Standing out among the achievements reached in Aranjuez in these years, however, was the 'production of certain antibiotics at competitive costs, improvement in all areas of production, and better working conditions for the producers'³⁵.

We have seen how patent applications construct chronologies and biographic narrations, and also suggest business strategies that contribute new elements to a re-evaluation of autarkic politics in the early years of the Franco government. Authorisation from the State to set up installations to produce penicillin and streptomycin encouraged a rise in applications, on the part of foreign companies, for patents in Spain that protected processes related to antibiotics (Table 1). For example, in 1949 OEPM registered applications relating to erythromycin, an antibiotic that was not produced industrially until after 1952³⁶. Eli Lilly & Company, the firm responsible for isolating it, was the owner of these patents and, as such, was protecting its future (Chart 4.3)³⁷.

In addition to these strategies to protect the future, information from patent applications suggests a sharing of the market, at least the Spanish market, by the industries that produced antibiotics. Chart 5 depicts the companies and the antibiotics each hoped to patent: it suggests that Merck and Løvens were concentrating on penicillin and aiming for a higher share of the market, at least in Spain; meanwhile, Eli Lilly introduced erythromycin, and Schenley and Merck tried to protect streptomycin; as has already been noted, these were the companies that had the license for Spanish production of

penicillin and they were attempting to use the same strategy with streptomycin.

Conclusions

Along with the role patents play in the standardisation, normalisation and control of knowledge, in this work I have presented them as determining agents in the circulation of antibiotic practices and also in political, economic and industrial practices.

The chronology of the procedures contained in the patents evokes a living history, that is, antibiotics in permanent change. Patent applications to protect procedures relating to the production of penicillin, streptomycin and erythromycin were made at the end of the 1940s, practically simultaneously. The largest proportion of them – seventy per cent – protected procedures relating to penicillin and its derivatives, while the remaining thirty per cent were shared between streptomycin, erythromycin and, just emerging at that time, tetracycline (Chart 2). The constant presence of applications at the Spanish patent office suggests a constant introduction of variations, although minimal, in the methods of antibiotic production. This indicates constant research and development activity both in and beyond the laboratories. Some of these documents suggest not only the testing and putting into practice of new techniques, but also the development of new political alliances and changes in economic and industrial models. The map these applications sketch out displays the clear leadership of the United States in antibiotic production during the post-war and Cold War (Chart 3).

These patents show Spain, as of 1948, not only participating in the expectations that penicillin opened up but also being aware – and the presence of other antibiotics also suggests this – of the complications the use of penicillin was generating. The resistance of certain microorganisms to the bactericidal action of the first commercialised antibiotics was the main stimulus for the subsequent development of

new antibiotics like streptomycin, effective against tuberculosis, an infection resistant to penicillin, and the later development of other antibiotics. These resistances also enriched and strengthened a market that was concerned with and engaged in – as the patents in the OEPM suggest – specifying and delimiting areas of economic and industrial power.

Antibiotic patents opened up a new industrial space in Spain, at the end of the 1940s and the 1950s, for foreign technologies, procedures and machinery. Inevitably, it was a space of learning and exchange, which clinical information demanded and the black market took care of supplying to the Spanish industry and its companies. This exchange was channelled through patents and also via the experience of collaboration and co-operation between the companies. The new processes that arrived brought with them new practices, new technologies and new forms of production. The entrance of these patents favoured the necessary technological appropriation to provide the Spanish market with frontline products, which antibiotics were, and encouraged the creation of new groups and lines of research that led to the development of new drugs such as fosfomycin³⁸.

Patent applications construct chronologies and biographic narrations, and also suggest business strategies that contribute new elements to a re-evaluation of the so-called autarkic politics in the early years of the Franco government.

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1. The autarkic period in Spain stretches from 1939, the year in which the civil war ended, to 1959, the year of the Plan Nacional de Estabilización Económica (National Economic Stabilization Plan). This plan was made up of a set of measures intended to liberalise the Spanish economy; it represented a rupture with autarkic politics and facilitated a period of economic growth in the country during the 1960s.
2. References in: SANTESMASES M.J., GRADMANN C., *Circulation of antibiotics: an introduction*. *Dynamis* 2011; 31(2): 17-27.

3. On the worldwide expansion of penicillin production as of the middle of the 1940s and the policy of international co-operation directed by, first, the UNRRA and after 1948 by the WHO, see BUD R., *Penicillin. Triumph and tragedy*. Oxford, Oxford University Press, 2007, pp. 75-96.
4. Although in the years studied other antibiotics were known, such as actinomycin, discovered by Waksman and Woodruff in 1940, chloramphenicol discovered by Ehrlich et al. in 1947, and neomycin discovered by Waksman and Lechevalier in 1949, patent applications for these antibiotics cannot be found in the OEPM Archive.
5. Penicillin was purified in 1939 and administered to a patient for the first time in 1941. As of that moment, large-scale production began. For a list of the first registered penicillin patents see HOBBY G.L., *Penicillin. Meeting the challenge*. New Haven and London, Yale University Press, 1985, pp. 284-285. In 1944, Albert Schatz, Elisabeth Bugie and Selman A. Waksman described the properties of streptomycin, see SCHATZ A., BUGIE E., WAKSMAN S.A., *Streptomycin a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria*. Proc. Soc. Exptl. Biol. Med. 1944; 55: 66-69. There are three patent applications related to erythromycin prior to 1952, the year in which the work of McGuire demonstrated the physical and chemical properties and antibacterial activity of erythromycin, see McGUIRE J.M., BUNCH R.C., ANDERSON H.E. et al., *Ilotycin, a new antibiotic*. Antibiotics and Chemotherapy 1952; 2(6): 281-283.
6. Estatuto de la Propiedad Industrial (Statute on Industrial Property), approved by the Royal Decree-Law of 26 June 1929. Published in La Gaceta num. 127, of 7 May 1930. Available at: <http://historico.oepm.es/archivohistoricow3c/index.asp>. Spain's entrance into the European Community in 1986 made it obligatory, as in many other areas, to make Spanish legislation compatible with European law. It was at this time that the current Patent Law (Ley de patentes de invención y modelos de utilidad 11/1986) was put into force. Published in the Boletín Oficial del Estado BOE 26 March 1986, no. 73.
7. Decrees published, respectively, in BOE of 6 October 1948 and in the BOE of 11 August 1949.
8. CEPA (Compañía Española de Penicilinas y Antibióticos) produced penicillin with patents from Merck, and Antibióticos S.A. did so with those of Shenley. On how these patents were introduced into Spain see ROMERO DE PABLOS A., *Regulation and the circulation of knowledge: Penicillin patents in Spain*. Dynamis 2011; 31(2): 363-383. On the new industrial space that was opened up, see PUIG N., *Networks of Innovation or Networks of Opportunity? The*

Making of the Spanish Antibiotics Industry. Ambix 2004; LI(2): 167-185. On the role that Spanish clinicians had in the negotiation process prior to the arrival of the first penicillin patents to Spain, see SANTESMASES M.J., *Distributing penicillin: the clinic, the hero and industrial production in Spain, 1943–1952*. In: QUIRKE V., SLINN J. (eds), *Perspectives on twentieth-Century pharmaceuticals*. Oxford, Peter Lang, 2010, pp. 91-118.

9. SANTESMASES M.J., *Antibióticos en la autarquía: banca privada, industria farmacéutica, investigación científica y cultura liberal en España, 1940-1960*. Madrid, Fundación Empresa Pública WP 9906, 1999, pp. 22-24, 47-48.
10. PUIG N., *Constructores de la química española. Bayer, Cepsa, Puig, Repsol, Schering y La Seda*. Madrid, LID Editorial, 2003.
11. Patent No. 209812 'Un nuevo procedimiento de obtención de una sal estable de penicilina' (A new procedure to obtain a stable salt from penicillin); Patent No. 216723 'Procedimiento para la producción de antibióticos por microorganismos desarrollados en un nuevo medio de cultivo' (Procedure for the production of antibiotics for micro-organisms developed in a new culture medium); Patent No. 225437 'Un procedimiento de obtención de penicilina G-quinina' (A procedure to obtain G-quinine penicillin); Patent No. 225454 'Un procedimiento de obtención de sales poco solubles de penicilina V-quinina' (A procedure to obtain low-soluble salts from V-quinine penicillin); Patent No. 235285 'Procedimiento de obtención de antibióticos' (Procedure to obtain antibiotics); Patent No. 235286 'Procedimiento de obtención de sales de antibióticos' (Procedure to obtain salts from antibiotics); Patent No. 280472 'Procedimiento de obtención de sales de penicilina con eficacia terapéutica y de baja toxicidad' (Procedure to obtain salts from penicillin with therapeutic effectiveness and low toxicity); Patent No. 280470 'Procedimiento de obtención de sales de penicilina con eficacia antihistamínica y antiserotonínica' (Procedure to obtain salts from penicillin with antihistaminic and antiserotonin effectiveness); Patent No. 280469 'Procedimiento de obtención de sales de penicilina con eficacia antihistamínica y antiserotonínica' (Procedure to obtain salts from penicillin with antihistaminic and antiserotonin effectiveness); Patent No. 293733 'Un procedimiento de separación de tetraciclinas de sus soluciones acuosas' (A procedure to separate tetracyclines from their aqueous suspensions); Patent No. 305303 'Un procedimiento de obtención de productos elevadores de los niveles de antibióticos en la sangre' (A procedure to obtain products that boost the antibiotic levels in the blood). All these patents were solicited by the Instituto de farmacología española, Sociedad Limitada (Fundación Marqués de Urquijo). OEPM Archive, Madrid.

12. SANTESMASES, *ref.* note 9, pp. 57-64.
13. *Ibid.*
14. On the influence of penicillin on the increase in life expectancy in the United States between 1920 and 1978 see HOBBY, *see* note 5, p. 236.
15. COMROE J.H., *Pay Dirt: The story of Streptomycin. Part I From Waksman to Waksman. Part II. Feldman and Hinshaw; Lehmann.* American Review of Respiratory Diseases 1978; 117: 773-781, 957-968. On the interaction between the development of streptomycin and work at the Mayo Clinic against tuberculosis, see FELDMAN W.H., *Streptomycin: some historical aspects of its development as a chemotherapeutic agent in tuberculosis.* The American Review of Tuberculosis. A Journal of pulmonary diseases 1954; 69: 859-868.
16. WAKSMAN S.A., WOODRUFF H.B., *Bacteriostatic and bactericidal substances produced by a soil actinomycetes.* Proc. Soc. Exptl. Biol. Med. 1940; 45: 609.
17. SCHATZ A., BUGIE E., WAKSMAN S.A., *Streptomycin a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria.* Proc. Soc. Exptl. Biol. Med. 1944; 55: 66-69.
18. WAKSMAN S.A., LECHEVALIER H.A., *Neomycin, a New Antibiotic Active against Streptomycin-Resistant Bacteria, including Tuberculosis Organisms.* Science 1949; 109(2830): 305-307.
19. SANTESMASES M.J., *ref.* note 8; ROMERO DE PABLOS A., *ref.* note 8.
20. At the Biblioteca Nacional de España (National Library of Spain) two typewritten texts are conserved with manuscript corrections and the autographed signature of Florencio Bustinza: 'Sobre el empleo de la estreptomycinina' (The use of streptomycin) and 'Waksman, el descubridor de la estreptomycinina: el sabio en el laboratorio y en su hogar' (Waksman, the discoverer of streptomycin: the sage in the laboratory and at home). These texts are not dated, but are catalogued circa 1950. (SEGOVIA DE ARANA J.M., *Estreptomycinina.* Madrid, Paz Montalvo; BUSTINZA F., *De Koch a Waksma: La estreptomycinina y la lucha contra el 'mycobacterium tuberculosis'.* Madrid, Espasa Calpe, 1948; SALA GINABREDA J.M., *Estreptomycinina y meningitis tuberculosa en la infancia.* Madrid, Relieves Basa y Pagés, 1949; EIZAGUIRRE E., *La estreptomycinina, el pas y el Tb.-1 en la tuberculosis pulmonar.* Madrid, Ed. Científico Médica, 1950.
21. Patent No. 187020 'Un procedimiento para la preparación de antibióticos' (Procedure for the preparation of antibiotics); Patent No. 187295 'Un procedimiento de producir estreptomycinina' (Procedure for producing streptomycin); Patent No. 187810 'Un procedimiento de preparar estreptomycinina'

- (Procedure for preparing streptomycin); Patent No. 187911 'Un procedimiento de producir estreptomicina' (Procedure for producing streptomycin); Patent No. 198931 'Un procedimiento para la producción de estreptomicina' (Procedure for the production of streptomycin); Patent No. 199311 'Un procedimiento para la producción de estreptomicina' (Procedure for the production of streptomycin). All these patents were solicited by Merck. OEPM Archive, Madrid.
22. WAKSMAN S.A., SCHATZ A., *Streptomycin and process of preparation*. Patent U.S. 2,449,866 of September 21, 1948.
 23. On changes in the public perception of penicillin see BUD R., *op. cit.* (note 3). On the practices and use of antibiotics in England see CONDRAU F., KIRC R.G., *Negotiating hospital infections: the debate between ecological balance and eradication strategies in British hospitals, 1947–1969*. *Dynamis* 2011; 31(2): 385-405.
 24. Patent No. 187274, OEPM Archive, Madrid. Two different versions of this patent have been saved. The first has 'seventeen sheets written on just one side,' and the other has 'twelve pages written on just one side.' It is customary with these documents, in order to avoid their possible alteration, to not only mark the lines with a number to the left, but also to note their total length at the end of the document. The writing of a second report indicates that the content of the first was unsatisfactory. These modifications show to what degree the writing of the protection determines the content of the same. ROMERO DE PABLO, *ref.* note 8.
 25. On the contract that CEPA signed with Merck for the production of penicillin see SANTESMASES M.J., *ref.* note 8, pp. 111-114.
 26. In the case of Merck, in addition to the patents already mentioned in footnote 12 see also Patent No. 187019 'Un procedimiento para preparar estreptomicina' (Procedure for the preparation of streptomycin); Patent No. 187314 'Un procedimiento para preparar dihidroestreptomicina' (Procedure for the preparation of dihydrostreptomycin); Patent No. 187377 'Un procedimiento para preparar sales complejas de estreptomicina' (Procedure for the preparation of complex salts from streptomycin); Patent No. 187758 'Un procedimiento para eliminar pirógenos de soluciones de estreptomicina por medio de carbón activado' (Procedure to eliminate pyrogens from streptomycin solutions using activated charcoal); Patent No. 187793 'Un procedimiento de preparación de hidrócloruro de dihidroestreptomicina cristalizado' (Procedure for the preparation of hydrochloride from crystallized dihydrostreptomycin); Patent No. 189725 'Un procedimiento de recuperar

- estreptomycina de soluciones de la misma' (Procedure to recover streptomycin from solutions of streptomycin). For the patents from Schenley see Patent No. 222613 'Un procedimiento para producir estreptomycina' (Procedure for producing streptomycin); Patent No. 230695 'Un procedimiento para la purificación de estreptomycina' (Procedure for the purification of streptomycin); Patent No. 234294 'Procedimiento para la producción de un concentrado sólido, seco, de triclorhidrato de estreptomycina' (Procedure for the production of a solid, dry concentrate from trihydrochloride from streptomycin), OEPM Archive, Madrid.
27. SANTESMASSES M.J., *ref.* note 8, pp. 113-114.
 28. Letter from Antonio Robert to the General Director of Industry. 7 May 1951. AGA.
 29. ROBERT A., *Un problema nacional: la industrialización necesaria*. Madrid, Espasa Calpe, 1943.
 30. ROBERT A., *Perspectivas de la Economía española*. Madrid, Cultura Hispánica, 1954.
 31. The statute of Industrial Property of 1929, in Article 62, establishes that patents should explain the innovations they seek to protect in a complete and detailed way, with the objective of being understood and able to be copied by an expert in the subject. If not, the application may fail.
 32. ZARZA I., *Declaraciones del Dr. José María Rubio, Jefe de producción de Aranjuez a su regreso de Estados Unidos*. Noticias 1964; 11: 1.
 33. This need had already been expressed in the CEPA report of 1952; although more than the agreed amount was produced, production was insufficient to cover demand from the market SANTESMASSES M.J., *ref.* note 8, p. 114.
 34. Archive NO-DO, broadcast 4 October 1954, n° 613B. Available at: <http://www.rtve.es/filmoteca/no-do/not-613/1482441/>. NO-DO (Noticiarios y Documentales, that is News Programs and Documentaries) was created in 1942 by the dictatorship of General Franco as a broadcasting service for news programs and features, and exhibition in Spanish cinemas was obligatory until 1975. This news service served, above all, as a propaganda arm of the Franco regime, and science and technology were two of the most utilized subjects. See MEDINA-DOMÉNECH R.M., MENÉNDEZ-NAVARRO A., *Cinematic representations of medical technologies in Spanish official news-reel, 1943–1970*. Public Understanding of Science 2005; 10(14): 383-408; MEDINA-DOMÉNECH R.M., MENÉNDEZ-NAVARRO A., *Ausencia y primor: 'Mujer', tecnologías médicas e identidad nacional en el discurso visual de NO-DO*. In: CARRETERO A., RUIZ FRANCO R. (eds), *X Coloquio*

- internacional de la AEIHM. Representación, Construcción e Interpretación de la Imagen visual de las Mujeres.* Madrid, Instituto de Cultura y Tecnología Miguel de Unamuno, 2003, pp. 395-403; ORDÓÑEZ J., RAMÍREZ F.E., *Los públicos de la ciencia española: un estudio del NO-DO.* In: ROMERO DE PABLOS A., SANTESMASSES M.J. (eds), *Cien años de política científica en España.* Madrid, Fundación BBVA, 2008, pp. 257-292. On the origin and creation of NO-DO and the models it was based on, see TRANCHE R., SÁNCHEZ-BIOSCA V., *Los años 50 en NO-DO, de la autarquía al desarrollismo.* In: YRAOLA A. (ed.), *Historia contemporánea de España y Cine.* Madrid, Ediciones de la Universidad Autónoma de Madrid, 1997, pp. 115-124; TRANCHE R., SÁNCHEZ-BIOSCA V., *NO-DO El Tiempo y la Memoria.* Madrid, Cátedra/Filmoteca Española, 2002.
35. ZARZA I., *ref.* note 32.
36. In 1952, McGuire demonstrated the physical and chemical properties and antibacterial activity of erythromycin, see MCGUIRE J.M., BUNCH R.C., ANDERSON H.E., *ref.* note 5.
37. In the acknowledgements of the article published to divulge the discovery they expressed it in this way: ‘The isolation and development of ‘Ilotycin’ [Trademark for Erythromycin, Lilly] was a cooperative program involving all divisions of the Lilly research Laboratories ...’
38. PUIG N., *ref.* note 8, pp. 183-184; SANTESMASSES M.J., forthcoming.

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