

Historical Social Research Historische Sozialforschung

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doi: 10.12759/hsr.44.2019.4.75-95.

Published in:

Historical Social Research 44 (2019) 4

Cite as:

Fernández Pérez, Paloma. 2019. Pioneers and Challengers in the
Global Plasma Protein Industry, 1915-2015.
Historical Social Research 44 (4): 75-95. doi: 10.12759/hsr.44.2019.4.75-95.

Pioneers and Challengers in the Global Plasma Protein Industry, 1915-2015

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Abstract: »Pioniere und Herausforderer in der globalen Plasma Protein Industrie, 1915-2015«. Entrepreneurship in the science-based industries is often the result of collective actions undergone by entrepreneurial groups. The origins of the biotech industry provide many examples. In the plasma protein industry, which has registered a continuous growth since 1910 and an accelerated process of mergers and acquisitions in the last decades, there are three leading corporations whose history reflects collective entrepreneurship: Baxter with headquarters in the United States (start 1931), CSL Behring in Australia (start 1916) and Grifols in Spain (start in plasma business in 1940). This article provides a historical overview of the industry and how the making of collective entrepreneurship allowed a challenger like Grifols, from a late industrialized country such as Spain, to cross entry barriers in the plasma industry, buy many of the pioneering corporations, and establish a global leadership position. This article argues that the long-term trust-based personal and professional relationships established by the entrepreneurial Spanish family lab, with managers from the US and Japanese corporations, produced a collective entrepreneurial hub of connections that made possible a long-term sustained process of innovation and globalization in a highly specialized biomedical industry.

Keywords: Biotech Industries, Plasma Protein Industry, Grifols, Baxter, CSL.

1. Introduction¹

Entrepreneurship is often an individual virtue, but in knowledge intensive industries it is more commonly the result of collective entrepreneurship (Mingloulou and Cassis 2005; Ács and Audretsch 2010; Jones and Wadwhani 2007). The world plasma industry analyzed in this article is a particularly good example that demonstrates the significance of trust-based entrepreneurial groups that

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¹ A previous draft was published as a Working Paper of the Spanish Association of Economic Historians, AEHE, in <<https://www.aehe.es/wp-content/uploads/2016/01/FERNANDEZ-PEREZ.pdf>>. Financial support for research and writing of this text came from one of the first Fundació BBVA I Ayudas en Investigación en SocioEconomía 2014-2016. Previous presentation of ideas took place in several scientific meetings: at the Universidad de Guadalajara in México on the 12th of May 2016, in the Health and Welfare in the Long Run at the

exchange knowledge over time, not just to grow and expand, but to reduce the potential risks their operations may have in the lives and well-being of millions of people and in their own business survival.

The plasma industry has experienced a strong growth, from \$5 billion in global sales in 2000 to over \$14 billion today.² The plasma industry's raw material is expensive (70% total costs) because of the small quantities collected from donors, the costs of the plasmapheresis equipment, the fractionation process, the highly qualified staff, and the costs of quality control processes involved in the collection, manufacturing and distribution of the products involved. The industry is now very concentrated in three big corporations, but they all started as small start-ups able to grow by creating tightly linked entrepreneurial groups in a long-term process that started one hundred years ago (Curling, Goss, and Bertolini 2015).

Plasma is the liquid portion of blood and constitutes 55% of blood, the remaining 45% being red blood cells. The first and most important human plasma protein whose obtention the industry sought from the 1940s until the 1980s was albumin (55-60% of plasma protein), which was helpful in the rapid resuscitation of people from life shocks due to heavy blood loss (Curling, Goss, and Bertolini 2015). In the last decades, new knowledge has allowed the obtention of new plasma proteins and the application of said plasma proteins in the development of new therapeutical products used in a great variety of neurological, autoimmune, and cardiovascular diseases (Robert 2015).

University of Groningen in the Netherlands on the 16th of June 2016, at the EBHA/World Business History Conference in Bergen in Norway on the 26th of August 2016, in the Ramón Carande seminar at the Universidad de Sevilla on the 3rd of October 2016, in a seminar at the Faculty of Economics in Nova University of Lisbon on the 21st of October 2016, in the Workshop "Innovation and Business in the Health Care Industries in the 20th century" at the Faculty of Economics and Business of the Universitat de Barcelona on the 29th of November 2016, and in a pre-conference organized in 2017 at the Universidad Complutense de Madrid by José Luis García Ruiz and Jesús M. Valdaliso. Important comments and suggestions received in all these meetings are kindly acknowledged with the usual disclaimer of responsibility. Also acknowledged is the cooperation of the Grifols Corporation in opening their archives and in facilitating interviews with its former CEO Victor Grifols Roura and several managers. In particular, two managers were extremely generous and kind providing time and comments in the last three years: Nuria Pascual and archivist director Rosa Avella. A recent article including data about the international alliances of Grifols and the financial complexities of their globalization after the 1980s was published by the author with J.L. García Ruiz as "Financing the Internationalization of Spanish Industrial SMEs, 1980s-2000: The case of the Grifols Group", *Universia Business Review* (2017). While in previous presentations and analysis of this case study I have particularly stressed the issues of strategy and networking, this contribution highlights collective entrepreneurship from an entrepreneurial group lens. I warmly thank Isabell Stamm for her continuous support and ideas as well as Ludovic Cailluet and Allan Discua for their comments and advice.

² <<http://marketingresearchbureau.com/plasma-industry/current-uses-affecting-the-plasma-industry/>> Access online 21/4/2016.

This article provides new empirical evidence about the role played by collective entrepreneurship in very specialized science-based industries, in the specialized market niche of the plasma industry. The hypothesis is that during almost half a century there has been a close communication between the pioneering entrepreneurs and firms that established the learning bases of the industry in the US, Australia, and Germany. They opened new communication channels with new small challengers from developing economies like Spain. The case of Grifols, one of the top three plasma producers in the world in the early 21st century, shows the enduring relevance of entrepreneurial groups in this industry. The dialogue between different business cultures and the construction of corporate alliances was facilitated, on the one hand, by personal friendship and trust-based professional relationships established between the Spanish lab and both relatives and close colleagues, and on the other by relationships with German labs and managers of scientific corporations from Cuba, North America, and Japan.

2. The Pioneers of the World Plasma Industry

Currently in the early 21st century, the plasma industry is heavily concentrated. The top seven plasma collectors owned by plasma fractionators collect millions of liters of plasma and are: BioLife (owned by Baxter), BioMat, PlasmaCare and Talecris Plasma Resources (owned by Grifols), CSL Plasma (owned by CSL Ltd.), Octapharma Plasma (owned by Octapharma), and Advanced Bioservices (owned by Kedrion SpA). The first three companies collect over 75% of the total US plasma. Most of the plasma-collecting companies are based in the US, as it is the main source of plasma worldwide.³

The early growth of the industry in the first four decades of the twentieth century is inextricably linked to the history of modern warfare and the power of imperial armies to spend a huge amount of effort and money from public sources on the investment into research and cooperation with private firms. The first blood banks for the massive collection of human blood for transfusion appeared in close connection with World War I (United Kingdom, Russia) and the Spanish Civil War, under the auspices of governments and armies.

Table 1: Pioneers in World Blood Banking (BB) and Plasma Fractionation (PF)

| COUNTRY | PIONEER | DATE BB | DATE PF |
|---------|-------------------|---------|---------|
| UK | British Red Cross | 1921 | |

³ <<http://marketingresearchbureau.com/plasma-industry/current-uses-affecting-the-plasma-industry/>> Access online 21/4/2016.

| | | | |
|-------------|------------------------------|-------|----------------|
| USSR | Sergei Yudin | 1930 | |
| Spain | Frederic Duran i Jordà | 1936 | 1951 (Grifols) |
| USA | Edwin Cohn/Armour Labs | 1940 | 1940 |
| Germany | Emil von B./ Behringwerke | 1939? | 1946 |
| Australia | William Penfold/ CSL | 1929 | 1952 |
| Switzerland | ZLB | 1939 | 1949 |
| Japan | Ryoichi Naito / Green Cross | 1950 | 1971 |
| Argentina | Laboratorio de Hemoderivados | 1914? | 1964/74 |

Source: Own elaboration with secondary sources from each country and corporation in table and Curling, Goss, and Bertolini (2015).

The blood banks were new organizations that allowed regular and abundant collection of human blood, the raw material from which plasma must be obtained. Plasma extraction was initially very expensive and difficult before the 1940s and national public health systems, with few exceptions, did not have enough highly qualified scientists able to focus in the long-term research involved in industrializing the production of abundant plasma extraction until after World War II.

The first large public-private agreements signed to finance new industrial ways to produce and distribute albumin quickly, safely, and in larger quantities came after the attack on Pearl Harbor in the United States in December 1941 and continued throughout World War II. This was done in order to be used for the resuscitation of soldiers in shock on the battlefield. The US Army drew up seven contracts in 1941 with Armour, Lederle, Upjohn Co., Eli Lilly Laboratories, E.R. Squibb, Cutter Laboratories, and Sharp and Dohme to expand fractionation and production of human albumin for the US soldiers. These companies became the first commercial fractionators, and two of them (Armour and Cutter Laboratories) remained in the business after the war and the expiration of the 1941 contracts. The others were concerned about availability of plasma and viability of the industry if they did not have a strong (or guaranteed) military demand (Kendrick 1942; Curling, Goss, and Bertolini 2015).

Cutter Laboratories was founded in 1897 and began plasma fractionation in 1942, becoming the first commercial producer of albumin (Cutter 1975). After completion of its facilities in Clayton, North Carolina, it was acquired by the German Bayer AG in 1974. In 2005, it became known as Talecris and, in 2011, was acquired by the Spanish Grifols in what was known as the largest foreign direct investment (FDI) in the pharma industry in the US that year (Grifols 2015; Fernández Pérez, Puig, García-Canal, and Guillén 2017).

Armour and Company built a manufacturing plant in 1943 under a US Navy contract at Fort Worth, Texas and was the largest supplier of albumin to the US Army during World War II. After the war in 1953, they established a new fractionation plant in Kankakee, Illinois. The company was acquired in 1977

by Revlon, by Rorer Pharmaceutical in 1986, and merged with Rhône-Poulenc in 1990.

Baxter, the world's largest manufacturer and distributor of hospital supplies and provider of medical specialty products serving over 5,000 hospitals, was founded in 1931 by two Iowa physicians, Ralph Falk and Donald Baxter. In 1933, they opened a plant in Glenview, Chicago with six employees and sold products through the American Hospital Supply Corporation⁴. During World War II, Baxter provided blood collection products and intravenous solutions to the US Army. In the 1950s, they expanded to Cleveland, Mississippi and, in 1952, acquired Hyland Laboratories of Los Angeles, a firm that had produced freeze-dried plasma during the war. In 1953, they built a large new manufacturing plant in Los Angeles (California) to produce a variety of blood and plasma protein products and, in 1959, acquired both Flint, Eaton and Company and Fenwal Laboratories of Boston. Baxter shares began trading on the New York Stock Exchange in 1961.⁵

Courtland Laboratories was founded in 1947, received a license to produce plasma products in 1950, and manufactured animal albumin based products for Max Factor, Merck Sharpe & Dohme. It was acquired by Abbott Scientific Products (a division of Abbott Laboratories) in 1967 and sold in 1978 to the Japanese Green Cross Corporation which changed the name to Alpha Therapeutic Corporation. The Spanish Grifols signed a joint venture with Alpha Therapeutic Corporation in 1982, which lasted until 1999, and, in 2009, they bought Alpha's assets and established the firm Grifols USA that year (Grifols 2015).

In the early years of the 1950s, plasma fractionation in the United States was a commercial enterprise with very few not-for-profit players (e.g., American Red Cross, Massachusetts Biological Laboratories), whereas in Europe there was an important not-for-profit plasma sector around national Red Cross societies, and a commercial sector. Among the commercial fractionators, the early pioneers in Europe were Behringwerke AG and Biotest in Germany, the Barcelona Blood Service in Spain, Institute Mérieux in France, Berna in Italy, and Kabi in Sweden. In Japan, there was a strong commercial private sector, as in the United States in the 1950s, led by the Green Cross Corporation. Until the 1990s in Australia, when CSL was privatized, and in China until today, public organizations led both in research and in plasma collection and fractionation (Curling, Goss, and Bertolini 2015; Grifols 2015).

In the 1990s and the first decade of the 21st century, pioneers such as the German Behringwerke and the Swiss ZLB had been acquired by the Australian CSL. At roughly the same time, world pioneering leaders of the US, like Cutter

⁴ <www.baxter.com> (July 12th 2018).

⁵ <www.fundinguniverse.com/company-histories/baxter-international-inc-history/>(Accessed July 12th 2018).

and Armour, had been acquired initially by German, Swiss, and Japanese competitors, and finally by the Spanish Grifols.

Grifols was a micro family lab in 1940, almost disappeared in 1965 when Spain prohibited plasma exports, and could have disappeared in the 1980s with the AIDS crisis, which led big leaders, such as the Green Cross Corporation of Japan or Landerlan in Madrid, into decline or collapse.

What competitive factors may help explain is how a small company in a late industrialized country like Spain could have challenged the pioneering leaders in a highly concentrated and knowledge intensive biotech industry like that of the world plasma protein industry? Available literature highlights the organizational and executive capabilities of emerging multinationals from developing economies and the accelerated process of acquisitions and investments abroad in the last decades (Guillén and Garcia-Canal 2009 and 2010), as well as their outward-looking networks (Fernández Pérez and Puig 2007; Fernández Pérez and Rose 2010). This perspective fits well with findings that highlight the role of relations and groups in the development of business opportunities in new industries (Aldrich and Ruef 2006). For this article, these perspectives allow the theoretical interpretation of empirical findings from private archives of the Grifols Corporation. This case study demonstrates that innovative entrepreneurial groups with close personal and professional links among them have been able to create tangible and intangible knowledge, helping the company overcome backwardness and become a world leader in a very specialized, knowledge intensive industry.

3. Challengers in the World Plasma Industry after World War II: Grifols

3.1 From a Partnership with Professional Colleagues to a Family-Based Laboratory 1880-1940s

Since the late 19th century, the Grifols family was a family of scientists. They were open-minded and innovative and, for this reason and despite the backwardness of their country, they maintained friendly networks with scientific colleagues from the foremost labs of leading countries, allowing them the ability to update their knowledge of laboratory analysis. There were three distinctive periods in this process of entrepreneurial networking: a) until World War II with German corporations, b) between the 1940s and the 1980s with North American corporations, and c) from then onwards with Japanese and North American corporations.

Small but technologically updated clinical laboratories were well established in Barcelona by the late 1880s and helped public authorities with the preven-

tion and control of cholera and malaria. Graduates of Medicine and Pharmacy from the University of Barcelona saw an opportunity to improve their lives by joining forces to open new laboratories with the new products and technology of the time (e.g., vaccines, nutritional products, microscopes, analytical proofs and devices). There was not much initial investment; for many, small, empty, rented shops could be the start. José Antonio Grifols y Roig was one of those graduates who, after finishing his degree in Medicine in 1909, studied clinical analysis with the professors at the University of Munich and in German laboratories. In 1909, he opened the Instituto de Análisis Clínicos in Plaza Urquinaona, near Plaza Cataluña, with two colleagues and friends who were doctors or lab specialists (Luis Celis, Ricardo Moragas, and the cooperation of Dr. Gordan, the former director of the Bacteriology Department in Danzig). The three Spanish partners shared technical and managerial responsibilities as well as ownership until 1923. The institute carried out biological research with the latest German technologies, elaborating preventive vaccines against typhoid fever, cholera, Mediterranean fever, and others. Also, the clinical tests of Abderhalden and Wasserman for the diagnosis of illnesses such as syphilis and other venereal diseases became very common in Barcelona at this time for patients entering public and religious hospitals (Grifols 2011; Arxiu Hospital Santa Creu i Sant Pau Llibres Majors and Entry Registers of New Patients 1921 and 1935). Their reputation and prestige was soon consolidated and the increase in clients (i.e., private doctors, hospitals, patients) encouraged them to invest the profits in a larger apartment in Rambla de Cataluña near Provenza Street in 1923. In the years that followed, 30 new clinics and institutes also moved from downtown to the healthier districts of the Eixample, far from the harbor. The success led the three Spanish partners to split and follow individual enterprises. Grifols Roig would be the only owner, director, and technical expert of his new firm, Instituto Central de Análisis Clínicos, Bacteriológicos, y Químicos. Concurrently, he would direct the Histopathology laboratory at the Hospital de Santa Cruz, teach hematology at the Academy of Medical Sciences in Barcelona, and intern in the laboratory of the Faculty of Medicine in Barcelona. The Barcelona House of Ganzer provided him with most of the clinical instruments and most of his clients were doctors who needed a clear diagnosis before recommending treatment to their patients. Grifols employed five doctors and chemists to help him in the technical tasks of the laboratory, four Spaniards and one German (Hellmut H. Hempel). Due to his experience in blood extraction, he started trying blood transfusion in 1925-26.⁶ Grifols would preserve his friendships and scientific cooperations he made with his first partners: Luis Celis Pujol became a full professor of Histology and Pathological Anatomy in the Faculty of Medicine in Barcelona in 1923 and Ricardo Mora-

⁶ Historical Archive Museu Grifols in Barcelona. Hemobanco de Laboratorio Grifols SA, Memoria. Reference 6353; Grifols 2011, 22-3.

gas was the director of the Laboratory of Bacteriology and Serology at the Hospital de Santa Cruz and owned his own private laboratory of analysis.

Since 1928, the activity of blood transfusion, collection, and the manufacturing of plasma derivatives would become increasingly the center of the entrepreneurship and innovation for the Grifols Company. That same year, Grifols presented a new, indirect method of blood transfusion at the Catalan Academy of Medical Sciences. In 1929, he presented new studies about blood groups in the Iberian Peninsula and, in 1933 he presented in the Vilafranca del Penedés Hospital his new device (“flébula”) for safe transfusions of blood, and in that year and 1934 the leading directors of the public hospitals of Barcelona require his services: Pedro Pons in Hospital Clínica; Dr. Ribas in Hospital de San Pablo; Dr. Clara in the Quinta de Salud La Alianza.⁷ Because his team of experienced professionals and his reputation were large, he registered many new incremental innovations to promote his method of indirect transfusion of blood between the late 1920s and 1930s.

The laboratory produced new clinical devices with registered patents, vaccines (against typhus, diarrhea), and nutritional products. German and Spanish experts in clinical analysis and in the production of microbiological products cooperated with Grifols (Dr. Oppenheimer, Dr. Hirsch, Dr. Hempel, Dr. Cantó, and Dr. Cuevas). His two sons, José Antonio (born 1917) and Victor (born 1919) Grifols Lucas grew up in the lab. From the very young age of 17 (José Antonio) and 15 (Victor), their father taught them how to help him perform urine tests, glucose tests, and even the Wasserman test (Grifols 2011, 40). Soon thereafter, the two sons were participating in the routine of the firm and actively engaging in the family’s entrepreneurial endeavors. During the Spanish Civil War, the sons gained pioneering experience working for the Spanish blood bank of Dr. Duran Jordà on the Republican battlefield. Their return home meant a redefinition of the father’s business. The Institute disappeared and a new firm was established in 1940, Laboratorios Grifols S.A., including Grifols Roig and his wife, Magdalena Lucas, as partners. In 1946, Mr. Brasó, a local business angel and friend, would become a financial partner and remain so until his death. Bringing in their experience from the blood bank, Grifols’ sons also participated in the newly expanded and renewed activities of the family lab while continuing their university studies. The family lab manufactured dry plasma, a new original product, which multiplied the output of each blood donation by several times.⁸ An entrepreneurial group based on family ties and

⁷ Historical Archive Museu Grifols in Barcelona. Hemobanco de Laboratorio Grifols SA, Memoria. Reference 6353. The flébula Device included three patented components: a needle, a glass container, and the container cover.

⁸ Archivo de Protocolos de Barcelona. Not. D. Cruz Usatore y Gracia. Copia de la Constitución de la Sociedad Laboratorios Grifols SA ante el que fue Notario de esta Ciudad Dn Jose Faura Boras en 18 de noviembre de 1940. Historical Archive Museu Grifols in Barcelona. Escrituras. Reference 59763.

friendship was born, reducing potential unaffordable expenses they could have had to face if they would have had to hire or partner external high qualified professionals in the hard times of post-civil war Spain.

In 1944, the good expectations of growth achieved with sacrifice, excellence, and trust, made the small family based entrepreneurial group move to a new large building. The change made it possible to divide activities strictly (e.g., vaccines, analysis, rabbit testing) and to maintain the administrative office in the apartment of las Ramblas. Grifols registered several patents with the support of a collaborator, Walter Oppenheimer, and his sons: after the instrument for indirect transfusion in 1928 and 1929, a process to dry plasma in 1943, a table to register blood groups in 1949, the brand “Banco de Sangre y Plasma” in 1950, and several products that improve the extraction and fractionation of blood in patents in 1957, 1961, 1964, 1965, and 1966.⁹

Grifols then decided to open the first civil blood bank in Spain in 1945, the Hemobanco.¹⁰ To maintain the reputation of the lab, the father decided that he would be only the manager of Laboratorios Grifols S.A. and that his son, José Antonio, would be the only manager at the new blood bank. From 1945 until 1960, the blood bank performed around 200,000 blood extractions, a volume that made the family decide to reinvest profits from the two family firms into a new plant for blood extraction in Badalona, a city near Barcelona. The experience in blood collection, preservation, storage, and manipulation made the father and sons experiment with dry plasma and with plasma fractionation to obtain and separate proteins with which to produce different plasma derivative products. The method of plasmapheresis was developed and officially presented in 1951 at a scientific congress in Lisbon where Edwin J. Cohn was in attendance. A centrifuge machine was also presented that performed plasmapheresis; it was patented in 1965 and soon used for plasma extraction in Spain and in the United States in the context of the joint alliance and agreements between Grifols and the US Corporation Dade Reagents which led to the foundation of Dade-Grifols.¹¹

The investments moved José Antonio Grifols Roig to expand the capital of the society and include in 1946, as indicated above, a client, businessman, and friend of Grifols, Domingo Brasó, as a new partner. The two young sons also became partners with the father, the mother, and Brasó. The capital of Laboratorios Grifols S.A. expanded in 1946 from 500,000 pesetas to 1,000,000 pese-

⁹ Historical Archive Museu Grifols in Barcelona. Hemobanco de Laboratorio Grifols SA, Memoria. Patentes relacionadas con la actividad del banco de sangre. Reference 6353.

¹⁰ Historical Archive Museu Grifols in Barcelona. Hemobanco de Laboratorio Grifols SA, Memoria. Reference 6353; and Laboratorios Grifols S.A. Banco de Sangre y Plasma. Funcionamiento económico. Reference 03178.

¹¹ Historical Archive Museu Grifols in Barcelona. Hemobanco de Laboratorio Grifols SA, Memoria. Reference 6353.

tas, which allowed for the expansion of the activities.¹² Brasó, and later on his son, would remain enduring shareholders in the business until the early 1990s. The times were very tough in the country's economy with scarcities of the post-civil war making investments and innovation difficult. Grifols was a singular exception of a very small lab developing and investing in innovative activities that had started in the early 1910s. The entrepreneurial attitude of the father was continued by the sons. Victor Grifols travelled to England in 1946, one year after the end of World War II and in the same year as the entrance of the new partner into the family firm, to explore new products and potential alliances with British subsidiaries in the UK of North American corporations like British Hayden to jointly produce penicillin in Spain. On that same trip, Victor Grifols visited the Royal Society of Pharmacy, distinguished Spanish doctors in the exile (e.g., Trueta and Gabarró, Duran y Jordà), and British houses producing medical instruments and products like Burroughs Welcome and Co.¹³

3.2 The Alliances with North American Corporations and the Role of Friendship Ties in the Enduring Cultural Management of the Alliances, 1950s-1970s

Friendship with the owner of a pharmacy in Barcelona, Ricardo Roca de Viñals, who was a distributor in Spain of the North American company Dade Reagents from Miami, Florida, fostered conversations in the 1950s about exporting Grifols serums to the United States in exchange for imports of reagents and other products for the Grifols and the Roca de Viñals firms. Rigid intervention in foreign payments and currency in Spain before 1959 made both confidential agreements based on trust and trustable networks necessary to begin the first monthly exports of Grifols plasma derived products to Dade Reagents in the United States during 1957 and 1958.¹⁴ The importance of this foreign trade lay more on the qualitative side than in the quantitative value; the relevant issues for the Spanish firms were to keep in touch with the most updated clinical analysis technology that was in the United States as of the 1950s and to learn how to establish a win-win alliance with a leading partner of that country. These early contacts provided knowledge about how a small lab should undertake international activities. This led to further agreements with Dade Reagents and American Hospital Supply Corp, two leading manufacturers and distribu-

¹² Historical Archive Grifols in Sant Cugat. Escrituras. Escritura 1.109, de aumento de capital, 9 de mayo de 1946.

¹³ Historical Archive Museu Grifols in Barcelona. Memoria sobre el viaje a Inglaterra realizado por Victor Grifols del 12 de julio a 22 de agosto de 1946. Reference 05898.

¹⁴ Historical Archive Museu Grifols in Barcelona. Letter of J.M. Potts Vice-President of Dade Reagents Inc. to J.A. Grifols-Lucas Hemobanco, 8 January 1958; and Confidential Letters Grifols/Dade Reagents 1957-59. References 2331, 2354, 2357, 02978.

tors of hospital supply equipment, in 1961, when the joint venture Dade Grifols was established (Fernández Pérez, Puig, García-Canal, and Guillén 2017).

In a long six-page letter addressed to Joe Potts of Dade Reagents Inc. and signed by Victor Grifols Lucas on the 29th of March, 1969, Grifols explained that, in 1965, the Barcelona company Hubber (founded in 1951 by Felix Gallardo Carrera who had been in the last ten years the most important local client of the plasma produced by Grifols) started investments to vertically integrate the production of plasma in their own factory, reducing the quantity of plasma bought to Grifols by half and formally pressing the Ministry of Health in Spain to forbid plasma exports. Grifols felt this was a threat. He shared with Potts his concern that this could be a strategy of Hubber to integrate the industry in Barcelona and get rid of Grifols by collapsing them in the domestic market (half of the sales in Spain went to Hubber in the early 1960s and, due to Hubber's size, they could not be easily substituted by an alternative client absorbing stocks of plasma in Spain) and in the international markets (where more than half of the Grifols' total sales went, a sign of their competitive entry into the tough and sensible health care markets of Europe and the US). Grifols had been exporting more than half of their total sales before 1965, the same year that, according to Victor Grifols Lucas' letter:

the Spanish Ministry, doubtlessly influenced by Hubber's complaints published the decree of prohibition of export of plasma ... Hubber S.A. has a great influence in the Dirección General de Sanidad as well as in other regulatory centers of the politics of this country.¹⁵

It may be for this reason, or for others, that Grifols complains in the letter about how they had problems with their main Spanish client in 1969, how they were accumulating blood and stocks due to the governance of the blood banks (regular paid donations and regular tests on the Health of donors), how they could not export their surplus from their network of blood banks due to the ban on blood exports of the government of 1965, and how they had losses and had to increase the holidays of their employees at the blood bank to reduce stocks and losses.

Grifols could have right then withdrawn from the business but instead decided a counter-cyclical strategy: they would enter the business of their main local competitor, Hubber, and manufacture plasma derivatives, they would integrate vertically forward, and they would invest in a US style factory that could produce FDA products authorized to be sold in the US in the future. The plans were indeed visionary, particularly in times of declining sales and burdensome regulatory problems. They involved convincing US partners to enter with them into a joint venture to help them grow in scale and scope and internationalize products of higher added value in the blood industries. The dream

¹⁵ Historical Archive Museu Grifols. Letter of Victor Grifols to Joe Potts of Dade Reagents Inc. 29 March 1969, p. 2. Reference 869.

was expensive, but the Grifols family signaled they would be open to sharing ownership, and management, with the big Corporation that had recently bought Dade Reagents in the US: American Hospital Supply Corporation. They signed a joint venture with them in 1961 which would lead to the construction of the new modern US style factory of Parets del Vallés in the late 1960s, one of the leading factories in the world today in the plasma industry.

Dade Reagents Inc. (DR) of Miami, Florida was a relatively medium-sized corporation that was very innovative in the United States. It had been founded in 1949 by John Elliott, a military officer and scientist who had participated in the creation of one of the first North American blood banks (the Dade County Blood Bank) during World War II. DR produced blood serums and solutions and their exclusive distributor in the United States in the 1950s was American Hospital Supply (AHS). When Elliott suddenly died in 1955, AHS's CEO, Foster G. Mc Gaw, made a formal proposal to merge with Elliott's widow and heirs and, on the first of July, 1956, DR became a subsidiary of AHS Corporation at a purchase price of 90,000 dollars.

Grifols' contact with DR, and subsequently with AHS, was made possible, as we mentioned above, thanks to Ricardo Roca de Vinyals, a well-known pharmacist from Barcelona acquainted with the Grifols family and a distributor of DR products. Roca de Vinyals was also acquainted with the representative of DR in pre-revolutionary Cuba, Dr. Guillermo Anido, who was well connected with the Cuban Institute of Tropical Diseases and the La Habana Faculty of Medicine, where he and his brother had been very actively innovating in the fields of clinical analysis and lab quality control in labs. In 1957, Roca de Vinyals offered to help connect Grifols with DR to obtain reagents and then mediated to help Grifols import reagents and solutions directly from DR. During 1958 and 1959, a continuous flow of imports, and some exports, was reported in letters and confidential invoices preserved in the Grifols archive. Problems in handling, storing, sending, and maintaining the small glass containers with blood derivative products in their long journey with Iberia airlines from Spain to Switzerland and then to the United States had to be solved and constituted very valuable training for the future.

Many difficulties arose from the loss of their most important client (Laboratorios Hubber, which decided to produce its own plasma) and the deflationary Plan de Estabilización designed by the government. In addition, there were concerns that the Franco authorities could block the commercial interaction and payments at any time because foreign currency was scarce. But the relationship with DR went ahead and a joint venture, Dade Grifols, was forged in 1960. The partners on the Spanish side of the agreement were the Grifols, Braso, and Dr. Roca de Vinyals, who died shortly before signing the notarized documents of the new firm.

In 1961, Víctor Grifols Lucas travelled for the first time to Miami and stayed for several months. There he met the Cuban Dr. Anido, who had been

distributing DR products in Cuba before the revolution. With his contacts, he was able to negotiate with the new owners (AHS) to get a job in Dade County when he arrived in 1961, after escaping from purges among the staff of clinical centers and medical faculties in Cuba. He was hired as medical manager of the corporation and as manager in charge of organizing international clinical quality control conferences with other big corporations in the United States and in Switzerland. These conferences were frequently attended by owners and managers such as Grifols. Grifols Lucas and Anido met in Miami at a very difficult time in the life of Anido and became friends and colleagues until the end of the twentieth century.

This friendship became extremely important in the history of Grifols in subsequent decades. Anido and other Cuban technical managers in AHS served as hybrid bridges for the Grifols firms, transferring know-how, in a more affordable way, about the standards of the Food and Drug Administration for registering patents and products in the United States, about how to deal with the US corporation, and about who was who for potential future partnerships and collaborations in the global plasma and hospital equipment industries.

The association with DR and the new joint venture Dade Grifols facilitated not only regular imports of much-needed reagents, solutions, and hospital and clinical supplies, but also the beginning of regular exports of plasma products from the Grifols blood bank and Laboratorios Grifols to the United States and Sweden up until the late 1960s. Between 1961 and 1966, exports represented more than half the total sales of the Grifols firms; however, the good times ended abruptly due to a regulatory change. In 1965, a Spanish law prohibited the export of human blood products and Grifols exports to the United States and Europe gradually declined and inevitably disappeared after 1968 – the prohibition lasted until the end of Francoism in 1975.

The 1956 alliance with the owner of DR (AHS) served to keep Grifols' expansion going. It sold a huge variety of hospital supply equipment from most of the North American manufacturers involved in the industry and was expanding beyond the United States in the late 1960s, changing its organization into that of a large professional corporation, integrating backwards, launching its own production and factories, and planning its own internationalization. In this context, AHS fully acquired the Grifols shares formerly owned by its subsidiary in 1968 and more visibly and directly became the lab's US partner, increasing the number of exclusive products distributed through Grifols among the growing number of Spanish hospitals.

It is important to keep in mind that AHS was founded in 1921 by an experienced salesman, Foster G. Mc Gaw, and a business angel from the construction sector, Harry L. Drake, to create and connect the previously fragmented market of the hospital supply business in the United States. They offered their commercial services to hundreds of small manufacturers dispersed throughout the country, offering to sell their products – on commission – to distant hospitals

that were sprinkled across the United States. They began production only in the 1960s, with backward vertical integration, and were tremendously innovative in the organization and training of their salesforce and their technical staff thanks to the leadership, experience, and organizational ideas of McGaw (Sturdivant 1970).

AHS had plenty to sell and to teach to the small yet ambitious Grifols lab. The abundance of products sent to Dade Grifols, particularly cardiovascular products and a diversity of supplies for hospital needs, required the Grifols staff to learn many new procedures (e.g., how to keep track of the movement of products in storage, how to maintain the products, how to write the invoices in a standardized way, how to train the sales staff, how to deal with staff in hospitals, how to handle logistics in the transportation and storage of products to reduce losses). The few preserved records of sales of AHS products through Dade Grifols reveal that, in the 1970s, sales and profits from Dade Grifols in some years represented up to ten times those obtained in the other firms in the Grifols network (i.e., the blood bank, Gri-Cel - a producer of lab instruments, Laboratorios Grifols).

The growth in sales and staff was so successful that it necessitated a new building outside the city of Barcelona, big enough to organize Grifols' large-scale production and commercialization. The factory in Parets del Vallès was launched in 1972 by CEO Víctor Grifols Lucas. Land was bought in 1966 for this purpose and authorizations were obtained. The factory was completed in 1970 and began operating with all the necessary licenses in 1972. It had been designed to closely follow North American standards of quality control in production, under the supervision and in close coordination with AHS's technical staff. Víctor Grifols Lucas, from the third generation of the Grifols family, and his son Víctor Grifols Roura, from the fourth generation, worked together to learn how a modern factory in the biopharmaceutical industries was built. More professional routines in accountancy were adopted, computers were introduced, and human resources began to be more efficiently organized. In Dade Grifols, women with degrees in Chemistry and Pharmacy occupied top managerial and technical positions.

There were not many competitors in the Grifols' niche market – Laboratorios Hubber, Laboratorios Leti, Landerlan, Llorente, and the Spanish subsidiaries of the German Behringwerke and the US Baxter were the most important ones—but all of them were expanding fast as they also perceived the same opportunities for growth.

3.3 New International Alliances, Organizational Challenges, and Generational Change, 1970s-1990s

Therefore, besides innovation in production, the young Víctor Grifols Roura, when he joined the company in 1973, took it upon himself to dramatically

improve the informal personalistic routines of the previous generation of commercial managers. Antonio Ruiz, who had been in the company managing the commercial and administrative functions of the lab in close connection with the Grifols owners since 1951, retired and died in the early 1980s and Grifols Roura took over these responsibilities with new energy.

He was able to create a new generation of commercial agents with whom he put together a team in charge of developing a sales network in Spain. For this, he employed the sales representatives as salaried staff and started organizing general meetings in 1981 to homogenize sales strategies. Coinciding with the radical organizational shift that took place after 1982, the firm Movaco was created to organize and create commercial offices with salaried employees devoted exclusively to Grifols products in different Spanish provinces – Valencia, Seville, Madrid, Barcelona, Bilbao, and A Coruña. Movaco was established at the same time as the Grifols Group holding was formed (1987) and its purpose was to overcome past inefficiencies in the coordination of sales and production, to organize the professional training of the sales workforce, and to increase efficiency in selling the diversity of exclusive products from their North American suppliers to Spanish hospitals.

The context changed in the country and the company after 1975 with the transition from dictatorship to democracy that came after Franco's demise and with the rapid integration of the country into European institutions and markets after 1986. Formerly scarce strategic resources now could be more easily introduced into the country and the lab transforming the company into a global corporation. Víctor Grifols Roura, from the fourth Grifols generation, joined the company and, following the family traditions of strategic alliances with leaders in their field, sealed a new alliance with Alpha Therapeutic Corporation (ATC), the North American subsidiary of the Japanese global Green Cross Corporation. After 1975, and particularly after 1982, mass production techniques, global channels of distribution, long-term capital invested by foreign banks and investors, and professional managers in business administration were introduced very rapidly. It was indeed a Chandlerian revolution, with dramatic changes taking place in three areas: improvement and increase of the production capacity following the US Food and Drug Administration's standards; organization of the sales force at home and foreign direct investments abroad; and the creation of the Grifols Group, a formal business group managed by a team of Spanish, North American, and Japanese professionals in business administration who shared top managerial responsibilities in the coordination of investments, production, and sales with a global perspective.

In management, three changes took place one after the other between 1975 and 1985 that made the previous growth in scale and scope in production and distribution possible: (i) the reorganization of the sales departments; (ii) the improved organization of internationalization; (iii) and the creation of a formal business group with functional divisions and business lines (e.g., hospitals,

solutions, diagnostics). All three changes took place during a time that is conflictual in most family businesses; a period of generational transition. The founder of Laboratorios Grifols, José Antonio Grifols Roig, died in 1976, three years after his grandson, Víctor Grifols Roura, of the fourth generation, had joined the company in the sales department, and only four years after the opening of the new US-style factory in Parets del Vallès in 1972. The emotional attachment to the family business and the shared long-term values focused on seriousness and professionalism in a very special business sector help explain the peaceful and very positive coexistence of the third (Víctor Grifols Lucas) and fourth (Víctor Grifols Roura) generations of the Grifols family in the top management, representing half of the shares owned in the different joint ventures with North American and Japanese partners.

Concurrently, there was a substantial shift and tensions among the managers on the board representing the North American shareholders in the Grifols firms. AHS – through its subsidiary DR and later alone – was on the managing board of Dade Grifols, Gri-Cel, and Laboratorios Grifols from 1960 until 1976. With AHS suffering the impact of powerful competitors at home and the negative effects of the late-1970s crisis on sales, it decided to sell its 50 percent of the shares in Laboratorios Grifols. AHS invited Grifols to choose the company it would sell its shares to in order to avoid damaging its interests. Dr. Guillermo Anido's advice was important in this regard; he suggested the name of ATC, a North American subsidiary of the Japanese Green Cross Corporation and a global player in the blood industries. In a later interview, the Japanese CEO indicated that they liked doing business with the small Spanish lab because it had a long-term conservative attitude, typical of a family business, and they preferred a partner like this over an aggressive short-term dividend-oriented North American or Western European company.

The Grifols accepted the suggestion from their Cuban colleague – with whom they would maintain a long-term friendship despite the termination of the joint venture with AHS – and signed a commercial and technical cooperation agreement with ATC in 1982, placing managers from ATC on the managing board. AHS still retained half of the shares in the Dade Grifols joint venture. However, just three years later, in 1985, Baxter Travenol, a traditional competitor of AHS in the United States, suddenly bought AHS and the 50 percent shares it had in Dade Grifols. This was considered a threat to the interests of Grifols' future expansion in global markets and in Spain. The Spanish shareholders of Dade Grifols decided to sell their 50 percent to Baxter, abandon their flagship company that had generated such huge profits in the 1960s and 1970s, and concentrate on their new partner and a new generation of managers in control of the future of Laboratorios Grifols. The holding company Grupo Grifols was created in 1987 with the remaining firms and new firms (e.g., Laboratorios Grifols, Movaco, Instituto Grifols, Diagnostic Grifols, Logister). ATC turned out to be a great “business school” during their partner-

ship (1982-1999), teaching Grifols how to become a global leader and to initiate exports and acquisitions on a large scale.

In 1958 and 1959, the Spanish lab had exported plasma to the United States and Switzerland, but in quite reduced amounts and of limited value. Between 1960 and 1966, exports to the United States continued, and small quantities were also sent to Sweden and Germany, until the Spanish government's 1965 prohibition on exporting human blood products. The prohibition was lifted in the early 1970s and in 1974 Víctor Grifols Roura, who had just joined the company as the first member of the fourth generation with managerial responsibilities, met a commercial agent with whom agreements to export products to the then Portuguese Angola were signed. Angola became independent soon after and some limited exports were sent to Denmark. The partnership with ATC represented a radical change in the company's international department. Victor Grifols Lucas and his son, Víctor Grifols Roura, travelled to China in 1983, the first year of the partnership, to start exports in a country where they had no idea how to do business. The Green Cross Corporation, owner of ATC, asked Grifols to export their plasma products together with Grifols' own products to China; at that time, Japanese blood products were forbidden in China. From 1983 to 1985, the Grifols entrepreneurs learned how difficult it was to find even a secretary through the embassy that could start the paperwork that would allow them to establish a commercial representative and to export to China. Due to this, they experienced great organizational difficulties of every kind. After 1982, when news of the AIDS epidemic started to spread and the Food and Drug Administration began recommending heating blood stocks, China soon increased controls and reduced, later stopping, imports.

Grifols became the leader in the supply of key plasma proteins for the Spanish market in the 1980s. In 1989, the name of the joint venture was established as Alpha Grifols. ATC is also very significant for understanding two key elements of the 1980s and 1990s (the relationship ended in 1999):

the fast speed of the joint venture's acquisitions and foreign direct investment; and its privileged contacts with foreign banks that provided huge amounts of external capital with which to finance international expansion and modernization in production, distribution, and the managerial professionalization of the group. (Garcia-Ruiz and Fernandez-Perez 2017, 74)

As the statistical information indicates, it was during the joint venture with ATC that three new focuses were added to the Grifols Group's previous trajectory: (i) long-term capital endowment from outside sources; (ii) huge investments in Europe, America, and Asia; and (iii) a rapid decline in the percentage of sales represented by the Spanish market in the structure of the group's total sales.

New premises, companies, and acquisitions evolved as follows: Portugal (1988), Argentina (1991), Mexico (1993), Germany/Italy/United Kingdom (1997), Brazil (1998), and Slovakia/France (1999). In 1999, ATC and Grifols

ended their joint venture due to a combination of problems related to a broader crisis affecting the Green Cross Corporation in Japan, and its subsidiaries in Europe, and to disagreements about how to manage the uncertainty of the first years of the AIDS epidemic in the industry (from a technical point of view). After their friendly separation, Grifols felt strong enough and with enough resources and know-how to go it alone and invested in subsidiaries in the United States (ATC's factory) and Malaysia (2003), in Poland (2004), once more in the United States (2006), in representative offices in Japan (2006) and in China (2007), and in more subsidiaries in Switzerland (2009) and in Colombia and Nordic countries (2010). In 2011, they acquired Talecris in the United States for around 3 billion US dollars, which was followed in 2014 with assets from Novartis Diagnostics and in 2015 by the purchase of 45 percent of Alkahest, both also in the United States. In recent years, beyond the United States (acquisition of assets of Hologic in 2017), Grifols has increased its presence in Canada and Ireland.¹⁶

Information from the corporation reveals that long-term sources of external capital played an increasingly relevant role in financing, innovations and patents, and acquisitions abroad. Internal resources became insufficient and syndicated bank loans, with a combination of local and foreign banks, made their appearance. After 2006, when Grifols was listed in the Spanish stock market, more dispersed investors contributed external capital to the group from all over the world.

The partnership with ATC ended in 1999, but the Spanish financial and commercial departments of Grifols had by then learned how to operate as a global corporation. During the first 15 years of the twenty-first century, staff graduated in business and economics in local institutions received fast practical training in how to export worldwide, how to operate with European and North American corporations, and how to obtain licenses in the toughest pharmaceutical markets of the world where the highest return on investments could be obtained. The accumulation of lessons and resources among Grifols' human capital also meant a capacity to deal with global sources of financing for internationalization, right during the years when deregulation and the globalization of finances offered many opportunities for global investment and funding (García Ruiz and Fernández Pérez forthcoming). Grifols had enough strength to take advantage of the new abundance of opportunities to access capital and to invest in tough markets, and it did so initially in the biotech industry in Western Europe and the United States and later in Asia.

¹⁶ Detail of acquisitions and financial information kindly provided by Nuria Pascual, from Grifols, by email to author 09/07/2017.

4. Conclusions

Biomedical industries seem to be a business of large Chandlerian corporations run by professional scientists and managers who take decisions based not on personal relationships but on market rationale and scientific organization methods. The plasma industry shows that, throughout more than half a century, the foundations of the industry had to do with trust-based personal and professional relationships between entrepreneurial owners and managers of small and large firms of very diverse business cultures. Long-term decisions to establish expensive acquisitions and investments, alliances, or risky new scientific projects were taken by a closely related group of people. Therefore, in this industry one could perfectly demonstrate the efficiency of collective entrepreneurship. The reduction of risks in a very sensitive health care industry may have played a role in the sustained relevance of entrepreneurial trust-based cooperation between Spaniards, Germans, North Americans, and the Japanese. But sharing similar long-term trust in family-based companies did also play a role. The different owners and managers involved in this story believed in similar values: reputation, safety, long-term investments, long-term results, trust, and reliability.

This article analyzes the story of the Grifols business in Spain to show that problems of a small size, lack of institutional support, competition or scarcity of financial resources were problems that could be overcome not only through specialization in market niches, but also, and that is the contribution of this article, through enduring and resilient trust-based personal and professional relationships in a very specialized science-based industry.

The opportunity to supply specialized products in Spain after the 1960s required new resources: technology, organizational know-how, and capital. These resources were sought after by leading corporations in the United States. In the 1950s, entry barriers for small labs trying to establish commercial ties with big North American corporations were high. Friendship with a Spanish colleague who had ties with a prestigious Cuban doctor helped. The Cuban Guillermo Anido, exiled to Miami in the 1960s, started working in two innovative North American corporations of the health care industries: Dade Reagents and American Hospital Supply Co. Anido's friendship with Grifols could help a North American corporation enter into the expanding Spanish market of hospital equipment of the 1960s and 1970s. At the same time, Anido's background in the quality control of laboratories in Cuba and his reputation in Miami's corporations was a channel through which Grifols benefitted to improve internal processes and accelerate their internationalization horizons.

Internal and external threats suffered in the 1970s transformed the internal composition of the Grifols entrepreneurial group in the years to come. The death of the founder of the lab, generational transition, changes in the top management, more powerful competitors in Spain and in the United States,

and the decision of the US partner to leave the partnership posed obstacles and initiated change. This time of transition was considerably smoothed by seeking new partners and new members of the entrepreneurial group, again with the intervention of their friend Dr. Guillermo Anido. The Cuban doctor recommended that the Spaniards accept Alpha Therapeutic Corporation as their new partners. ATC was the subsidiary in the United States of the Japanese Green Cross Corporation. It was a giant in the industry with up to 50 times the production capacity of Grifols. It meant a globalization of the entrepreneurial group's projects and corporations. The new Japanese partners declared later that they decided to seal an alliance with the small Spanish firm because they were a family firm seeking long-term goals and quality, values shared by the Japanese firm. Personal friendship with the Japanese managers started and remained for decades. Friendships also endured with the Cuban Dr. Anido until his death, with the son of their 1946 local business angel Brasó, and the widow and relatives of their friend Roca Vinyals who had provided the link with Dr. Anido. Loyalty to their partners ensured trust, stability, a long-term approach to the business, and a stable distribution of dividends to all throughout the decades. *Collective entrepreneurship paid off.*

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