When a Dream Comes True

An Illustrated History of 75 Years of Grifols

GRIFOLS

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“To revere the past is
to ennoble the present and to think of the future.”

Santiago Ramón y Cajal,
Nobel Laureate in Medicine, 1906

This book is dedicated to a number of different groups. Firstly, to all those employees who, over the years, have been at the forefront of the company's activities. It is their contribution that enables Grifols to manufacture the safe, high-quality medicines and health products that are used to save human lives on a daily basis.

Secondly, to those people who have expressed their solidarity with their fellow human beings by generously donating their plasma to improve the quality of life of others.

Thirdly, to the millions of patients whose health and well-being are the reason why this company exists.

And finally, to the health professionals with whom Grifols continues to work hand in hand to improve the quality of health care. It is a relationship that we hope to carry forward into the future.

Contents

Industrial Growth and International Expansion

A Company for People

Prologue

Fifteen years have passed since we decided to publish *A Passion for Life*, the book that told the story of the company's origins and that ended in 1982, when Grifols formed its partnership with Alpha Therapeutic Corporation. Since then, the company has experienced dramatic growth, driven primarily by the internationalization of its business. The group's present size can only be understood in the context of the company's recent past: the final decades of the twentieth century and the first decade of the twenty-first century, during which it has been transformed from a family firm into a multinational company. And this is why we have decided that the time is right to look back over the past and record our history in a single volume that celebrates the seventy-fifth anniversary of Grifols.

This journey covers two of the most significant events in the company's history. The first was the association with Alpha Therapeutic Corporation, a partnership that enabled us to become serious players in plasma derivatives. And the second was the successful stock market launch in 2006, which provided the platform for growth that culminated in 2011 with the acquisition of Talecris Biotherapeutics, a company that was actually slightly larger than our own at the time. This operation made Grifols the world's third largest producer of plasma derivatives.

Over the last twenty years, Grifols has grown with the vision of becoming a global company. The fact that over half of our employees are now based in the United States is proof that this goal has been achieved. In this book, which I am honored to present, we revisit some of the most significant episodes in this transformation, and in doing so, pay homage to the wishes of my father, Dr. Víctor Grífols Lucas, to leave a written record of our history. It is a history with a fixed objective: to save and improve the quality of life of people suffering from rare or chronic diseases, through the use of our plasma-derived products.

While the previous book was primarily the chronicle of a family that had created a business out of its passion for research and its commitment to the quality and safety of its products, this new publication also tells the tale of how this family business transformed itself into a multinational corporation. It illustrates how a family business in which 50 percent of

the shares had been owned by U.S. companies (from whom we learned a great deal) became a multinational that maintains its legacy and its identity: the "Grifols spirit", consisting in a job well done, effort, commitment, and innovation, the demand for quality, and the search for innovative solutions that help improve people's health.

The transformation of the company has affected every sphere of its activity, including organization, manufacturing, research and development, sales, and communications. Sometimes these changes have followed a careful plan, but on other occasions circumstances have required us to take rapid decisions to respond to sudden threats or to seize the opportunities of the moment. However, our decisions have always been supported by all of our employees; a commitment that has been essential to their success.

It would of course be impossible to recount every detail of our history, and we have therefore chosen to focus on those whose significance has been confirmed by the passage of time, leaving aside the recent, but no less important, acquisition of the Novartis Transfusional Diagnostics Unit. The appearance of AIDS, the creation of the holding company, the opening of various international subsidiaries, obtaining FDA licenses, and the changes in the shareholders of the company are just some of the events described here. This account draws both on the company's documentary archives and on interviews with key protagonists, who have provided a first-person perspective on events.

Before you read this history, I think it is only fair to recognize that, on some occasions, luck has made a major contribution to the achievement of our goals. However, I would also like to point out that, whenever this fickle friend has crossed our path, he has found us hard at work.

To write history is to record the events of yesterday so that we can read about them tomorrow. It is our aim to continue to make our own history and to record it as each day goes by.

Víctor Grífols Roura
President and CEO
Grifols

Barcelona, January 2015

Introduction

No history is irrelevant; the past is shared by all. We go to it for understanding and guidance. It can be instructive or reassuring.

George Santayana, the Spanish-American philosopher, said that those who do not remember history are condemned to repeat it. But history also can suggest examples and patterns worthy of extension.

When the history being reviewed is that of a modern business enterprise, and the business itself has done the recording, one might presume outcomes. Yet, autobiographies of hardly disinterested historical figures—think of Augustine, Jefferson, Neruda and on and on—reveal them and inform us as no other documents could. There is much to be gained from a business biography, especially when every instinct has been toward candor and accuracy.

In contemporary business literature, there are frequent references to some characteristics shared by truly outstanding companies. These organizations are built to be sustainable, they develop ideas internally and are imitated by others, they have a global mindset and make some attempt to change the world for the better; and they are led by entrepreneurs who have a history and involvement in the company and who make decisions based on long-term goals. A shared business culture, including a philosophy that guides the day-to-day activities of everyone in the company, also is characteristic of those organizations. A priority is placed on customer experience and end-user benefit. All personnel are respected as management equals and are listened to.

Anyone familiar with business senses the extraordinary effort, insight, investment and cooperation required for accomplishing even a few of those aspects of excellence. Too often such aspirations are reduced to a framed inscription on a board room wall rather than exhibited in the everyday behavior of the company.

But in rare instances, one can observe a company whose practices and performance demonstrate that, in some astonishing way, all of those concepts have been carefully planted, consistently nurtured and are flourishing still.

That is the story of Grifols. For the many thousands who have been part of a unique history, *When a Dream Comes True* will evoke a past

upon which they are building the future. For those dependent on life-preserving discoveries and the providers involved, there are new insights. Certainly business readers will find much to ponder. And even a general reader will be surprisingly informed.

It has been said that we are what we repeatedly do; that excellence is not an act but a habit. The Spanish philosopher José Ortega y Gasset wrote, "Excellence means when men and women ask more of themselves than others do." We encounter just such people in the chapters ahead.

Neal Ball
Advisor to Corporations

Origins

Family Origins

From Homeopathic Medicine to Clinical Analysis

The Grifols saga begins with Dr. José Antonio Grífols Morera. He was born in the small town of Vilanova i la Geltrú, just south of Barcelona, in 1857, and was an avid proponent of homeopathic medicine at the end of the nineteenth century and during the first years of the twentieth. A leading member of the Medical Homeopathic

Advertisement for the Central Institute of Clinical Analysis, illustrated by R. Esclasans Batlle. 1925.

José Antonio Grífols Roig in the 1930s.

Portrait of Dr. Luis Celis Pujol, colleague and personal friend of José Antonio Grífols Roig.

Academy of Barcelona, he transmitted his love of medicine to his son, José Antonio Grífols Roig (1885–1976), who completed his medical degree in 1909. Although José Antonio Grífols Roig initially followed his father's path into homeopathic medicine, he soon decided to travel to Germany to further his knowledge of histology and pathological anatomy, specializing in clinical analysis in Munich. Upon his return to Barcelona in 1910, he decided to establish his own laboratory in partnership with some of his fellow graduates, including Dr. Luis Celis. The skills of the young doctors, along with the new techniques they applied, quickly earned the laboratory a good reputation. In 1923 it moved to new premises at 102 Rambla de Catalunya, and changed its name to the Central Institute of Clinical, Bacteriological, and Chemical Analysis.

Dr. Grífols Roig, now the sole head of the institute, also established his family home at the same address. The apartment and the laboratory measured around 5,000 square feet between them, with the balcony being used to rear rabbits and guinea pigs for experiments. Dr. Grífols Roig and his wife, Magdalena Lucas, had three children: María Josefa (b. 1915), José Antonio (b. 1917), and Víctor (b. 1919), all of whom were

At work in the testing lab.

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1 Raising rabbits and guinea pigs on the balcony of the Rambla Catalunya laboratory, for use in analytical tests.

2 Magdalena Lucas, wife of José Antonio Grífols Roig. 1950s.

3 The three Grífols Lucas children in the early 1920s: María Josefa, José Antonio and Víctor.

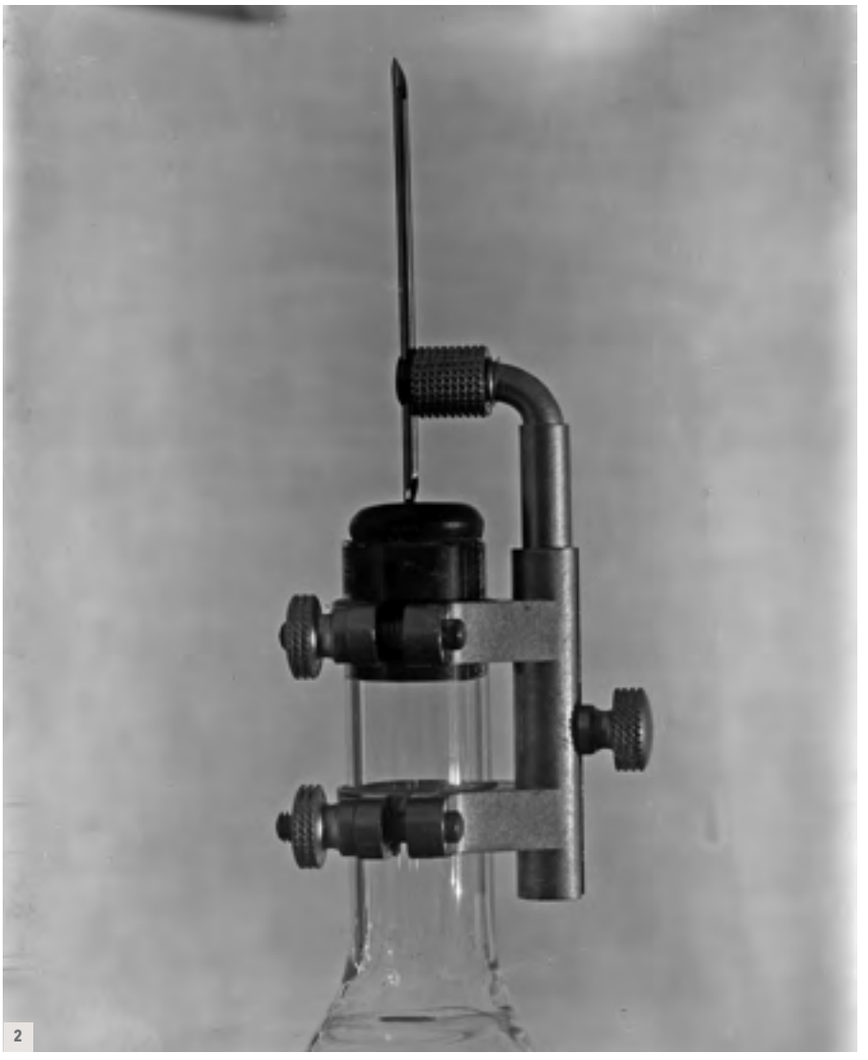
4 Laboratory of the Central Institute of Clinical Analysis in Rambla Catalunya.

imbued with his love of science, and who learned from an early age how to handle the instruments used in the laboratory.

A powerful personality, Dr. Grífols Roig argued during the 1930s for the need to standardize analytical procedures, and to send samples by mail as an alternative to opening laboratories in every town. He was also a prominent figure in two more fields. He published scientific articles in the leading medical journals of his time. Additionally, he disseminated new analytical techniques in his capacity as the director of the histopathology laboratory of the Hospital of the Holy Cross in Barcelona, as a teacher of hematology classes at the Academy of Medical Sciences, and as a visiting specialist at the laboratory of the Faculty of Medicine of Barcelona.

His concern with patient welfare inspired him to personally perform blood extractions, and he also enjoyed talking with patients to gather clues that helped him select which tests to use in each case. His research in the field of blood extraction led him to develop an innovative new device, the transfusion flebula for indirect transfusions, presented at the Royal Academy of Medicine of Barcelona on May 23, 1928. This helped doctors avoid the problems associated with direct transfusion (which required the simultaneous presence of both donor and recipient) by means of a cylindrical glass ampoule with a capacity of between 8 and 20 fluid ounces, tapering at each end to a tubular shape, whose axis formed a 45-degree angle with the axis of the ampoule.

1



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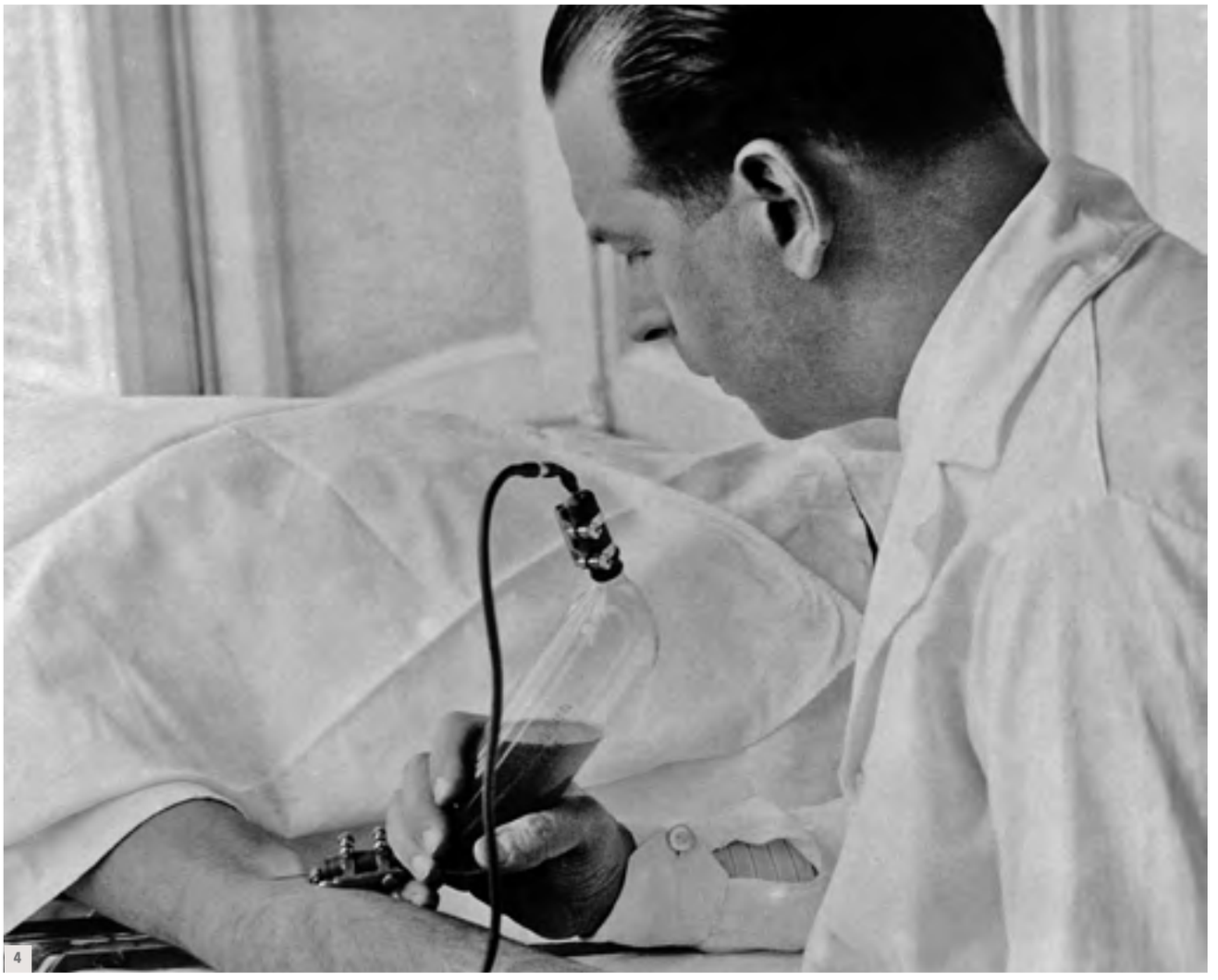
A vacuum was created inside the ampoule so that the donor's blood would automatically be sucked in, where it was combined with sodium citrate to prevent it from clotting.

The "Grifols flebula" was accepted into the Spanish Register of Industrial Property on April 12, 1929, and was patented in Spain, France, Canada, and Germany. However, it was to be many years before the indirect transfusion method proposed by Grífols Roig would find general acceptance. The flebula would eventually inspire another device for the extraction of blood samples, the popular Vacutainer manufactured by Becton Dickinson in the United States many years later.

The Spanish Civil War broke out in 1936, followed by World War II in 1939, with millions dying both on the battlefield and in air raids of towns and cities in which the victims included women, children, and the elderly. The blood banks—and the medical innovations upon which they depended—saved thousands of lives, underlining the



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1 Components of the extraction flebula: glass tube, rubber stopper, needle-holder, and sterile needles in glass tube. 1928.

2 Close-up of transfusion flebula needle. 1929.

3 Preparing the transfusion flebula.

4 José Antonio Grífols Roig injects a blood transfusion using the transfusion flebula.

true importance of Grífols Roig's contribution. Even at this early stage of the family history, the features that would come to characterize Grifols companies could be clearly identified: a concern with patients, a commitment to the discovery and exchange of scientific knowledge through the publication of articles and studies, and the invention and development of new devices.

The Birth of Laboratorios Grifols

The Foundation of Laboratorios Grifols and the Association with Dade

By the time the Spanish Civil War ended in 1939, Dr. José Antonio Grífols Roig was already a highly regarded specialist and a pioneer in blood transfusion and clinical analysis. With his sons, José Antonio and Víctor, he founded Laboratorios Grifols, the successor company to the Central Institute of Clinical Analysis, on November 18, 1940, in Barcelona. The poverty and devastation of war had increased the prevalence of infections among the general population, while the isolation of General Francisco Franco's regime deprived Spain of access to vaccines and other immunological treatments. Faced with this challenge, Dr. Grífols Roig's innovative spirit and his desire to contribute to the public good led him to found the new company, which focused on clinical analysis, the

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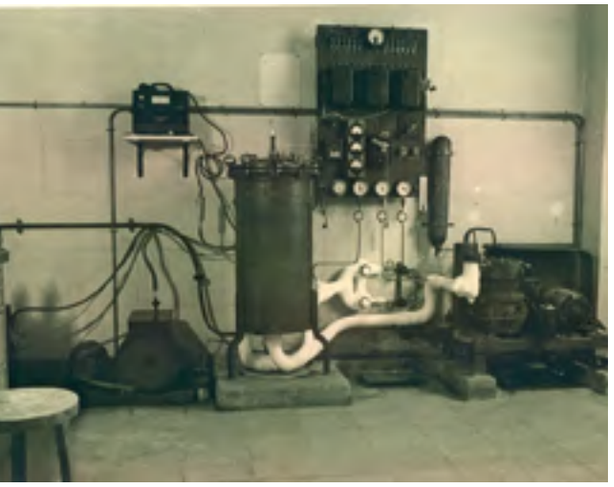


First plasma lyophilizer manufactured by Laboratorios Grifols. 1943.

manufacture of vaccines, and the performance of blood transfusions.

José Antonio and Víctor Grífols Lucas gradually acquired more responsibility within the company after finishing university: José Antonio obtaining a degree in Medicine and Pharmacy, and Víctor graduating in Chemistry and Pharmacy. In their work for the company, they applied the new analytical techniques they had learned about from the many publications they subscribed to. As early as 1935 they had begun to investigate the newly discovered process of lyophilization or freeze-drying, and to apply it to human plasma. This method, also known as sublimation, consists of evaporating the water from a frozen solution and then subjecting it to a vacuum. At the same time, the water vapor has to be captured using a condenser operating at subfreezing temperatures. Industrial applications of the technique were developed in the second half of the 1930s, and made rapid progress during World War II.

Laboratorios Grifols patented the procedure in Spain and developed a lyophilizer, in addition to manufacturing injectable plasma infusion kits. However, the scarcity of materials in 1940s Spain meant that the first lyophilizer prototype, designed by Víctor Grífols Lucas, had to be made using secondhand components, including a vacuum machine from a light bulb factory. The lyophilization procedure was officially patented on June 5, 1943, as a method of "drying plasma, biological liquid serum in general, and simple organisms, while preserving their original properties to the maximum extent."

1 José Antonio Grífols Roig. 1935.

2 Víctor Grífols Lucas. 1935.

3 José Antonio Grífols Lucas. 1935.

3


Laboratorios Grifols, S. A.

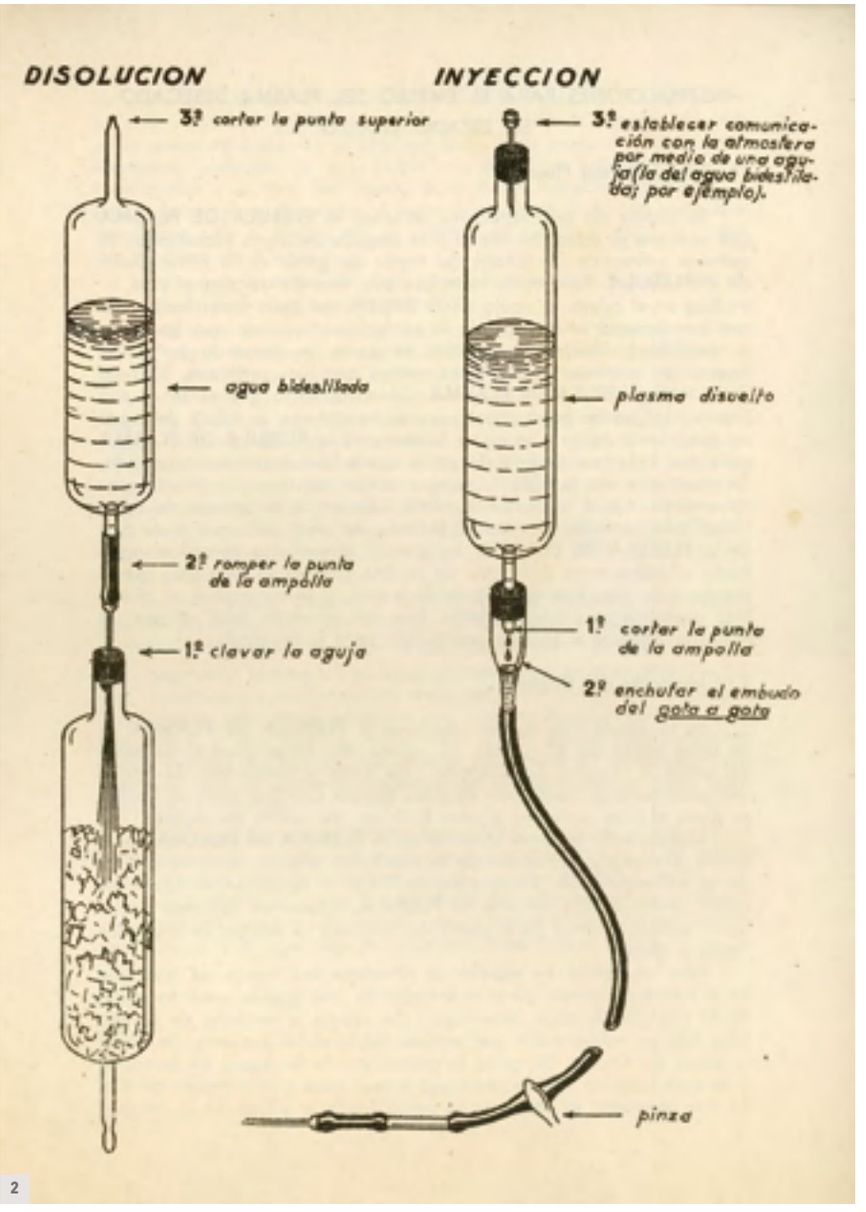
SERVICIO DE PREPARACIÓN
DE
PLASMA HUMANO DESECADO EN ESTADO LIÓFILO
POR EL
Banco de Sangre y Plasma
DE ESTA SOCIEDAD

Dr. Walter Oppenheimer
Dr. José A. Grifols Lucas
Dr. Manuel Ibern Esquerda
Dr. Víctor Grifols Lucas

Características, indicaciones y modo de aplicación de nuestro plasma desecado

BARCELONA

1



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1 Leaflet for the newly created Blood and Plasma Bank. 1944.

2 Reconstitution of lyophilized plasma with injectable water. 1944.

3 Sample of penicillin prepared at Laboratorios Grifols. 1948.

In addition, the company's partnership with the Sociedad General de Farmacia produced the first penicillin in Spain. In 1946, Víctor Grífols traveled to London to study at first hand the work for which Sir Alexander Fleming had received the Nobel Prize for Medicine in 1945. It was shortly after this visit that the first penicillin strains were isolated, and these were combined with sulfonamide to create a new pharmaceutical preparation that went on sale on May 28, 1948, under the name Pentalcilina.

A few years earlier, in 1944, the company had opened new premises at 6 Jesús i Maria street in Barcelona. The size of the new building allowed the testing laboratory to expand its activities, including the manufacturing of vaccines. The ground floor housed the extractions

1

1 José Antonio Grífols Roig and his son Víctor at the analysis laboratory.

2 Main entrance to the laboratory, at Jesús i Maria street, Barcelona. 1944.

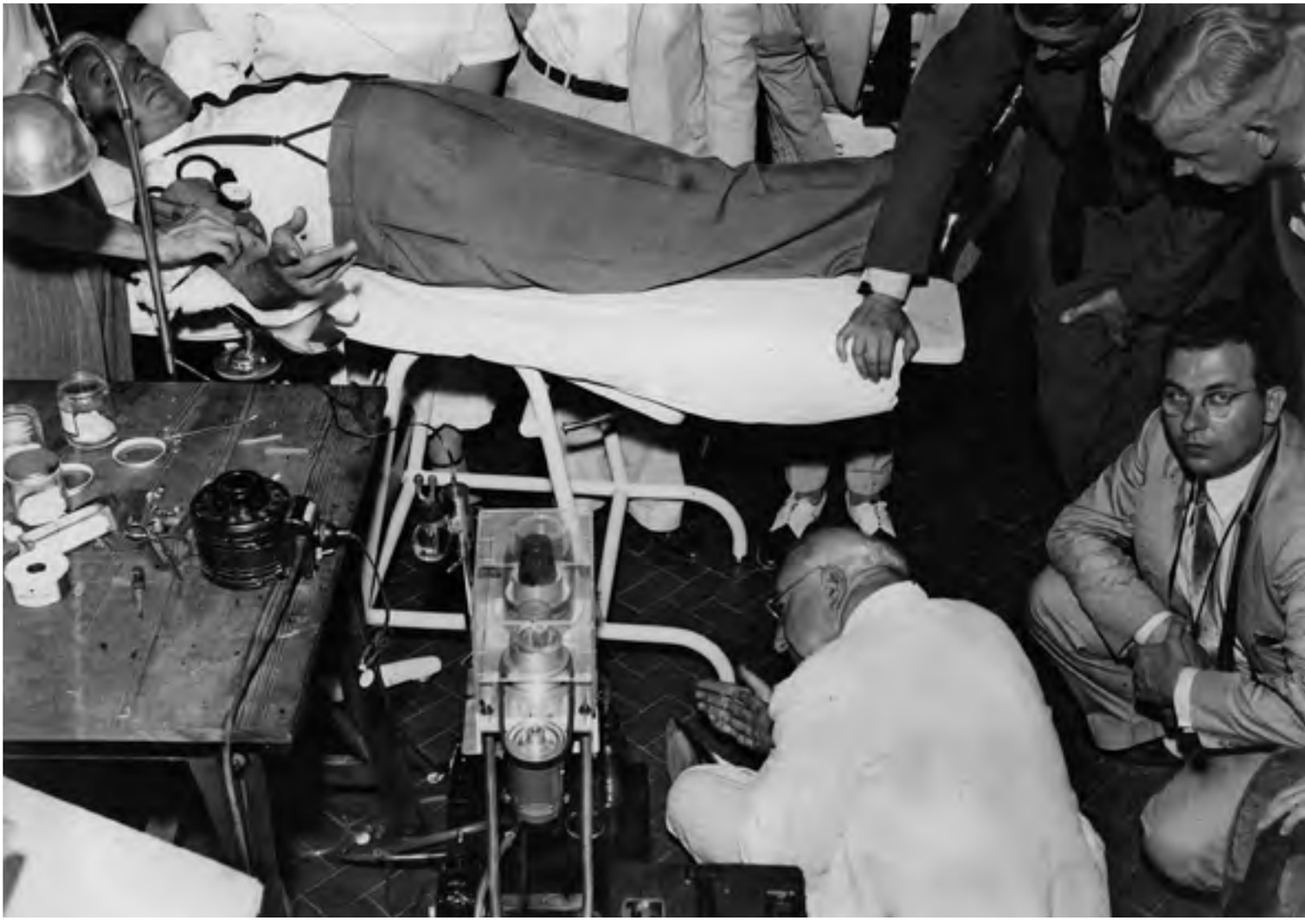
2

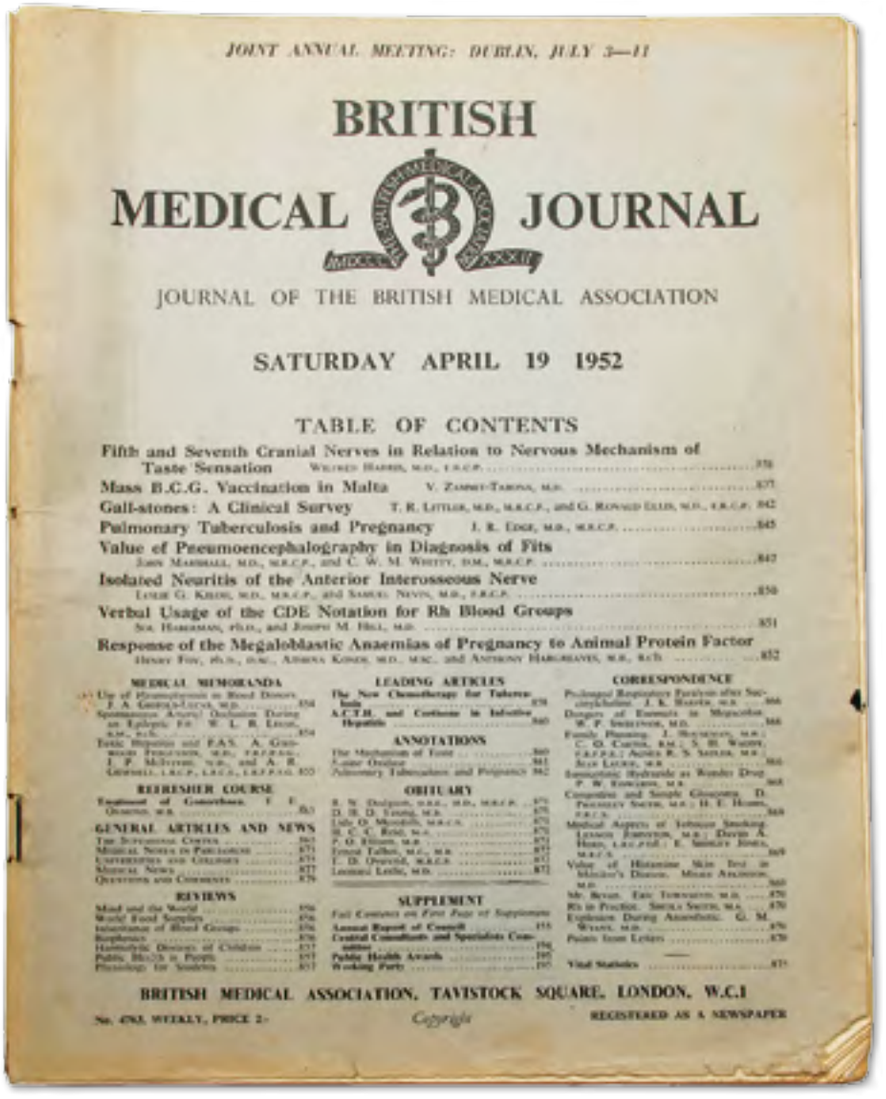
room, along with a waiting room for donors, while the company's administrative offices continued to be based in the apartment on Rambla de Catalunya.

The company's new products helped lay the foundations for the opening of Spain's first private blood and plasma bank in September 1945. The category of potential donors consisted of all those individuals of "proven good health, with good veins, and of fixed abode in Barcelona or a nearby town." In 1951, six years after it had opened, Laboratorios Grifols' blood and plasma bank had 1,300 regular, registered donors.

At the start of 1950, the young Dr. José Antonio Grífols Lucas developed the technique of plasmapheresis, allowing red blood cells to be reinfused into the donor immediately following extraction, based on the earlier research of Abel and Tui. Grífols found that plasmapheresis allowed donors to donate more frequently without compromising their

José Antonio Grífols Lucas and Edwin J. Cohn at the 4th International Blood Transfusion Congress in Lisbon, Portugal. 1951.





JOINT ANNUAL MEETING: DUBLIN, JULY 3—11

BRITISH

MEDICAL JOURNAL

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SATURDAY APRIL 19 1952

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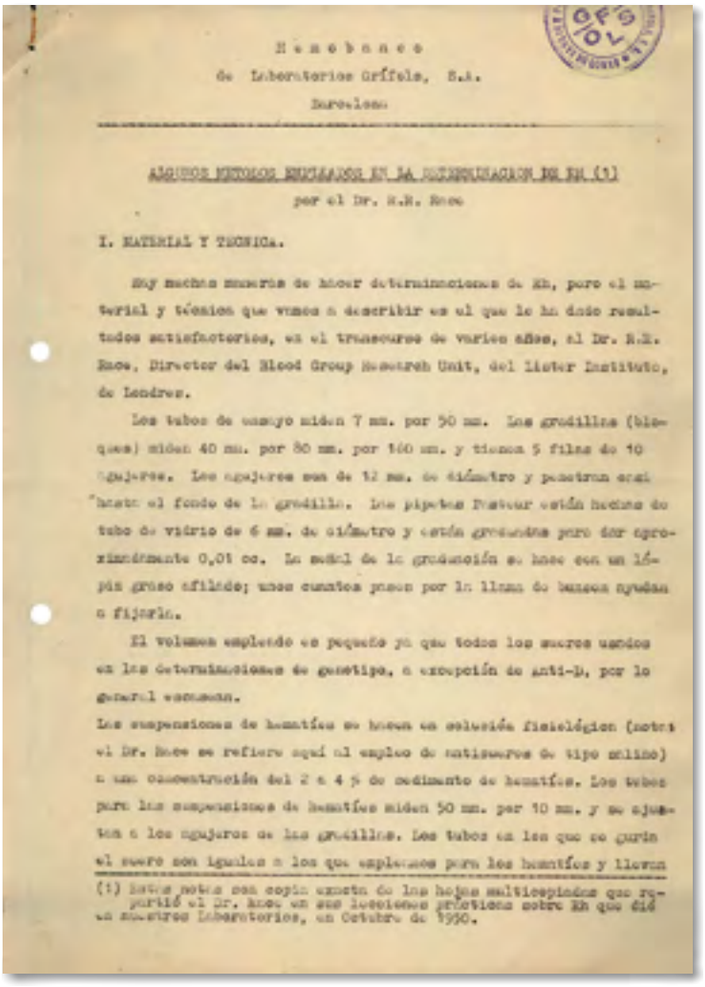
BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4763, WEEKLY, PRICE 2/-

REGISTERED AS A NEWSPAPER

The *British Medical Journal* published José Antonio Grífols' article, "Use of plasmapheresis in blood donors" in its April 1952 issue.

health, and this made it possible to respond more effectively to the demand for plasma, which exceeded the demand for whole blood or red blood cells: the component of blood that takes the longest to regenerate. José Antonio Grífols Lucas tried out the technique on himself, and, once he had confirmed that the technique was harmless, he practiced it on volunteer donors and gradually perfected it. He presented the results of his work in 1951 at the Fourth International Congress of Blood Transfusion in Lisbon, and in 1952 he published them in the *British Medical Journal*, thereby giving the international scientific community access to the technique that to this day remains the most common way of obtaining plasma. Plasmapheresis made greater quantities of this component available, and prevented the waste of red blood cells. As a result, it was quickly adopted as a method of collecting plasma for the preparation of antibodies and albumins, and for improving the treatment of hemophilia. It also



Hemobanco

de Laboratorios Grifols, S.A.

Barcelona

ALGUNOS METODOS EMPLEADOS EN LA DETERMINACION DEL Rh (1)

por el Dr. R.R. Race

I. MATERIAL Y TECNICA.

Muy muchas numerosas de hacer determinaciones de Rh, pero el material y técnica que vamos a describir es el que le ha dado resultados satisfactorios, en el transcurso de varios años, el Dr. R.R. Race, Director del Blood Group Research Unit, del Lister Institute, de Londres.

Los tubos de ensayo miden 7 mm. por 50 mm. Las gradillas (bloques) miden 40 mm. por 80 mm. por 160 mm. y tienen 5 filas de 10 agujeros. Los agujeros son de 12 mm. de diámetro y penetran casi hasta el fondo de la gradilla. Las pipetas Pasteur están hechas de tubo de vidrio de 6 mm. de diámetro y están graduadas para dar aproximadamente 0,01 cc. La unidad de la graduación se hace con un lápiz graso afilado; unas cuantas pasadas por la llama de bunsen ayudan a fijarla.

El volumen empleado es pequeño ya que todos los sueros usados en las determinaciones de genotipo, a excepción de anti-D, por lo general escasean.

Las suspensiones de hematíes se hacen en solución fisiológica (entre el Dr. Race se refiere aquí al empleo de antisueros de tipo salino) a una concentración del 2 a 4 % de sedimento de hematíes. Los tubos para las suspensiones de hematíes miden 50 mm. por 10 mm. y se ajustan a los agujeros de las gradillas. Los tubos en los que se curan el suero son iguales a los que empleamos para los hematíes y llevan

(1) Estas notas son copia exacta de las hojas multicopiadas que repartió el Dr. Race en sus lecciones prácticas sobre Rh que dió en nuestros laboratorios, en Octubre de 1950.

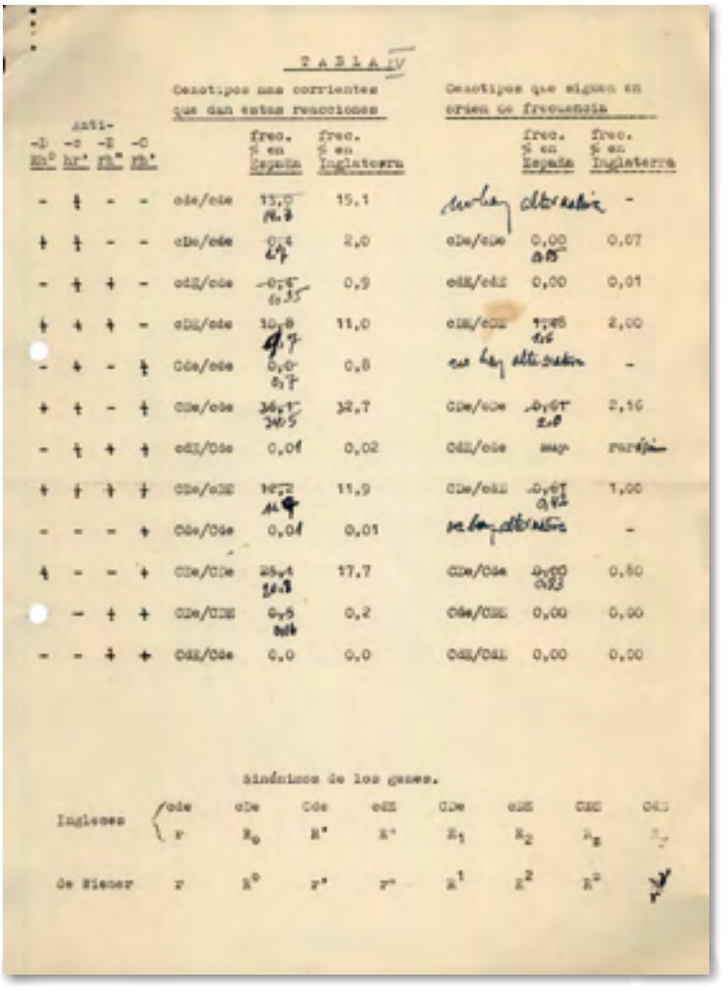


TABLA IV

-D Rh°	-C hr'	-E rh"	-C rh'	Genotipos mas corrientes que dan estas reacciones	frec. % en España	frec. % en Inglaterra	Genotipos que alguna en orden de frecuencia	frec. % en España	frec. % en Inglaterra
-	+	-	-	cde/cde	13,0	15,1			-
+	+	-	-	cDe/cde	0,4	2,0	cDe/cDe	0,00	0,07
-	+	+	-	cdE/cde	0,5	0,9	cdE/cdE	0,00	0,01
+	+	+	-	cDE/cde	10,8	11,0	cDE/cDE	1,96	2,00
-	+	-	+	Cde/cde	0,0	0,8			-
+	+	-	+	CDe/cde	36,1	32,7	CDe/CDe	0,67	2,16
-	+	+	+	cdE/Cde	0,01	0,02	CdE/cde		
+	+	+	+	CDe/cDE	11,9	11,9	CDe/cDE	0,67	1,00
-	-	-	+	Cde/Cde	0,01	0,01			-
+	-	-	+	CDe/CDe	25,4	17,7	CDe/Cde	0,00	0,80
-	+	+	+	CDe/CDE	0,5	0,2	Cde/CDE	0,00	0,00
-	-	+	+	CdE/Cde	0,0	0,0	CdE/CdE	0,00	0,00

Sinónimos de los genes.

	cde	cDe	Cde	cdE	CDe	cDE	CDE	CdE
Ingleses	r	R_0	R'	R''	R_1	R_2	R_z	r_y
de Wiener	r	R^0	r'	r''	R^1	R^2	R^z	r^y

Manuscript of the paper on methods used to determine the Rh factor, published by R. R. Race. Laboratorios Grifols blood bank. 1950.

made it possible to collect other plasma fractions with therapeutic applications.

José Antonio Grífols' prolific activity included the organization in February 1953 of a pioneering practical correspondence course on Rh, with the participation of 98 specialists in hematology and hemotherapy from across Spain. The prerequisites for participation included possessing a refrigerator and a heater capable of heating to body temperature (37 degrees Celsius), and being located within two days' postal distance from Barcelona. Dr. Grífols provided all the material needed for the course, from reagents to capillary tubes for tests. This course revealed the strong interest of doctors throughout the country in learning about and applying the latest analytical techniques.

The blood bank's work soon expanded to include the manufacture of intravenous solutions, a product line that Grifols has retained to the present day, and one that constituted its core business for several decades. Initially, these solutions were developed in response to the need to preserve donated blood, and industrial production started in May 1952, with the registration of the first solution of glucose with

Autoclaves for the sterilization of intravenous solutions. 1951.

sodium chloride. Laboratorios Grifols acquired new equipment to manufacture these solutions, including demineralizers to prepare salt-free water for injection, and secondhand autoclaves from a dye factory, which were used to sterilize the glass containers for parenteral solutions.

The activity of the blood bank continued to expand, with a growing list of regular donors, all of whom were carefully classified. A number of products were made from the collected plasma, including lyophilized plasma and pasteurized liquid plasma (PLP), in addition to Plasmoid (a blood plasma replacement), infusion kits, reagents to determine blood groups, blood types, Rh, etc., and parenteral nutrition solutions. The main focus of the bank's research was the identification and standardization of blood types and Rh factors, in close collaboration with Dr. Robert Race at the Lister Institute in London.

By the mid-1950s, Grifols was a diversified company consisting of four clearly structured divisions: the blood bank, the Central Institute of Clinical Analysis, the Pharmaceutical Laboratory, and the Study and Research Division. The blood bank division included:

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1 Extraction bottles used by the Laboratorios Grifols blood bank.

2 José Antonio Grífols Lucas with fellow researchers.

3 José Antonio Grífols Lucas. 1917–1958.

- a bank for the supply of fresh blood and plasma
- a plasma bank for the preparation of dried plasma
- a fractionation laboratory, dedicated to the collection of fibrinogen, albumin, gamma globulin, and liquid, pasteurized plasma
- the central blood type laboratory, which provided diagnostic serums, control red blood cells, and a service that determined blood types and factors, and identified antibodies
- the *Hemoteca*, a scientific information service for blood professionals.

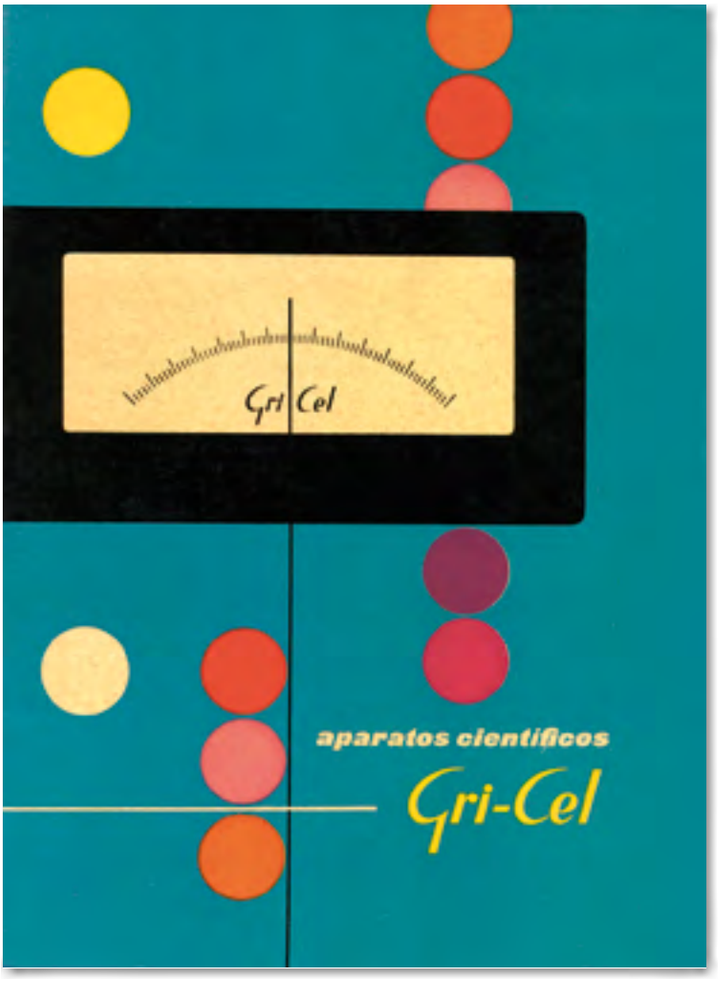
The *Hemoteca* had been created by José Antonio Grífols Lucas in 1955, and provided free access to a selection of articles from the leading hematology journals. Subscribers received photocopies of the articles, with a total of 325 copies of the bulletin being printed in 1958. The positive response to this bibliographic service led to the creation of two more specialist services: the *Coaguloteca* and the *Bioteca*, which continued to operate until the mid-1980s. The Central Institute of Clinical Analysis also performed tests and prepared vaccines and reagents. The Pharmaceutical Laboratory focused on the manufacture of intravenous solutions and stabilizing solutions for transfusion, and on the sale of extraction and injection kits. The Study and Research Division was, in the words of José Antonio Grífols Lucas, "a kind of mental gym, a source of knowledge and information for the identification of possible future trends," a forerunner of today's research and development departments.

3

From the manufacture of devices to the partnership with Dade

During the hard times of the 1940s and 1950s, shortages of technology and raw materials were the norm. As a result, Dr. Víctor Grífols Lucas was forced to find ingenious ways of developing laboratory devices, and in 1957—in conjunction with his university colleague and fellow doctor Guillermo de Celis—he founded Gri-Cel, a company dedicated to the manufacture of laboratory instruments. In addition to manufacturing products of their own design, Grífols and Celis were also appointed as representatives of several international companies, and these relationships would make a major contribution to the growth of the company during the 1960s and beyond.

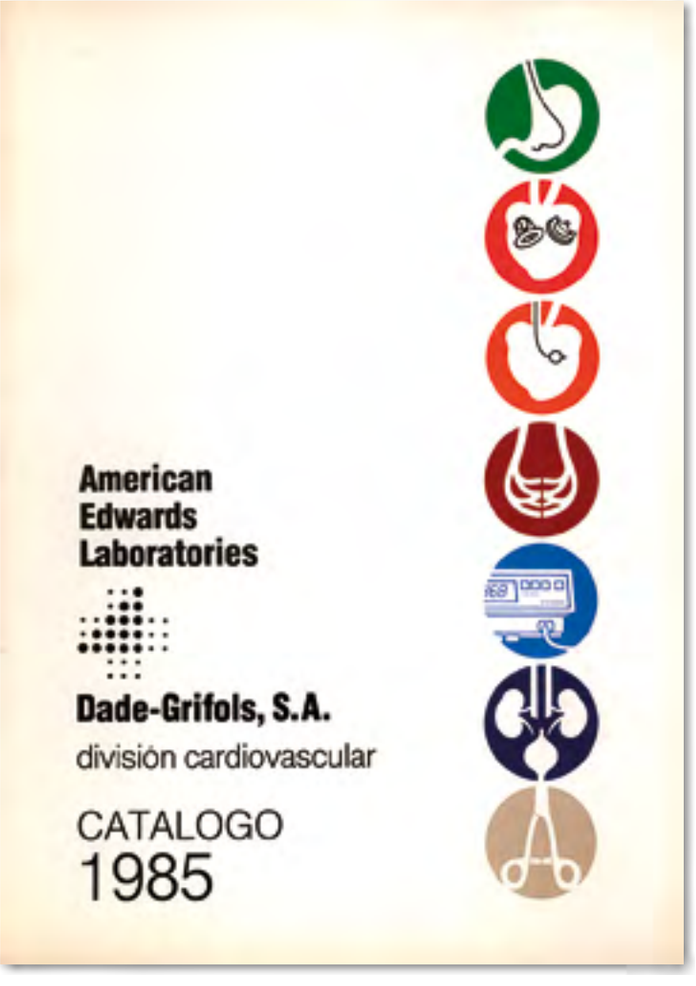
However, Laboratorios Grifols suffered a heavy blow in 1958, when the sudden death of José Antonio Grífols Lucas from leukemia at the age of 41 cut short a life that had been dedicated to hematology and hemotherapy. Of his many activities, perhaps the most important had been his work on Rh factors, conducted with Dr. Race, along with his



research into plasma fractionation, completed with his brother, Víctor, during the last years of his life.

Three years later, in 1961, Grifols formed a partnership with Dade, a U.S. company that produced reagents and instruments; a move that represented a further step in the diversification of products and markets. The result was Dade-Grifols S.A., with 50 percent of the new company's equity retained by each of the parent companies. This association had been promoted by Dr. Víctor Grífols Lucas as a response to the vacuum left by the death of his brother, José Antonio, and to the advanced age of his father. The relationship with Dade was not merely a professional one, and ties of friendship soon developed between the management of both companies. Ever since that time, knowledge of the English language has been a requirement for the group.

In 1966, consolidation in the American pharmaceutical sector led to the acquisition of Dade by American Hospital Supply Corporation (AHS) and, on October 28, 1968, following intense negotiations, this company also acquired a 50 percent share of the three Grifols companies: Laboratorios



Foster McGaw, CEO and founder of American Hospital Supply Corporation.

Grifols, Gri-Cel, and Dade-Grifols. This development contributed to the growth of Grifols' exclusive representation and distribution of the products of other North American companies through Dade-Grifols, with the result that, in addition to Dade's reagents, the company began to sell diluents, cardiology equipment, surgical instruments, and other scientific devices produced by companies that had relationships with AHS. Out of these relationships, Dade-Grifols created its cardiovascular line, which included American Edwards medical devices for use in cardiology and therapeutic radiology—devices that Grifols distributed in Spain on an exclusive basis. By the start of the 1980s, this line constituted a portfolio of cutting-edge cardiovascular products. The partnership also enabled the group to expand its customer base in the hospital sector, and to export its own devices, such as the Coombs centrifuge, designed by Grifols and patented in 1968. The international sale of this product brought great prestige to the company, which until then had been largely unknown outside of Spain.

Health: Our Commitment

A Major Boost

The Creation of a New Sales Network

At the end of the 1970s, as Spain made its transition to democracy following the death of General Franco in 1975, plasma-derived medicinal products were not yet the core business of Grifols. In contrast with today, the company was driven by the production of solutions and reagents for diagnostics. It had 350 employees, primarily at the new factory it had opened in 1972 at Parets del Vallés, north of

Aerial view of the Parets del Vallés plant, Barcelona, 1972.

Offices of Laboratorios Grifols in Barcelona. 1970s.

Barcelona, and at its offices on Jesús i Maria street, in Barcelona, where the blood and plasma bank was also located.

The association with American Hospital Supply Corporation (AHS), which had begun in 1968, kept the company abreast of developments on the other side of the Atlantic, and enabled it to distribute the latest health products in Spain and to stay up to date with good manufacturing practice and new management styles. According to the company's current CEO, Víctor Grífols Roura, AHS was nothing short of a business school for the group's management team. With only a modest sales network, Grifols was able to sell everything it produced, manufacturing to order to meet laboratories' needs for technology and instrumentation. There was even a waiting list for some devices. As production increased, the business structure underwent reorganization. The sales division received more resources, and employees were also given technical training in the product line as part of a strategy of establishing a skilled sales network.

The sales division received a further boost when Víctor Grífols Roura, son of the company's President, was appointed Director of Sales.

Plasma fractionation zone. 1972.

In 1981 Víctor Grífols Roura became head of the Commercial Department.

He implemented ideas and systems from a number of AHS companies, with one of his first steps being to modernize the sales network and employ the representatives as salaried staff. His aim was to provide the company with a sales force dedicated exclusively to Grifols products. These salespeople were employed by the existing regional branches: Valencia, Seville, Madrid, Barcelona, Bilbao, and A Coruña.

It was a difficult time in Spain, with an attempted military coup taking place on February 23, 1981. However, the coup's failure had the paradoxical effect of strengthening the country's infant democracy. It was in this context that the group organized its first sales convention in Madrid in December 1981, attended by over 60 representatives. This brought the sales team together for the first time and gave its members the opportunity to learn about the new commercial strategy. During the meeting, the business results were presented: the company's total annual sales had reached 1.2 billion pesetas (around $13 million at the exchange rate of the time).

Pharmaceutical and hospital products

Solutions, cardiology supplies, needles, plasma derivatives, instruments: Grifols' commercial offering at the start of the 1980s was extensive, covering a range of specialties and aiming to supply hospitals with the products and equipment they needed to care for their patients.

These products were grouped into three business lines: hospital, solutions, and diagnostic. The hospital line sold plasma-derived products manufactured by Laboratorios Grifols, the company that had been created in 1940. Plasma-derived medicinal products were the end result of a lengthy process that started with the collection of plasma at the company's blood banks. After the plasma had been tested, the industrial stage began with fractionation to precipitate and isolate the different proteins, in order to obtain products to treat particular conditions or diseases. Although the plant and its technology have been modernized and capacity has expanded dramatically, this is in essence the same process that is still used today to obtain plasma derivatives—medicines on which thousands of patients depend in order to cope with diseases such as hemophilia or those caused by immunological deficiencies. Since its inception, Laboratorios Grifols had manufactured a range of physiological solutions to hydrate and nourish hospital patients, and these also formed part of this business line. With the opening of the new factory, in 1972, these physiological solutions became even more important to the company's fortunes. The company's commercial offerings were rounded out by products for blood banks.

Plasma-derived products marketed by Grifols in the 1980s.

Diagnostic products

Clinical laboratories analyze patients' samples in order to diagnose their conditions and determine the most appropriate treatment for them. Through their diagnostic line, Dade-Grifols and Gri-Cel supplied both reagents and instruments to the clinical laboratory sector.

Dade-Grifols was the Spanish distributor for the reagents of its American partners, who had extensive experience in biochemistry as well as an innovative quality control system that this group applied in Spain. This system made it possible to monitor the correct performance of analytical tests, and each laboratory technician had to record the results of tests using a template, which was then submitted on a monthly basis to Miami, where the data was processed and the results recorded. This made it possible to establish comparisons between laboratories, and to perform statistical analysis. The instruments manufactured by Gri-Cel also represented a significant

Catalog of American Edwards Laboratories products distributed by the cardiovascular division of Dade-Grifols. 1985.

part of the business. The devices were designed primarily to perform pretransfusion blood tests: centrifuging samples to determine the hematocrit or red blood cell percentage, identifying blood types, and measuring glucose. Both Dade-Grifols and Gri-Cel contributed to the modernization of Spanish laboratories, with new techniques and instruments.

With the support of its partner in the United States, Grifols was at the forefront of clinical laboratory diagnostics. At the same time, Dade-Grifols was the Spanish distributor of the products of other companies with links to AHS. Building on its hospital pharmacy business, it forged relationships with other hospital departments and sold heart valves, catheters, prostheses, tubes, and disposable materials. At that time, the cardiovascular line and the diagnostic line were the most important, and the margins on these products were the key to sustaining and consolidating the physiological-solutions and plasma-derivatives business.

Commercial branches in Spain in the 1980s.

After 1980, the commercial activity of the different branches throughout Spain underwent consolidation. The Levante branch, covering Spain's southeastern coast, had outgrown its base and moved to a new building with better facilities. The Northeast branch, located in Barcelona, had a team of fifteen, covering Catalonia, Aragón, Andorra, and the Balearic Islands. Until this time, Dade-Grifols employees had only sold the company's own products, a strategy that changed with the development of a sales network covering the entire product portfolio. The Southern branch, based in Seville, was the oldest, having been created in the mid-1970s. The Central branch had great potential, covering a vast territory that included the city of Madrid, along with the neighboring regions of Castilla-La Mancha and Castilla-León. However, the going was tough at first, and it was decided to start with the neighboring provinces and work towards the capital. As a result of this strategy, the branch gained its first customer: the pharmacy of the hospital of Talavera de la Reina, near Toledo. The good reports from this hospital smoothed the way for Grifols to enter the hospitals of Madrid. Finally, the north of Spain was reorganized at the start of the 1980s, with two independent branches being created: a Northern branch, serving the provinces of Álava, Burgos, Cantabria, Guipúzcoa, La Rioja, Navarra, and Vizcaya, and a Northeastern branch, covering the Asturias and Galicia regions.

Plasma-derived products

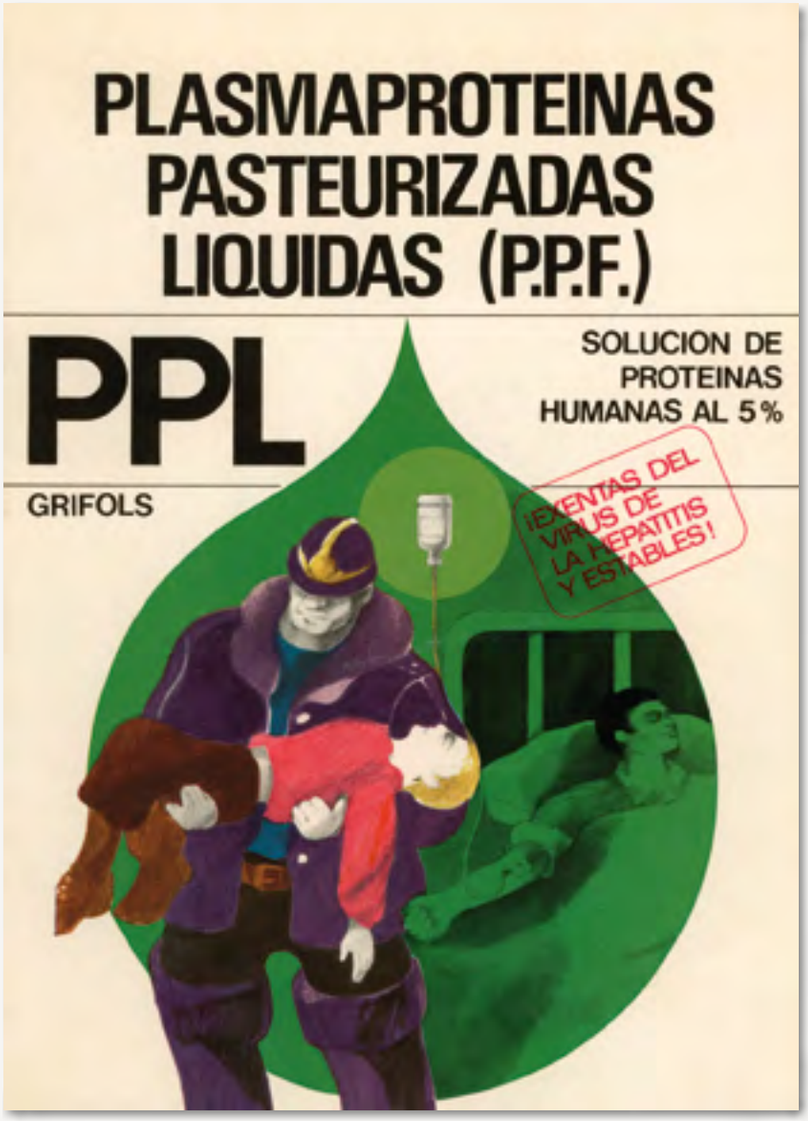
Albumin
- Human albumin at 20 percent: to reconstitute plasma volume, indicated in cases of shock, burns, and non-cardiac edema.

Clotting factors
- Cryoprecipitate, lyophilized plasma: rich in factor VIII, for the treatment of hemophilia A and von Willebrand disease.
- Criostat: factor VIII, indicated for the treatment of hemophilia A.
- Fibrinogen: designed to stop hemorrhage, and for cases of a deficiency of this clotting factor.
- Hemofactor: prothrombin complex for the treatment of hemophilia B.

Plasma
- Lyophilized plasma: easier to store and with a longer shelf life than liquid plasma, used for transfusions.

Plasma protein fraction
- Liquid, pasteurized plasma proteins: protein concentrate, without clotting factors, used as a plasma substitute in the event of blood loss.

Antibodies
- Gamma globulin. Indicated for protection from German measles, measles, acute hepatitis, and poliomyelitis, and for the treatment of bacterial infections.
- Antitetanus gamma globulin for the treatment of tetanus.
- Anti-D gamma globulin to prevent immunization in Rh-negative women who are pregnant with an Rh-positive fetus.



Parenteral solutions

- Injectable water used as a solvent.
- Saline solution for water and salt-retention therapy.
- Potassium chloride: indicated in patients with potassium deficiency.
- Plurisaline solution: used to remedy mineral imbalances due to plasma or fluid loss.
- Glucose: dextrose solution, used to provide water and energy when oral feeding is not possible.
- Levulose: fructose solution, also used to provide water and energy when oral feeding is not possible.
- Glucose with sodium chloride solution: administered in cases of medical and surgical dehydration.
- Ammonium chloride: acidifying solution.
- Sodium lactate: solution used to correct acid-base balance.

Plasma replacements:

- Plasmoid: indicated in the event of reduced blood volume.
- Fisiodex: dextran solution, for treatment of reduced and altered capillary, arterial, and venous blood flow.

A New Partner

The Decision to Specialize in Plasma-derived Products

In the early 1980s, the devaluation of the Spanish peseta and the freeze in the prices of health products combined to put severe pressure on Grifols' performance. For this reason, the company decided to focus on the plasma products sector.

At the same time, American Hospital Supply (AHS) was no longer providing the services that had been agreed upon between the two companies. As a result, Grifols decided to seek a new partner in the United States and—after considering various candidates, including Cutter and Baxter—the decision was made to work with Alpha Therapeutic Corporation (Alpha), owned by the Green Cross pharmaceutical corporation of Japan. Upon the successful completion of negotiations in September 1982, Alpha bought AHS's shares and went into partnership

1 Alpha Therapeutic Corporation head office in Los Angeles, California.

2 Marketing leaflet for Courtland human plasma. 1943.

3 Corporate brochure for Japanese company The Green Cross Corporation in the 1980s.

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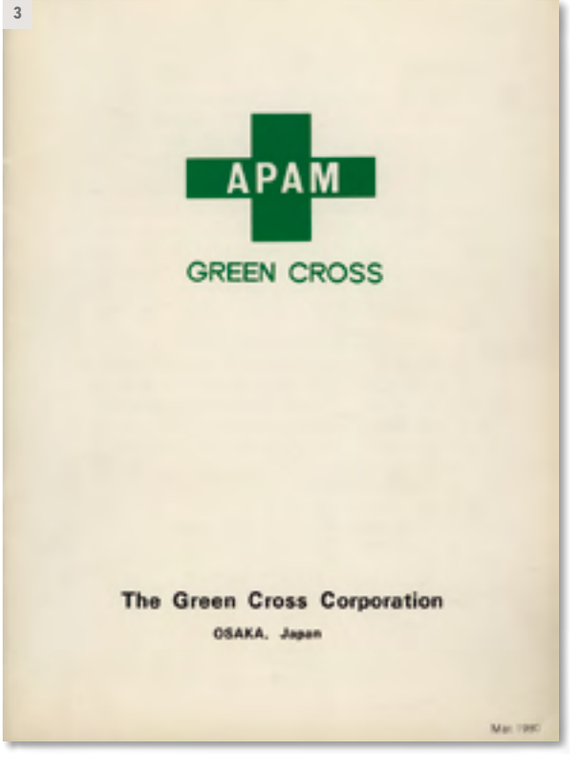


with Laboratorios Grifols. The agreement meant that ownership of the three Grifols companies was divided as follows: AHS retained a 50 percent holding in Gri-Cel and Dade-Grifols, while Alpha owned 50 percent of the shares in Laboratorios Grifols. This was the start of a new stage in the internationalization of the group.

The first contact with Alpha had actually taken place two years earlier, when the company began to supply Grifols with plasma. At the time, it was the largest plasma collection company in the United States—a giant compared to Grifols, a family business that fractionated 23,000 liters of plasma per year, which was about the same amount that Alpha processed in a single week. The volume and capacity of the two companies were so different that nobody could have imagined that 20 years later Grifols would not only buy back its shares, but also be in a position to acquire all of its partner's assets.

Alpha was one of the leading North American companies in the plasma-derived products sector, and had undergone several changes of ownership during the preceding years. It had initially been owned by Courtland, then Abbott, and had finally been bought by the Green Cross Corporation, a Japanese firm. At the time, the Japanese economy was taking off with one of the highest growth rates of any industrialized nation, coupled with low rates of inflation. The technology and automobile sectors led the way, bolstered by overseas investment and the creation of subsidiaries across the globe. Naturally, Green Cross Corporation was eager to participate in this expansion. Like Grifols, this Japanese company traced its origins to the creation of a private blood bank, but when it started attempting to expand into new markets, it came up against the health policies of its government. Japanese legislation did not permit the export of plasma products, due to the shortage of plasma within the country. As a result, the products manufactured at the Green Cross Corporation plant in Osaka could only be sold domestically. The purchase of Alpha, including its plant in Los Angeles, enabled the Green Cross Corporation to meet 80 percent of its demand for plasma products in global markets. In addition, it had a foothold in Europe, through Alpha's German subsidiary, providing it with a basis for further international expansion.

Grifols offered the Green Cross Corporation a further opportunity to increase its European presence. Working with a partner that had its own production plant meant that Grifols could sell its plasma products in more European

countries, and even in the Asian market. Furthermore, when Spain joined the European Community, it would be easier to distribute and sell its products. For Grifols, then, the new partnership brought several benefits: liquidity, technical support in the manufacture of plasma products, and, above all, a strategic partner in the development of blood substitutes, such as Fluosol—at the time viewed as holding great promise. This was a very important consideration for Laboratorios Grifols when it came to selecting a new partner.

The partnership with Alpha also expanded Grifols' equity base, enabling it to pursue a more vigorous research and development policy, and to open up new markets. Under the terms of the partnership, Alpha assigned American managers to Grifols, unlike Dade Reagents or American Hospital Supply Corporation (AHS); neither of whom had allocated staff to Barcelona. In Grifols, these new American managers found a company with a solid ethical base and a commitment to quality, but one that needed to modernize its management techniques. In the years that followed, the influence of Alpha would lead to the development of business plans and a greater emphasis on strategy.

While the staff of Laboratorios Grifols were cautiously optimistic as they waited to see what Alpha would do, the members of the team at Dade-Grifols and Gri-Cel were more wary of the newcomer, given their ongoing relationship with AHS. At first, the most significant change was the increased level of international contact, because it was not just managers who visited the United States, but also members of the technical team, who crossed the Atlantic to learn about the production techniques used in America. Such trips involved numerous meetings between the managers and employees of the two companies, and highlighted a number of differences. Alpha's organization was stronger, with far more resources for research and industrial processes

Leaflets for Alpha Therapeutic Corporation plasma-derived products. 1985.

and greater experience in the sale of plasma products, while Grifols, by contrast, was a far smaller company and had to rely on effort and ingenuity to progress.

In some aspects of fractionation, the processes used by Grifols were practically identical to those of Alpha, and Grifols was even able to offer some improvements, such as the use of double-lined chambers to maintain temperature, or the systems used to add alcohol for precipitation. However, Grifols was a long way behind in terms of manufacturing volume, research and development, and the adoption of good manufacturing practices. Alpha's advice would prove vital years later, when Grifols obtained Food and Drug Administration (FDA) licenses for its manufacturing facilities and for new products to treat hemophilia and primary immunodeficiencies.

Managers from The Green Cross Corp. and Alpha Therapeutic Corporation visited Grifols on a frequent basis. 1980s.

Groundbreaking exports to China

The partnership with Alpha created new commercial opportunities for Grifols. The largest of these was the export of plasma products to China, starting in 1983. This was a major new undertaking given that, until then, Grifols had only exported small quantities of plasma products to European countries such as Portugal and Denmark. China was the first truly important export customer, due both to the volume of product involved and to the particular challenges related to selling into a country that, in the early 1980s, was so politically and culturally different from Spain.

The first product to be exported was intramuscular gamma globulin, administered to treat a number of infectious diseases, including measles, acute hepatitis, polio, and German measles. Alpha did not manufacture this product, and the Green Cross Corporation was

unable to export plasma products from Japan, so the task of supplying the Chinese Ministry of Health with gamma globulin fell to Grifols. The company exported through Great Year Trading Co. Ltd., a subsidiary of the Green Cross Corporation based in Hong Kong, which was the port of entry to the Chinese market. In 1984, exports of gamma globulin totaled approximately 2 million vials. However, the following year China approved a decree prohibiting the import of this product due to concerns about AIDS, and these exports were abruptly halted. Fortunately, Grifols soon received orders for albumin, becoming the first foreign company to obtain authorization to sell albumin in that country, and its sales recovered and actually increased. Sales of this protein were crucial to the group's ability to survive the challenges of the early 1980s. It was a time when the Spanish authorities delayed payments by months (or even years), and the plasma-derived products market was rocked by fears of AIDS. In this context, the large volume of albumin sales to China helped cover the company's fixed costs and ensure the profitability of each liter of plasma by providing a market for all the products obtained from it.

Victor Grífols Lucas on a commercial visit to China. 1984.

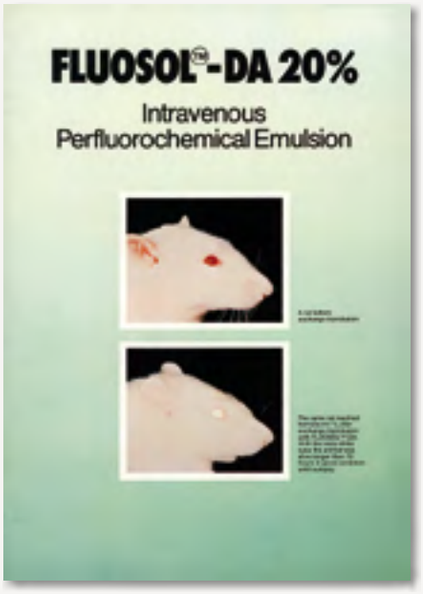
As part of the commercial relationship with China, managers and technicians from the company visited the country on several occasions. And representatives from the Chinese Ministry of Health and Great Year Trading also came to Parets del Vallés to inspect the plasma protein manufacturing facilities. One of their main concerns was the possibility that the vials of albumin could contain particles, and, to allay their fears, Grifols designed a particle inspection machine specifically for the albumin destined for the Chinese market.

For internal reasons, in July 1987 China halted the import of this protein, which in that year had

Blood substitutes

In the early 1980s, there was intense media coverage of synthetic blood substitutes, which were seen as offering real promise. There were two lines of research: one aimed at identifying a substitute for hemoglobin, the other at finding substances capable of transporting oxygen. Such a product would make it possible to meet the rising demand for blood, resolve some of the problems relating to the storage of blood, and provide immediate availability in emergency or disaster situations, in cases where transfusion was not possible, and in the treatment of patients with religious objections to receiving blood. On the basis of these arguments, a number of pharmaceutical companies invested significant financial and scientific resources in the search for new products. Green Cross Corporation was one of the leaders in this field, the result of its involvement, since 1977, in studies of Fluosol-DA, a substance that acted as an oxygenator. The largest study had been carried out in Japan, with almost 200 patients in various hospitals. The company also carried out a trial in the United States, the results of which were published in the *New England Journal of Medicine*.

Coinciding with the agreement between Grifols and Alpha in 1982, an international symposium was held in San Francisco to present the latest developments in blood-substitute research, including the studies of Fluosol-DA. Despite its initial promise, clinical trials unfortunately did not deliver the results that had been hoped for, and the product was ultimately deemed unsuitable for use as a blood substitute in transfusions.



earned Grifols 700 million pesetas (5.5 million dollars). Unfortunately, the company's overall plasma purchasing plan was proportional to sales of albumin, and it was impossible to simply cancel these imports. Instead, Grifols was bound by its supply contract for over three months given that, from an industrial perspective, it was not possible to shut down albumin production overnight. By the end of the year, stock levels had reached 250,000 vials, with a value of 750 million pesetas (6.2 million dollars). Output at the plant, which had been manufacturing between 15,000 and 20,000 liters of plasma per month, fell to little more than 2,000 liters at the end of 1987. In March 1988, sales of albumin recovered slightly. However, at the end of the year the Chinese government once again took the decision to unilaterally halt imports. As a result, production volumes were permanently scaled down, and it would be many years before they would return to previous levels.

The Virus of the Twentieth Century

The Appearance of AIDS Profoundly Affects Humanity

It arrived silently, but it was not long before it was causing widespread concern among the scientific community and society at large. AIDS, an acronym of Acquired Immunodeficiency Syndrome, destabilized the immune system in a manner that had not been seen before, baffling researchers and testing health systems to the limit. It was both one of

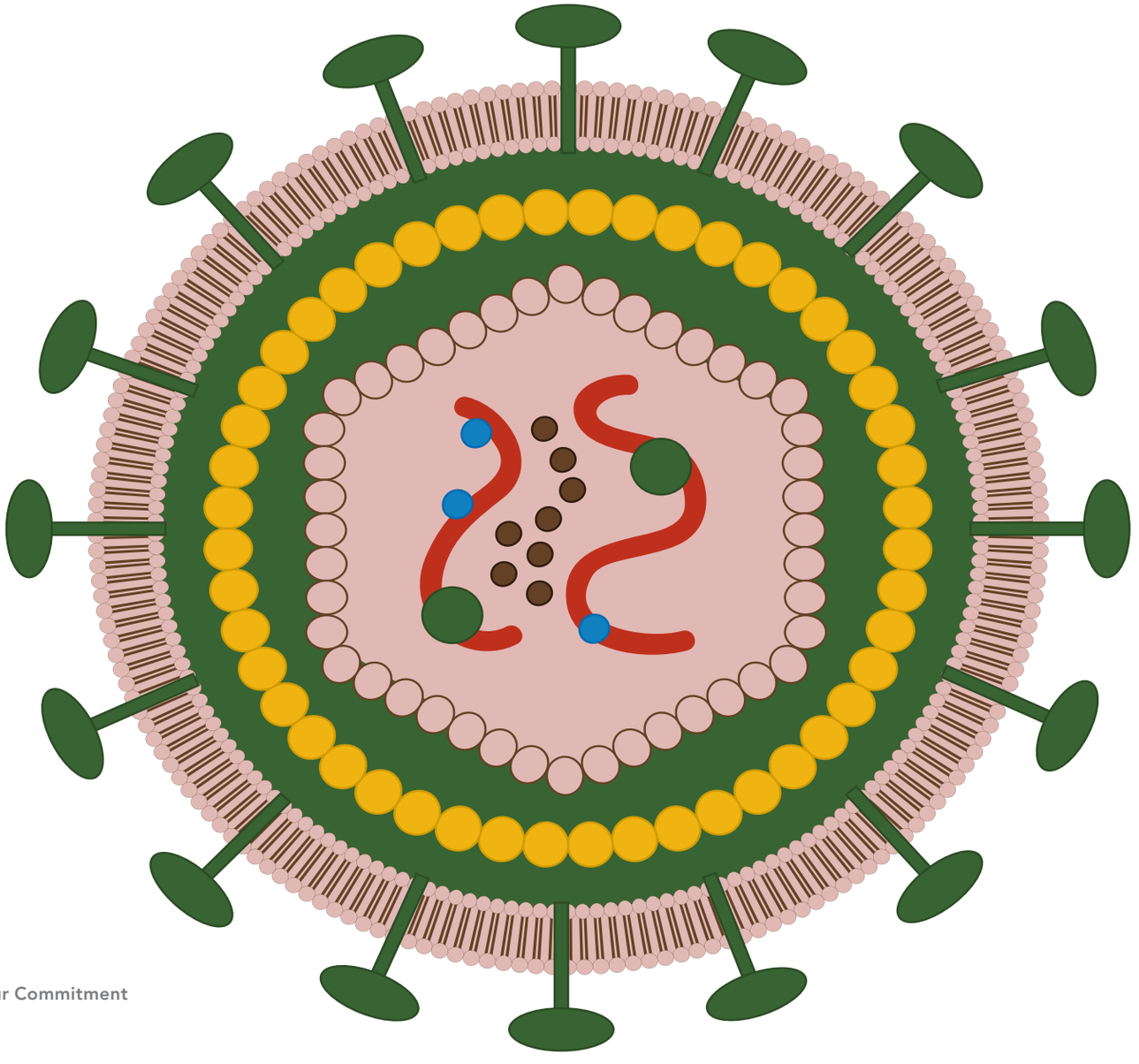
the greatest scientific challenges of the twentieth century and a cause of great social upheaval. However, the immediate response was to treat it as a taboo; a shameful illness whose sufferers were stigmatized, and it was only when it struck down its first famous victims that it received sufficient attention.

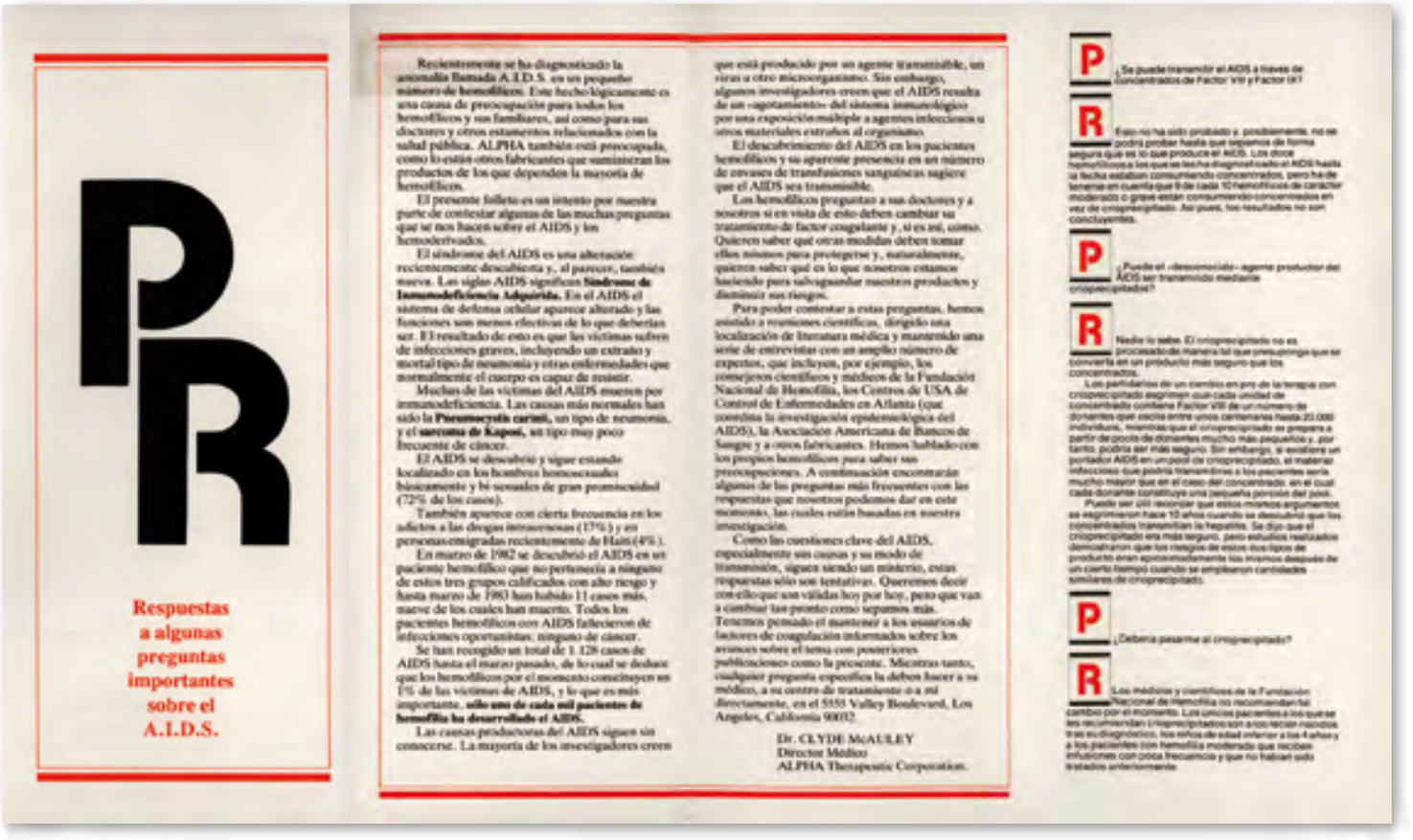
Grifols learned of the existence of AIDS through the international scientific literature. At the start of the 1980s, reports began to emerge of a new disease caused by a virus detected in the blood, of which both the causes and the consequences were still unknown. The group was in the front line of the fight against AIDS, increasing the levels of monitoring and improving standards to ensure that it could continue to provide safe plasma-derived products that would not represent a threat to the health of those groups who were most vulnerable to the virus; groups whose quality of life the company had helped to improve for many years. All sorts of theories abounded, and laboratories, universities, hospitals, and research centers worked around the clock

to try to explain the origins and action of this strange disease, which attacked the immune system and left the organism vulnerable to a wide range of infections that did not normally develop in those with a healthy immune system. Between June 1981 and November 1982, 700 cases had been detected in the United States. Of these, 0.8 percent were diagnosed in hemophiliac patients, and this led the Food and Drug Administration (FDA) to launch an investigation to determine whether plasma derivatives, such as factor VIII, used to treat hemophilia, could transmit AIDS. Both the FDA and the health agencies in other countries asked that any suspicious cases be reported, to enable further investigation of this disease.

In response to the growing level of concern in the industry and the lack of available information, in June 1983 Grifols organized a meeting to facilitate the exchange of information about AIDS.

Alpha Therapeutic Corporation leaflet providing hemophiliacs with information about AIDS/HIV. 1983.





Respuestas a algunas preguntas importantes sobre el A.I.D.S.

Recientemente se ha diagnosticado la anomalía llamada A.I.D.S. en un pequeño número de hemofílicos. Este hecho lógicamente es una causa de preocupación para todos los hemofílicos y sus familiares, así como para sus doctores y otros estamentos relacionados con la salud pública. ALPHA también está preocupada, como lo están otros fabricantes que suministran los productos de los que dependen la mayoría de hemofílicos.

El presente folleto es un intento por nuestra parte de contestar algunas de las muchas preguntas que se nos hacen sobre el AIDS y los hemoderivados.

El síndrome del AIDS es una alteración recientemente descubierta y, al parecer, también nueva. Las siglas AIDS significan **Síndrome de Inmunodeficiencia Adquirida.** En el AIDS el sistema de defensa celular aparece alterado y las funciones son menos efectivas de lo que deberían ser. El resultado de esto es que las víctimas sufren de infecciones graves, incluyendo un extraño y mortal tipo de neumonía y otras enfermedades que normalmente el cuerpo es capaz de resistir.

Muchas de las víctimas del AIDS mueren por inmunodeficiencia. Las causas más normales han sido la **Pneumocystis carinii,** un tipo de neumonía, y el **sarcoma de Kaposi,** un tipo muy poco frecuente de cáncer.

El AIDS se descubrió y sigue estando localizado en los hombres homosexuales básicamente y bi-sexuales de gran promiscuidad (72% de los casos).

También aparece con cierta frecuencia en los adictos a las drogas intravenosas (17%) y en personas emigradas recientemente de Haití (4%).

En marzo de 1982 se descubrió el AIDS en un paciente hemofílico que no pertenecía a ninguno de estos tres grupos calificados con alto riesgo y hasta marzo de 1983 han habido 11 casos más, nueve de los cuales han muerto. Todos los pacientes hemofílicos con AIDS fallecieron de infecciones oportunistas; ninguno de cáncer.

Se han recogido un total de 1.128 casos de AIDS hasta el mayo pasado, de lo cual se deduce que los hemofílicos por el momento constituyen un 1% de las víctimas de AIDS, y lo que es más importante, **sólo uno de cada mil pacientes de hemofilia ha desarrollado el AIDS.**

Las causas productoras del AIDS siguen sin conocerse. La mayoría de los investigadores creen que está producido por un agente transmisible, un virus u otro microorganismo. Sin embargo, algunos investigadores creen que el AIDS resulta de un «agotamiento» del sistema inmunológico por una exposición múltiple a agentes infecciosos u otros materiales extraños al organismo.

El descubrimiento del AIDS en los pacientes hemofílicos y su aparente presencia en un número de casos de transfusiones sanguíneas sugiere que el AIDS sea transmisible.

Los hemofílicos preguntan a sus doctores y a nosotros si en vista de esto deben cambiar su tratamiento de factor coagulante y, si es así, cómo. Quieren saber qué otras medidas deben tomar ellos mismos para protegerse y, naturalmente, quieren saber qué es lo que nosotros estamos haciendo para salvaguardar nuestros productos y disminuir sus riesgos.

Para poder contestar a estas preguntas, hemos asistido a reuniones científicas, dirigido una localización de literatura médica y mantenido una serie de entrevistas con un amplio número de expertos, que incluyen, por ejemplo, los consejeros científicos y médicos de la Fundación Nacional de Hemofilia, los Centros de USA de Control de Enfermedades en Atlanta (que coordina la investigación epidemiológica del AIDS), la Asociación Americana de Bancos de Sangre y a otros fabricantes. Hemos hablado con los propios hemofílicos para saber sus preocupaciones. A continuación encontrarán algunas de las preguntas más frecuentes con las respuestas que nosotros podemos dar en este momento, las cuales están basadas en nuestra investigación.

Como las cuestiones clave del AIDS, especialmente sus causas y su modo de transmisión, siguen siendo un misterio, estas respuestas sólo son tentativas. Queremos decir con ello que son válidas hoy por hoy, pero que van a cambiar tan pronto como sepamos más. Tenemos pensado el mantener a los usuarios de factores de coagulación informados sobre los avances sobre el tema con posteriores publicaciones como la presente. Mientras tanto, cualquier pregunta específica la deben hacer a su médico, a su centro de tratamiento o a mí directamente, en el 5555 Valley Boulevard, Los Angeles, California 90032.

Dr. CLYDE McAULEY
Director Médico
ALPHA Therapeutic Corporation.

P ¿Se puede transmitir el AIDS a través de concentrados de Factor VIII y Factor IX?

R Esto no ha sido probado y, posiblemente, no se podrá probar hasta que sepamos de forma segura qué es lo que produce el AIDS. Los doce hemofílicos a los que se les ha diagnosticado el AIDS hasta la fecha estaban consumiendo concentrados, pero ha de tenerse en cuenta que 9 de cada 10 hemofílicos de carácter moderado o grave están consumiendo concentrados en vez de crioprecipitado. Así pues, los resultados no son concluyentes.

P ¿Puede el «desconocido» agente productor del AIDS ser transmitido mediante crioprecipitados?

R Nadie lo sabe. El crioprecipitado no es procesado de manera tal que presuponga que se convierta en un producto más seguro que los concentrados.

Los partidarios de un cambio en pro de la terapia con crioprecipitado esgrimen que cada unidad de concentrado contiene Factor VIII de un número de donantes que oscila entre unos centenares hasta 20.000 individuos, mientras que el crioprecipitado se prepara a partir de pools de donantes mucho más pequeños y, por tanto, podría ser más seguro. Sin embargo, si existiere un portador AIDS en un pool de crioprecipitado, el material infeccioso que podría transmitirse a los pacientes sería mucho mayor que en el caso del concentrado, en el cual cada donante constituye una pequeña porción del pool.

Puede ser útil recordar que estos mismos argumentos se esgrimieron hace 10 años cuando se descubrió que los concentrados transmitían la hepatitis. Se dijo que el crioprecipitado era más seguro, pero estudios realizados demostraron que los riesgos de estos dos tipos de producto eran aproximadamente los mismos después de un cierto tiempo cuando se ampliaron candidatos similares de crioprecipitado.

P ¿Debería pasarme al crioprecipitado?

R Los médicos y científicos de la Fundación Nacional de Hemofilia no recomiendan tal cambio por el momento. Los únicos pacientes a los que se les recomiendan crioprecipitados son a los recién nacidos, tras su diagnóstico, los niños de edad inferior a los 4 años y a los pacientes con hemofilia moderada que reciben infusiones con poca frecuencia y que no habían sido tratados anteriormente.

P ¿Debo cambiar mi tratamiento y consumir menos Factor VIII?

R Especialistas como el Dr. Louis Aledort (Mt. Sinai Hospital de Nueva York), el Dr. Shelby Dietrich (Orthopedic Hospital de Los Angeles), la Dra. Margaret Hilgartner (Cornell University Medical Center) y el Dr. Peter Lewine (Worcester Memorial Hospital) consideran el riesgo de hemorragias las consecuencias a largo plazo de una terapia inadecuada de Factor VIII como muy superiores en el presente momento al riesgo del AIDS. Cualquier posible disminución de la exposición al AIDS que sea resultado de recortar el aporte de Factor VIII debe sopesarse teniendo en cuenta los peligros conocidos contra la salud que Vd. tendría que afrontar por un tratamiento inadecuado de su alteración coagulatoria.

P ¿Debo considerar en la actualidad la posibilidad de una intervención quirúrgica?

R Sí. El Dr. Marvin Gilbert, traumatólogo del Mt. Sinai Hospital de Nueva York y co-Director médico de la Fundación Nacional de Hemofilia ha afirmado: que si un paciente ha de vivir sin dolor o incapacidad física existen ciertas intervenciones que no pueden esperar a tener respuestas al problema del AIDS. Además estas intervenciones quirúrgicas si se hacen a tiempo, disminuirán más tarde el uso de Factor VIII y IX.

El Dr. Shelby Dietrich, Director del Centro de Hemofilia en el Orthopedic Hospital de Los Angeles ha afirmado: «En diciembre de 1982 suspendimos las operaciones de cirugía ortopédica, pero actualmente estamos realizándolas en ciertos pacientes. La mayoría de los pacientes que necesitan cirugía ortopédica ya han tenido una exposición notable a los concentrados y en ciertos casos la cirugía ortopédica puede reducir considerablemente la cantidad de concentrado a utilizar para aliviar los problemas ortopédicos. La cirugía no debe suspenderse o rehusarse simplemente por evitar el riesgo del síndrome AIDS».

P ¿Proporciona algún tipo de protección la tipificación del Factor VIII en concentrados?

R Probablemente, no. La hepatitis puede transmitirse tanto en preparados liofilizados como líquidos y si está presente un agente productor de AIDS, lo más probable es que el mismo sea transmisible por ambos tipos de preparados.

P Sólo un pequeño número de hemofílicos tienen realmente AIDS, pero yo he leído que un gran número tienen los primeros síntomas de esta anomalía. ¿Es esto cierto?

R No se sabe. Un síntoma de AIDS lo constituye el cambio en el número y proporción de unos leucocitos inmunológicamente protectores llamados células T. Los estudios recientes indican que una proporción bastante elevada de hemofílicos tienen anomalías similares al margen de si reciben crioprecipitados o concentrados, pero no está claro si esta anormalidad es nueva o antigua, ni lo que significa.

En los hemofílicos esta anormalidad de células T puede ser consecuencia de transfusiones múltiples, no de AIDS. No sabemos todavía si esta anomalía empeora en los pacientes con hemofilia a medida que el tiempo pasa, pero el asunto está siendo cuidadosamente estudiado. La mayoría de los hemofílicos, incluyendo a los que tienen proporciones de células T aparentemente anormales, parecen tener unos sistemas inmunitarios que funcionan de manera efectiva para protegerlos de infecciones y otras enfermedades, lo que son noticias positivas.

P ¿Qué es lo que están haciendo los fabricantes para disminuir el riesgo que sufrimos?

R Todos los fabricantes comerciales de concentrados, siguiendo los pasos de Alpha, han tomado medidas para eliminar a los miembros de los grupos de alto riesgo de sus pools de donantes. Alpha está llevando a cabo un programa educativo con sus donantes sobre los riesgos del AIDS e identifica a donantes de alto riesgo como, por ejemplo, homosexuales varones, drogadictos y haitianos. A todos los donantes se les estudia mediante historial médico, exámenes físicos y cuestionarios a fin de detectar los primeros síntomas de AIDS, como por ejemplo la pérdida de peso e inflamación de glándulas. Alpha no acepta plasma de ningún donante sospechoso.

P ¿Pueden realizar pruebas con el plasma?

R No disponemos en este momento de ningún tipo de prueba específico para el AIDS. Aunque se han sugerido ciertas posibilidades, hasta la fecha ninguna ha demostrado su especificidad frente al AIDS.

P ¿Qué más se está haciendo?

R Se sabe desde hace tiempo que mediante el tratamiento de las fracciones plasmáticas con calor (en otras palabras, mediante pasteurización) el virus de la hepatitis muere o se inactiva. El problema es que el calor también disminuye la capacidad de los productos de Factor VIII de inducir la coagulación. Actualmente, dada la posibilidad de que el agente del AIDS sea un organismo vivo y susceptible al calor, se están haciendo grandes esfuerzos para desarrollar, probar y ganar la aprobación de la FDA (Food and Drug Administration) para los concentrados de Factor VIII tratados con calor.

Es éste un objetivo de la mayor prioridad para la FDA y se puede anticipar que estos productos estarán en el mercado en un futuro próximo. Sin embargo, no hay ninguna garantía de que así se elimine el AIDS. Como todavía no se ha identificado y excluido ningún agente productor del AIDS, la efectividad del tratamiento por calor es sólo una posibilidad optimista.

P ¿Cuándo podremos contar con concentrados artificiales de Factor VIII que eliminen este riesgo?

R Las investigaciones se están orientando hacia ese objetivo, pero nadie sabe si es posible y, si lo es, cuándo se podrá conseguir esto.

P ¿Hay algo que pueda hacer ahora en mi tratamiento o en mi forma de vida que me proteja contra el AIDS?

R No sabemos qué medidas se pueden tomar que sean útiles. La amenaza más grave de los pacientes con hemofilia hoy y sigue siendo la amenaza de las hemorragias. La terapia con Factor VIII o Factor IX evita o pone término a las hemorragias y sigue proporcionando un gran beneficio con un riesgo bajo. El Dr. Dietrich recomienda: «Traten las hemorragias a tiempo, no cabe ningún retraso. Un estilo de vida saludable no lo va a proteger necesariamente contra el AIDS, pero, ¿quién sabe? Trate de disminuir el stress, el ejercicio y siga una dieta equilibrada».

En base a lo que se sabe hasta ahora, los Centros de Hemofilia de New England y de Nueva York están recomendando a sus pacientes que sigan los mismos tratamientos que en el pasado, excepto en cuanto al punto de que se deben utilizar crioprecipitados en niños menores de 4 años y en aquellos pacientes que no necesiten de un tratamiento continuo.

Yo creo que es un buen consejo.

Un servicio público de

LABORATORIOS GRIFOLS, S.A.

Jesús y María, 6
Teléfono 247 42 00
BARCELONA - 22

Alpha

ALPHA THERAPEUTIC CORPORATION
5555 Valley Boulevard
Los Angeles, California 90032

The event, held at the Hotel Alameda in Madrid, was attended by Dr. Lou Aledort, secretary of the World Federation of Hemophilia and a member of staff at the Mount Sinai Hospital, and Guillermo Anido, biopathologist at Broward General Medical Center in Miami, who informed the hematologists and health authority representatives about the cases they had treated.

This was only the start of Grifols' collaboration with other hematologists, and the company became one of the founders of the Catalan and Balearic Blood Transfusion Society, created to facilitate the exchange of information about AIDS. This association brought together medical teams from a network of leading hospitals. As a result of its involvement with this society and with other health bodies, in 1983 the company received the declaration on acquired immunodeficiency syndrome drawn up by nine health organizations in the United States, including the American Red Cross, the Council of Community Blood Centers, the FDA, the National Hemophilia Foundation, and the Centers for Disease Control. This declaration explained that, while transmission via blood or blood products had not been demonstrated, the cases detected in hemophiliacs and patients who had received blood transfusions meant that blood banks and transfusion services should take preventive measures.

Investigating a new virus

The notion that AIDS was caused by a virus was gaining ground, and since the early 1980s both Luc Montagnier, in France, and Robert Gallo, in the United States, had conducted research on the basis of this hypothesis. When a newborn infant caught human immunodeficiency virus (HIV) after receiving a blood transfusion from an infected donor, these suspicions were confirmed.

Scientists and laboratories stepped up their virus research in an attempt to find the best way to combat the threat. Alpha Therapeutic Corporation and Grifols focused on research into heat inactivation of the virus during the process of manufacturing and obtaining plasma derivatives. Alpha developed a liquid phase heat inactivation method that was found to be effective in the two viruses studied, hepatitis B and Sindbis virus, with the latter virus having similar characteristics to HIV. In parallel, Grifols studied whether heating factor VIII could increase the appearance of inhibitors or cause allergic reactions in patients. With positive results from both research projects, the two companies applied to the health authorities for authorization of the inclusion of a heat inactivation stage in the liquid phase of the factor VIII manufacturing process. In July 1984, the group received approval to become the first laboratory to manufacture heptane-heated

Commercial leaflet for Grifols' new heat-treated factor VIII Criostat HT.

factor VIII in Spain. The new product was marketed as Criostat HT (heat-treated).

This was only the start of virus inactivation research. In need of a partner to help it perform virus testing, Grifols established links with Sobrino veterinary laboratories in Girona, a firm specializing in the manufacture of animal virus vaccines, and performed a study that was also supported by other plasma derivative manufacturers, including Hubber, Behring, and Landerlan. It was decided to conduct the research with a lipid-coated virus similar to the human immunodeficiency virus that had been identified as the cause of AIDS. The results were positive: heating the product to 60 degrees Celsius for 80 hours successfully inactivated the virus.

Impact on the plasma products industry

After the uncertainty of the early years of the disease, the health authorities began to take measures. In Spain, the Department of Health made HIV testing compulsory for plasma fractionators, manufacturers, and importers of plasma products in September 1985. Any products that did not comply with this requirement were withdrawn from the market. This was a huge blow for the plasma protein industry, with a whole raft of measures having to be taken at short notice, including the withdrawal of large batches of finished product, major investments in laboratory testing, changes to manufacturing procedures, and the recruitment of additional staff. Not all companies were capable of meeting the challenge. Some of the more diversified participants in the industry decided to divest themselves of their plasma-based therapies business. Others, unable to meet the costs imposed by the new legislation, closed down.

The appearance of HIV gradually altered the map of plasma protein therapeutics industry, and by the time the dust had settled only four such firms remained in Spain, one of which was Grifols. Elsewhere, the situation was broadly similar. While some companies had cut corners, others did everything possible to ensure the safety of their plasma-derived products. One thing was certain. The advent of HIV/AIDS marked a turning point in the history of the industry.

The next study conducted by the group involved diagnostic tests to identify the presence of HIV. In March 1985, the firm started pilot testing at its blood bank, using a reagent supplied by Abbott Laboratories, several months before such testing was made compulsory in Spain.

The Creation of the Grifols Group

An Opportunity for Diversification

A New Corporate Structure

By the 1980s, the Gri-Cel instrumentation company, created in the 1950s by Dr. Víctor Grífols Lucas and his friend, Dr. Guillermo Celis, was struggling to make a profit. The diagnostic business was structured on the basis of a division between Dade, which was responsible for reagents, and Gri-Cel, which handled the sale of devices. The reagents generated ongoing demand and did not

George Darnell, President of American Hospital Supply, makes a presentation to Dr. Víctor Grífols to mark the 25th anniversary of the partnership with Dade.

require after-sales service, in direct contrast to the instrumentation business, in which customers, primarily clinical laboratories, made an initial investment in equipment, with Gri-Cel then having an ongoing obligation to provide technical support. The mechanical devices required frequent adjustment and repair, and it was decided that the best way to resolve this problem was to restructure the business and merge the two companies.

As a result, Gri-Cel was absorbed by Dade-Grifols in 1983, when Gri-Cel ceased to exist as a separate company and was transformed into a commercial brand instead. This was only the latest step in the long history of the group's diagnostic line, with more surprises lying in wait in the future. In the next two years, the Grifols companies continued to work closely with their respective partners: Laboratorios Grifols with Alpha Therapeutic Corporation (Alpha), and Dade-Grifols with American Hospital Supply Corporation (AHS).

In 1985, the companies celebrated the twenty-fifth anniversary of the partnership with AHS, and the attendance of the company's shareholders also provided the opportunity to hold a general meeting. There was nothing to lead the participants to suspect that events unfolding elsewhere would dramatically change the future of the company. A phone call raised the alarm. A competitor company, Baxter-Travenol, had bought AHS, despite the fact that AHS was twice the size of its purchaser. After four weeks of negotiations, Baxter-Travenol had finally succeeded in closing the deal, and the next day the news was all over the front pages of the international press.

Baxter-Travenol was a pharmaceutical multinational dedicated to the manufacture and sale of intravenous products, plasma-based therapies, and products to treat renal disease. It had invested heavily in Spain, with manufacturing plants in Valencia and Cuenca, and was therefore one of Grifols' biggest competitors. And now it was also one of its shareholders. This uncomfortable situation would make for a tricky relationship with Alpha Therapeutic Corporation, and as soon as the news had been digested, Grifols' management began to consider the different options available.

The loss of Dade-Grifols

Baxter wanted to purchase the whole of Dade-Grifols, but the group was reluctant to lose such an important and profitable business, particularly given that the company included Gri-Cel, now reduced to the status of a commercial brand, but historically the Grifols company that had made such an important contribution to the development of laboratory instrumentation in post-war Spain. Retaining the whole of Dade-Grifols was not an option, as the company's core business was the distribution of AHS products. And in the event of this

company deciding not to renew these distribution contracts, the business, too, would be lost. There was no choice, but to sell. Before completing the deal, Dade-Grifols set a new sales record, selling the equivalent of three months' worth of goods in a fortnight as its customers, afraid of losing the source of their products and appreciative of the service the company provided, stocked up on everything they could lay their hands on in the hope that the company would once again reorganize its diagnostic business. As the final orders were fulfilled, the sale of Dade-Grifols was brought to completion, a transaction that was far from easy, given the fact that the two companies shared the same sales department. All the work of the preceding two years to create a strong sales network had

to be undone. Lists were drawn up and submitted to Baxter, indicating who worked for Laboratorios Grifols and who worked for Dade-Grifols, with staff being divided between the two companies. Personal preferences also came into play, with some opting to move to Baxter while others, despite the uncertainties that lay ahead, choosing to stay with Grifols. Under the purchase agreement that was finalized on June 29, 1987, those who wished to remain at Grifols were free to do so.

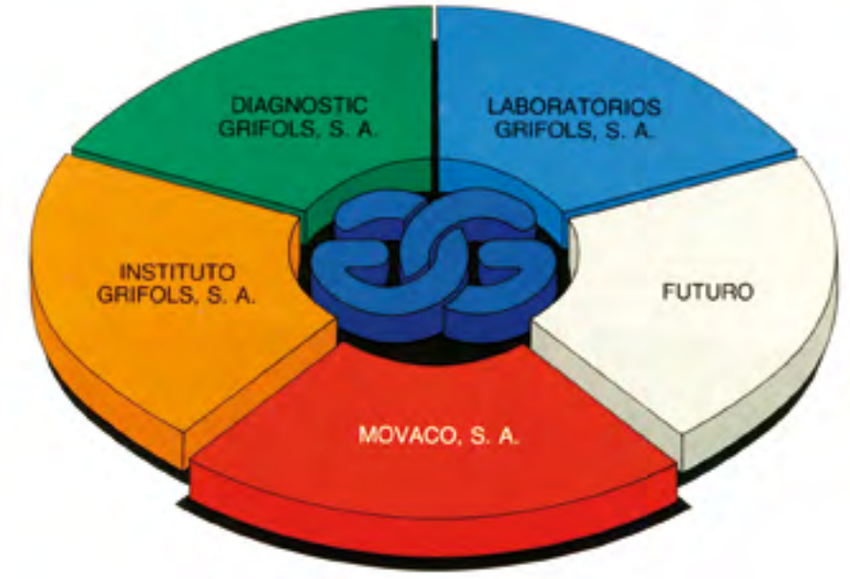
The birth of the Grifols group

As a result of the sale of Dade, the Grifols companies had to be completely restructured, and the original shareholders decided to reinvest the proceeds of the sale in the creation of the Grifols group. Alpha, with extensive experience in business reorganization, backed the Spanish shareholders with further investment of its own. The aim was to create a structure that would gradually strengthen and diversify the business, and thus ensure a more stable future.

To achieve this, a new structure was designed, requiring the establishment of various companies and the provision of sufficient capital and resources within the framework of a new business plan for the group. One of the biggest problems arising from the sale of Dade-Grifols was financial. The Spanish health system was notorious for its slow payment of suppliers, and this meant that Grifols depended for its short-term funding on a system of cross-guaranteed loans under which loans taken out by Dade-Grifols were guaranteed by Laboratorios Grifols, and vice versa. With the sale of Dade-Grifols, it was necessary to renegotiate loans worth 1.5 billion pesetas ($12 million) with a total of 16 banks. Fortunately, the financial operation—the first of many that Grifols would have to conduct over the next few years—was a success, and all of the banks renewed the loans without requiring guarantees.

Although this first obstacle had been overcome, other problems remained. Under the terms of the sale, Dade had retained some of the company's offices, and new premises thus had to be found. While all of this was happening, the team at head office was busy designing organization charts, recruiting new staff, changing working systems, and creating new infrastructure.

This reorganization process culminated in November 1987 with the creation of the Grifols holding. "Our aim is to maximize the diversification of our activities while remaining, as far as possible, within the health sector. With regard to the future, we believe that the best approach is to create a group of companies, rather than divisions within a single company," explained Grifols' current President and CEO, Víctor Grífols Roura, in a report.



The problems associated with the split from Dade, when expenses, employees, and salaries shared between the two companies had to be divided up, was behind the decision to go with a holding company of specialist firms. This was headed by the parent company, Grupo Grifols S.A., with the other companies being Laboratorios Grifols, Instituto Grifols, Diagnostic Grifols, Movaco, and Logister.

Laboratorios Grifols

With the creation of the holding company, Laboratorios Grifols ceased to be involved with the manufacture of plasma therapies, focusing instead on intravenous fluid therapy and parenteral solutions. A new company, Instituto Grifols, would focus exclusively on plasma-derived medicinal products and on ensuring compliance with the demanding quality and safety standards associated with these products. This meant that Laboratorios Grifols could focus on the production of parenteral solutions in flexible or plastic containers, a project that could finally be launched after many years of preparation.

There were also improvements to the manufacturing facilities, and the filling line for small containers was moved to make space for production in flexible containers. The company not only adapted to the new structure and took on a new set of responsibilities, but also developed new intravenous therapy products.

Output of parenteral solutions reached 10 million units, and a third autoclave—specifically designed to process solutions in flexible


GRUPO GRIFOLS,S.A.


movaco
sociedad anónima


INSTITUTO
GRIFOLS, S.A.


LABORATORIOS
GRIFOLS, S.A.


DIAGNOSTIC GRIFOLS,S.A.


LOGISTER

containers—was commissioned as part of a series of adaptations needed in order to minimize the risk of microbial, particulate, and pyrogen contamination. The incorporation of the third autoclave provided an opportunity to computerize the sterilization process, making it both more accurate and more efficient.

Instituto Grifols

In addition to the challenge of adapting to the changes arising from the sale of Dade, Instituto Grifols found itself fighting on another front, when sales of albumin to China were suspended. Fortunately, sales resumed in March 1988 and remained stable, providing Grifols with a steady income stream that helped it meet its cash flow needs.

Diagnostic Grifols

In July 1987, Grifols had inherited 80 employees from Dade-Grifols, but its portfolio of diagnostic products was almost non-existent, as was its offering of reagents and laboratory supplies, while the sale of Dade meant it had no distribution contracts.

Although some suppliers remained faithful to Grifols, there were too few of them to provide the basis for a viable business. The new company, Diagnostic Grifols, responded by drawing on its past experience with the cardiovascular product line. The aim was to establish a stable portfolio of medical devices for which Diagnostic Grifols would act as the Spanish representative. Distribution offered high profit margins, and the newly created medical division specialized in cutting-edge products. The only weak point was the instability of commercial relations with suppliers, and for this reason the division always worked hard to support the companies it represented. During the 1990s, it offered a competitive portfolio of devices and disposable material for use in hospital procedures and surgery by radiology, urology, and vascular surgery departments. It also expanded into neurosurgery, neuroradiology, and general surgery.

Of all the new Grifols companies, this was the one that underwent the most radical restructuring of its business, with the recruitment of new product managers responsible for developing policies to launch and sell these items, some of which were completely new for the company and its sales network. The whole Diagnostic team threw itself body and soul into the new enterprise and, as a result, monthly sales went from zero to 70 million pesetas ($650,000) in just ten months. Although this figure was still some way short of the peak levels during the Dade period, it was a very

positive start, and one that augured well for the future of Grifols' involvement in clinical diagnostics.

Movaco

Movaco was created to provide centralized sales and marketing functions for the new holding group. Like the other companies in the group, the most pressing challenge was the need to establish a new structure and reorganize its branches throughout Spain. Movaco's external products division handled sales of third-party products (those not manufactured by members of the Grifols group). The new company needed to raise 400 million pesetas ($2.75 million) to fund sales, in particular those to the Spanish health system. In addition to its capital requirements, the company also needed a new head office, and in 1988 it moved into new premises on the Parets del Vallés industrial estate, north of Barcelona.

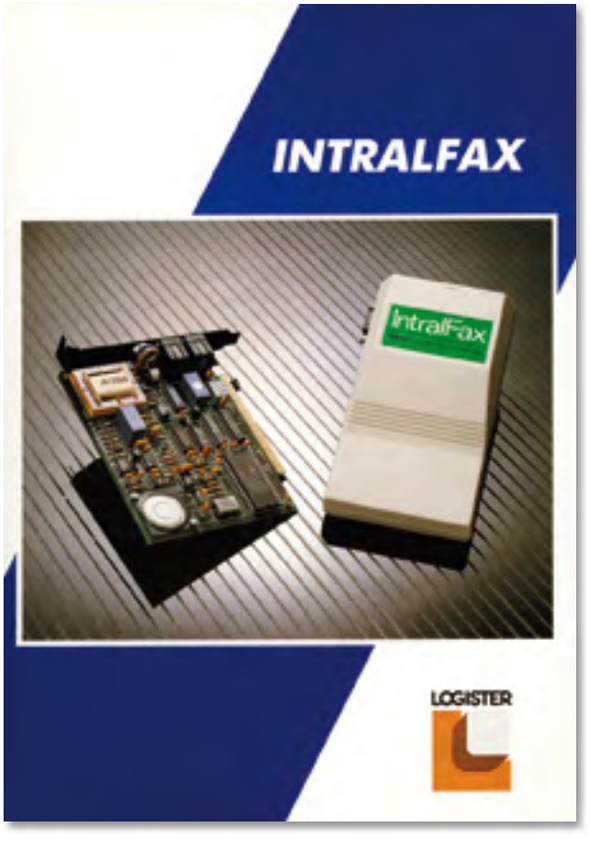
Commercial branches in Spain in 1987.

Logister

The final company in the Grifols group was Logister, which provided a means for Grifols to diversify into a new area: information technology. It was created to supply Spanish hospitals with hardware and software, as a means of adding value to the hospital pharmacy services that used Grifols solutions. This experience provided a starting point for the development of specific inventory management software, and was also the basis for the new hospital logistics line that would grow in importance as the 1990s progressed.


Laboratorios Grifols, S.A.
1940
1988
LABORATORIOS GRIFOLS, S.A.


DIAGNOSTIC GRIFOLS, S.A.
EL FRUTO DE LA EXPERIENCIA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Plasma Safety

From the First Blood Bank to Biomat

The Spanish health system had come a long way since its establishment in the 1960s. New health infrastructure had been created, along with new bodies to manage it. Following the transition to democracy in the mid-1970s, Spain gradually devolved some

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1 Vehicles used to distribute plasma-derived products. 1966.

2 Entrance to the Laboratorios Grifols blood bank. 1966.

3 Donor waiting room. 1966.

4 Plasma extraction room. 1966.

5 Extraction cubicle. 1966.

competencies in health matters to regional governments, and also invested in a major hospital building program to address imbalances in the system. The private sector was also affected by these changes and, while it continued to exist, in some cases its operation was significantly limited by new legislation. An example of this was Spain's first private blood bank, founded by Grifols back in 1945, which supplied blood to Spanish hospitals and also provided plasma to Grifols for use in the manufacture of plasma products. Donors attended the blood bank at Jesús i Maria street in Barcelona, where they were subject to strict monitoring in the form of medical checks and lab tests.

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300 c.c. de sangre estabilizada con Solución ACD (Fórmula B-USP XVI) de cualquier grupo y Rh.	450'—
Hematíes concentrados de cualquier grupo y Rh, procedentes de 500 c.c. de Sangre	600'—
Plasma Líquido Fresco	
Hasta 75 c.c.	3'50 c.c.
de 75 c.c. en adelante	3'— »

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Blood donation, for which people had always been paid, gradually began to be seen as something that should be done on an altruistic basis, in a similar way to organ donation. Although charitable blood donation was insufficient to meet the country's needs, health legislation made the operation of private blood banks increasingly difficult, and eventually threatened their very existence. To guarantee the availability of plasma for use in the production of plasma derivatives, the law continued to allow plasmapheresis centers to compensate plasma donors for their time. However, this exemption came with the condition that these centers must be nonprofit organizations, and Grifols therefore established Hemobanco de Barcelona, with its articles of association expressly stating that it was a nonprofit body. Following the establishment of the company in 1987, the Bank of Spain claimed that the name Hemobanco (Spanish for blood bank) could lead to confusion by creating the impression that it was a financial institution, and Grifols finally opted for the name Hemo Barcelona.

The combined pressure from the media and the authorities resulted in the gradual closure of the country's blood banks, and despite its attempts to survive, the Grifols blood bank at Jesús i Maria street

Barcelona blood and plasma bank reception area. 1987.

closed its doors in 1989, bringing to an end a 44-year history of service to hospitals and hematologists. It was the last surviving member of Grifols' network of donation centers that had once covered much of Spain.

While the trade in Spanish plasma had been forbidden, purchasing it from other countries for import continued to be legal. What is more, plasma-derived products produced using this commercially obtained, imported plasma were also purchased by the health system to supply its hospitals. The blood used by Spanish hospitals for transfusions had a very short shelf life: stored at 4 degrees Celsius, it lasted for an average of 28 days, after which time the red blood cells degraded. Normally, it was only the red blood cells that the hospital required, with the result that the other components were discarded. However, if the blood was centrifuged, the expired red blood cells could be separated from the plasma, which could then be used to obtain albumin and gammaglobulin. In 1978, the blood donors' association of Jerez de la Frontera, in the south of Spain, proposed that Laboratorios Grifols be granted access to its surplus blood to manufacture these products, in return for which it would return the processed plasma. To shield itself from potential legal complications,

Extraction room. 1987.


PLASMA FRESCO CONGELADO
Grupo (ABO)
Rh (D)
Unidad n.º 1083
Dto. n.º 21910
Fecha extracción 21-1
Procedente de sangre donada benévolamente
Negativa para HIV y AG HBs y Anticuerpos irregulares
Conservar por debajo de -32 °C
Se considera fresco por un plazo de 6 m

Viral inactivation of plasma bags.

a notarized certificate accompanied each delivery of bags.

The authorities encouraged hospitals to support this approach in order to become self-sufficient in plasma. In October 1985, legislation passed to regulate blood donation and blood banks, finally providing a clear legal framework for the process of obtaining blood components and collecting plasma destined for the fractionation industry.

It was in this context that Grifols organized its program for the integrated processing of hospital plasma. Under the program, the relationship between the industry and the public blood banks was governed by a fractionation contract, with Grifols returning the plasma-based therapies the center from which the excess plasma had come. To promote a standardized response to logistical and quality control issues, the group organized a seminar for the directors of blood banks in 1986. With the support of the Department of Health, this initiative delivered major improvements to the quality of plasma, and also increased hospital participation in the program. In four years, the volume of plasma processed under the arrangement rose from 9,292 liters in 1983 to almost 40,000 liters in 1986. By 2010, this figure had reached 382,000 liters.

The economic crisis subsequently had an impact on the level of donations and on demand for blood components from the Spanish health system. This decline had a significant influence on the amount of plasma available to produce plasma products in terms of national self-sufficiency, and for this reason hospitals promoted the use of plasmapheresis as a means of reversing the fall in plasma volumes.

Bag of fresh frozen plasma, for use in the AIPH (Hospital Plasma Processing Program). 1990s.

The creation of Biomat

Following the closure of the blood bank, and in order to optimize use of the excess plasma from hospitals, Grifols decided to create a company dedicated exclusively to the logistics of collecting, controlling, and analyzing biological material in the form of plasma. The company was therefore called Biomat. To avoid any possibility of error when handling plasma batches for fractionation, in 1991 Biomat was housed in a different location of the Parets del Vallés industrial estate.

The Biomat laboratory conducts tests to ensure the quality of the plasma for fractionation. And the company keeps samples of every single unit of plasma that makes up each fractionation batch, so that any unit of product can be traced. After it has been tested, Spanish plasma, plasma from the United States, and plasma from other countries with which Grifols has a fractionation agreement is stored in refrigeration chambers at temperatures of minus 30 degrees Celsius and then sent to Instituto Grifols.

In 1995, new laboratories were established to perform nucleic acid amplification tests to detect both HIV and the hepatitis C virus, before such steps became compulsory. Alpha had initially resisted the application of this technique for financial reasons, but Dr. Víctor Grífols Lucas, who was always such a stickler for safety, insisted on it. The test was made compulsory in Germany one year later, and in 1997 it became obligatory throughout the European Union. In the same year, in order to increase product safety, it was decided to extend

Biomat building at the Parets del Vallés industrial complex.

the quarantine period for plasma, a move that meant the workforce had to be expanded and working procedures had to be revised. Biomat ceased to work exclusively for companies in the Grifols group when its inactivation division began to offer its services directly to hospitals. As part of this initiative, Biomat established the hospital transfusion plasma inactivation program in 1997, designed to prevent viral transmission during transfusion via units of plasma collected at hospitals. It also signed a technology transfer agreement with the German Red Cross, enabling it to apply a methylene blue viral photoinactivation method.

New Production Methods

The Long Road to FDA Approval

Fears of the risk of viral infection of biological material, the higher incidence of hepatitis, and concerns about the side effects of biological products led the manufacturers of plasma-based therapies to focus on two objectives: more effective purification of clotting factors, and quality selection of plasma.

Alpha Therapeutic Corporation clotting factors VIII and IX. 1980s.

Grifols worked hard to produce safer, higher quality products for patients. The first new licenses and product launches reflected the successful development of Criostat. This was indicated for the treatment and prevention of hemophilia, and was the first concentrated clotting factor VIII to be manufactured by the company. Laboratorios Grifols, like its partner Alpha Therapeutic Corporation (Alpha), was conducting trials in this field, and submitted an application to register its new heat-treated factor VIII based on the latest scientific literature and on Russian studies that discussed a viral inactivation system for lyophilized plasma and antihemophilic globulin for the hepatitis virus. As AIDS had not yet been identified, and the theory that it was a virus had not been completely accepted, Grifols' application to submit factor VIII to heat treatment was based on evidence that heating produced significant inactivation of the hepatitis virus, and was therefore named Criostat HS (Hepatitis Safe). Because the hepatitis virus was one of the most resistant, the hope was that this treatment would be equally valid for the hypothesized AIDS virus. However, the application was rejected on November 19, 1982, on the grounds that it

was not innovative. Despite the refusal, Grifols continued to work on developing a product that would not transmit any type of virus, as the idea that AIDS was caused by an infectious agent was gaining ground. Again, several laboratories submitted work on different heat-based methods of viral inactivation at the hemophilia congress the following year, in Stockholm.

Two years later, in 1984, Grifols submitted an application to the Spanish Department of Health for authorization to market factor VIII, Criostat HT (Heat Treated), a product whose manufacturing process included a viral inactivation and heat treatment and heptane method. The method, designed by Alpha, had been authorized in the United States, but did not receive the same response in Spain because, according to the authorities, it was "a modification of the manufacturing process of a pharmaceutical preparation that had already been authorized."

The Food and Drug Administration (FDA) had already approved the product in the United States, giving doctors a choice between a heat-inactivated factor VIII or a product that had not been treated in this way, and thus helping to ensure the supply of this product to the hemophiliac community. Unfortunately, the Spanish Department of Health did not share this view, and suggested that the group choose between one of the two preparations. Finally, in June 1984, Grifols took the decision to opt for the heat-treated version of factor VIII. This decision was a risky one, with significant financial implications for Laboratorios Grifols, as heat treatment significantly reduced plasma yields, from 140 to 80 units per liter.

Heat-treated factor IX. 1980s.

In July 1984, Laboratorios Grifols received approval of the change from the Department of Health. At that time, of the six factor VIII preparations available in Spain, only two were heat-treated, although with different methods. The Laboratorios Grifols version was heat-treated at the liquid phase, with heat treatment being applied when the product was in suspension, while the product sold by other companies underwent heat treatment during the final stage of the lyophilized product. At the time, this difference did not seem too important, but heating of the final, lyophilized product was rejected in some countries because of its far more limited viral inactivation capacity. The company applied the same method to its prothrombin concentrate, another product used in the treatment of hemophilia and certain congenital deficiencies. The product went on sale in 1986 under the name Hemofactor HT.

The group's research to improve the quality and safety of its products continued. Although heat treatment was found to inactivate certain lipoprotein-coated viruses, such as hepatitis C and HIV, to offer a totally virus-free product it

was necessary to apply an additional method that used a solvent-detergent chemical process to inactivate non-lipoprotein-coated viruses. Combined with pasteurization, the solvent-detergent method was found to be one of the most effective procedures. In 1989, Grifols became the first manufacturer of plasma-derived products to apply double viral inactivation to factor VIII, using both heat treatment and a solvent-detergent process. The resulting product was marketed as Criostat SD-2. This plasma derivative enabled Instituto Grifols to achieve a 55 percent share of the Spanish market for clotting factors.

The development of these new plasma-derived products incorporating viral inactivation coincided with the appearance of so-called recombinant factors. While Grifols opted to continue to manufacture from plasma, several pharmaceutical companies focused their efforts on attempts to develop clotting factors by means of genetic engineering. Although it initially seemed that these recombinants, as they were known, would replace treatment with plasma products, subsequent studies found that plasma-derived products were both safer and more effective. What was more, they were associated with lower incidences of inhibitor generation and with better outcomes in their elimination.

First factor VIII with double viral inactivation. 1989.

The FDA: the big challenge

Given the lack of Spanish regulation on good manufacturing practices, Grifols had always followed its technological partners in applying U.S. legislation in this area. Since the 1970s, it had begun to implement North American Good Manufacturing Practices. Following the creation of the group and the consolidation of the companies, a new team of quality engineers began working to improve product safety and quality; although applying procedures, improving quality controls and integrating the different departments to achieve a shared goal was no easy task. The factory had grown rapidly in the preceding years, but it maintained very well-established routines, with a lot of work going into documenting processes and perfecting production methods and quality control.

Following the successful launch of double-inactivated factor VIII, in 1988 Grifols faced one of its greatest challenges: obtaining an FDA

license for its facilities. The aim was not so much to export to the United States—where it already manufactured Alpha—but rather to obtain certification that would endorse the processes and advanced technology used in the Parets del Vallés plant. This was a longstanding ambition of Dr. Víctor Grífols Lucas, who wanted to demonstrate that the facilities at Parets del Vallés complied with much stricter standards than those established by the Spanish authorities. With FDA approval, the group aimed to lay the foundations for its entry into new markets, and to achieve this goal the support and experience of Alpha would once again be vital. Following their advice, Grifols decided to apply to the U.S. administration for authorization of the manufacture of albumin. This move made the group the first Spanish company to seek FDA approval for a biological product.

The first step was to outline the modifications that would need to be made to the factory; a process that would require a major investment program. The first inspection of the facilities by the FDA took place on June 18, 1990. At the time, the road surfaces in the industrial park where the plant was located had not yet been asphalted, and this somewhat undermined the image of cleanliness that one might seek to

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1 First pasteurized liquid intravenous immunoglobulin. 1992.

2 Food and Drug Administration inspection at Parets del Vallés plant. 1992.

project for a plasma-derived products plant. However, first impressions of the interior of the site were very positive.

Striving to satisfy the FDA requirements did not prevent the group from continuing to work on the launch of new products. In the field of antibodies, which until then had been intramuscular, the group was evaluating two types of products available to Grifols: Alpha's lyophilized version, and the Green Cross's liquid version. Despite the fact that the companies had the same shareholders, the three factories did not make the same products or apply the same processes. Grifols was in the lucky position of being able to study the two presentations, and Dr. Víctor Grífols Lucas chose the Japanese version, a pasteurized liquid immunoglobulin. However, the product was only licensed in Japan and the information available was limited, in contrast with the North American process. As a result, it was decided to apply first for registration of the lyophilized product—which already held FDA approval—and then the liquid one. To this end, a clinical trial was conducted in the United Kingdom and in Spain, and at the same time the manufacturing process was optimized, something that would take two years to complete.

By improving the processes used by the Green Cross Corporation, the group developed a pasteurized liquid intravenous immunoglobulin with the commercial name Flebogamma IV, indicated for the treatment of primary immunodeficiencies. The product, launched in 1992, made Grifols one of the first companies in the world to offer a product of this sort, and the launch required significant investment in new facilities to deliver increased production levels. Total plasma fractionation capacity was increased by 50,000 liters to 300,000 liters per year. Germany and the United Kingdom were the first countries to register and authorize this product, which was marketed through

the subsidiaries of Alpha, before it was made available in Spain. As the group's 1993 Annual Report noted, this pasteurized liquid gammaglobulin would be "one of the company's star products in the years to come."

The commitment to internationalization also began to bear fruit, and by 1994 foreign sales accounted for 25 percent of total turnover, which was twice the level of 1993 and four times that of 1992. An added benefit was that these sales generated immediate cash flow, in contrast with the situation in Spain, in which the group continued to suffer from lengthy delays in payments due from the Spanish authorities.

For some time, Grifols had been working on an improved version of double-inactivated factor VIII, which was already available in Germany, but had not yet been granted a license in Spain. With the launch of Fanhdi (double-inactivated human antihemophilic factor), the group introduced a high-purity concentrate obtained using a new purification process. One of the key advantages of this process was its ability to retain von Willebrand factor, a protein that acts as a natural stabilizer. Subsequent research would demonstrate the major advantages of its presence in this plasma derivative, compared to the recently released recombinant clotting factors. Authorization to sell Fanhdi in Spain arrived just in time for Christmas, on December 23, 1994.

This period of new product launches and manufacturing improvements culminated in 1995 with the granting of the FDA license, when Grifols successfully came through the third inspection and obtained an establishment license for the Instituto Grifols facilities and a product license for albumin. This was a huge step for the company, and one that had been achieved as a result of the motivation and hard work of its staff. It was the first license that this body had granted in Spain to a biological product for human use and to a plasma-derived products manufacturing plant, making it only the second European company to be recognized in this way and helping to convert Grifols into a global player in the plasma proteins therapeutics industry.

Leaflet for high-purity, human antihemophilic factor. 1994.

More Practical Containers

Parenteral Solutions in Glass and PVC

One of the motives behind the change of partner from American Hospital Supply (AHS) to Alpha Therapeutic Corporation (Alpha) was that AHS lacked its own technology to manufacture plasma products. But this was not the only reason. AHS manufactured its parenteral solutions using a technology that it had licensed to a Madrid company; a fact that meant it could not be transferred to Grifols. For this reason, following the creation of the holding group and with

Aerial view of Las Torres de Cotillas plant. 1998.

the aim of offsetting chronic delays in payment by the public sector in Spain, Grifols decided to diversify its product range across all of its divisions. The aim was to open up new markets and to achieve a better balance of sales, so that each of its divisions—biological products, pharmaceutical products, and non-pharmaceutical medical-hospital products—would generate a third of the group's income. The group explored new presentations for parenteral solutions, which until then had been presented in glass bottles, and Grifols' experience of the U.S. market led it to believe that the future lay in a flexible container: the PVC bag.

The first attempts to find a bag that would be suitable for solutions and the filling process caused quite a few headaches, until contact was finally made with a specialist company that designed bags to meet the group's technical requirements. These bags were filled with the appropriate solution at Parets del Vallés, using a machine developed by Dr. Víctor Grífols Lucas. The product was so successful that the initial supplier was unable to meet demand, and an alternative manufacturer had to be found. Hypnos, a company based in the Murcia region of southeastern Spain, was selected. The company manufactured blood storage bags, and it had previously supplied Grifols' blood and plasma banks. This history helped to smooth the path, and a formal relationship was quickly established, with demand for the new product that would make Grifols a major customer for the plastic containers manufactured by Hypnos.

In the mid-1990s, when its supplier was experiencing financial difficulties and Grifols was purchasing 80 percent of output, it was decided to acquire the company. The Parets del Vallés plant manufactured parenteral solutions in glass and flexible containers, while the Murcia plant was modernized to meet Grifols' standards. Some years later, due to the increased production of plasma derivatives, the original parenteral solutions plant was transferred to a new building in the Parets del Vallés industrial complex, a facility that was granted a license from the Spanish Department of Health in 2002. Occupying an area of 6,000 square meters (65,000 square feet), it had been designed by a team of Grifols engineers, and incorporated a high level of automation and a number of proprietary manufacturing solutions. The plant was officially opened in September 2003 and had the capacity to produce up to 45 million bottles per year.

At the time, Grifols was Spain's leading producer of solutions in glass containers and the second-largest producer of solutions in flexible containers. Its plants at Parets del Vallés and Murcia held ISO 9001 quality certification and ISO 14001 environmental management certification. Despite this dominant position, the parenteral solutions market was saturated and offered few opportunities for growth. What was more, there was no way of accessing international markets due to the high distribution costs, and as a result the majority of the

Laboratorios Grifols production plant in Parets del Vallés. 2004.

1 Automated control room for sterilization autoclaves. 2003.

2 Automated control of solutions preparation. 2003.

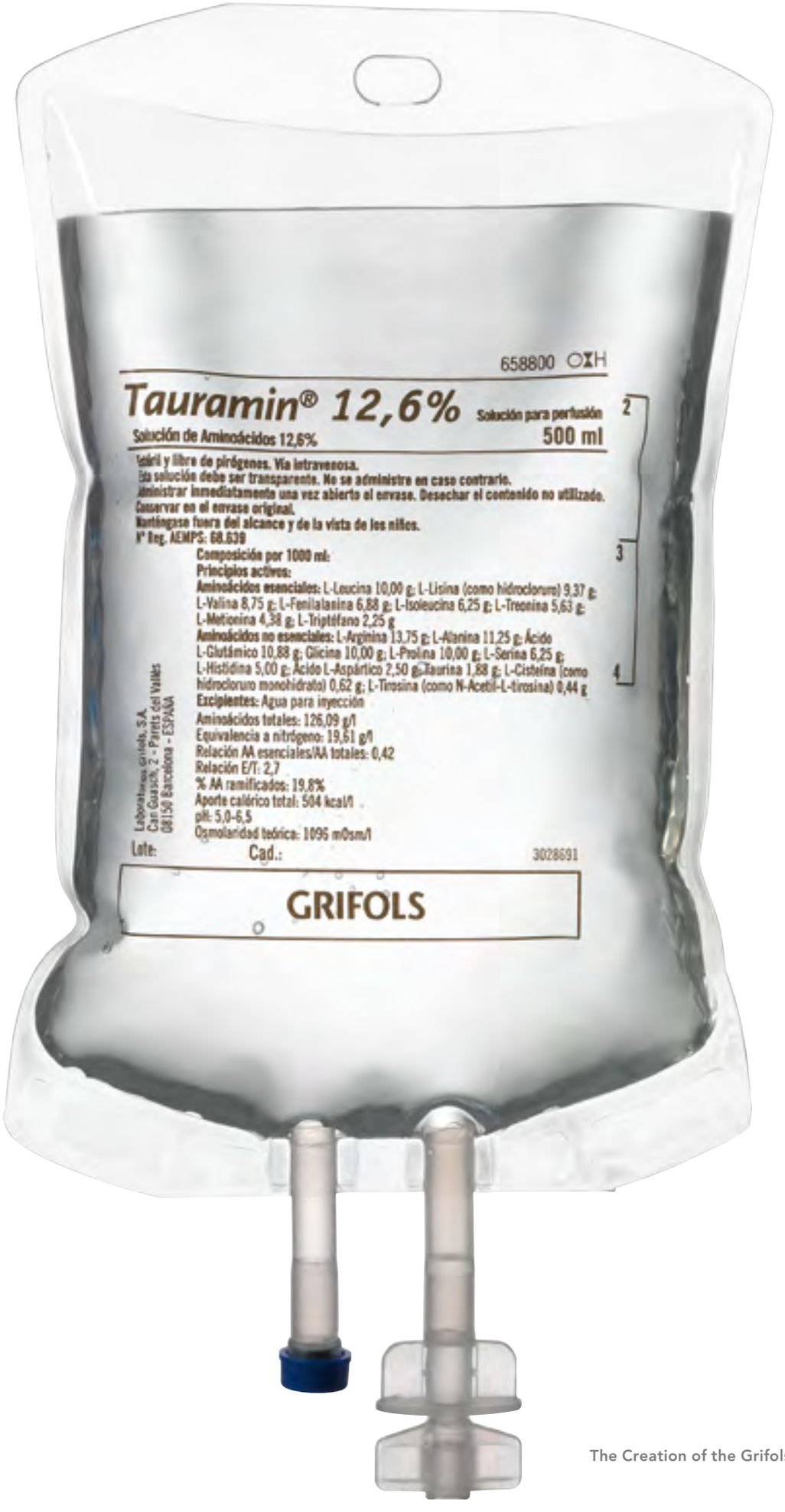
3 Particle inspection system using artificial vision. 2003.

division's sales were generated in Spain and Portugal. To increase the division's activities, two new objectives were established: to expand its hospital logistics offering, and to begin third party manufacturing in order to capitalize on the industrial infrastructure of Laboratorios Grifols and its plants at Parets del Vallés and Murcia. Third party manufacturing of fluid therapy products was channeled through Grifols Partnership, a service that drew on all the group's experience and knowledge of the documentation required for product licensing applications.

Parenteral nutrition

As part of the product diversification policy, the group developed amino acid and lipid solutions for parenteral nutrition (the intravenous administration of the basic nutrients required by patients). In 2000, the Soyacal lipid emulsion was launched, manufactured under license from Japan's Green Cross Corporation. Staff from the technical department traveled to Japan to learn about the production method with a view to adapting it to develop a more stable process. Some years later, both the composition of the formula and the production method would be changed in order to increase the yield and obtain a more resilient product.

In addition to this launch, the Regulatory Affairs Department worked hard to obtain product licenses for Argentina, Chile, Italy, Portugal, and the United Kingdom, countries in which Grifols had well-established subsidiaries, providing a platform for overseas sales to commence in 2001 as part of the internationalization of the newly created parenteral nutrition product line. Tauramin amino acid solution was launched in 2005. This was a product developed by Grifols to extend the existing range of nutrients for intravenous administration to hospital patients, consisting of other lipid and carbohydrate solutions. The product line was extended in 2006 with the approval by the Spanish Agency for Medicines and Health Products of the new 8 and 10 percent solutions of Tauramin, and registration of 10 and 20 percent lipid emulsion in Germany, Italy, Spain, and the United Kingdom. In 2008, the Hospital division accounted for 10.6 percent of the group's total sales, of which 83 percent was generated in the Spanish and Portuguese markets. Of this, 50 percent of income came from fluid therapy; 9 percent from clinical nutrition; 19 percent from medical supplies, and the remaining 22 percent from the new hospital logistics line that was already well on its way to becoming a major contributor to the division.


658800 OXH
Tauramin® 12,6%
Solución para perfusión
Solución de Aminoácidos 12,6%
500 ml
Estéril y libre de pirógenos. Vía intravenosa.
Esta solución debe ser transparente. No se administre en caso contrario.
Administrar inmediatamente una vez abierto el envase. Desechar el contenido no utilizado.
Conservar en el envase original.
Manténgase fuera del alcance y de la vista de los niños.
Nº Reg. AEMPS: 68.639
Composición por 1000 ml:
Principios activos:
Aminoácidos esenciales: L-Leucina 10,00 g; L-Lisina (como hidrocloruro) 9,37 g; L-Valina 8,75 g; L-Fenilalanina 6,88 g; L-Isoleucina 6,25 g; L-Treonina 5,63 g; L-Metionina 4,38 g; L-Triptófano 2,25 g
Aminoácidos no esenciales: L-Arginina 13,75 g; L-Alanina 11,25 g; Ácido L-Glutámico 10,88 g; Glicina 10,00 g; L-Prolina 10,00 g; L-Serina 6,25 g; L-Histidina 5,00 g; Ácido L-Aspártico 2,50 g; Taurina 1,88 g; L-Cisteína (como hidrocloruro monohidrato) 0,62 g; L-Tirosina (como N-Acetil-L-tirosina) 0,44 g
Excipientes: Agua para inyección
Aminoácidos totales: 126,09 g/l
Equivalencia a nitrógeno: 19,61 g/l
Relación AA esenciales/AA totales: 0,42
Relación E/T: 2,7
% AA ramificados: 19,8%
Aporte calórico total: 504 kcal/l
pH: 5,0-6,5
Osmolaridad teórica: 1095 mOsm/l
Laboratorios Grifols, S.A.
Can Guasch, 2 - Parets del Vallès
08150 Barcelona - ESPAÑA
Lote:
Cad.:
3028691
GRIFOLS
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Murcia: the PVC bag manufacturing plant

Following the acquisition of Hypnos, Grifols invested in improvements to machinery, modifying the design of some manufacturing lines and reviewing quality standards. The first phase of the works at Las Torres de Cotillas plant, in Murcia, was completed in 1993. With a staff of almost 120 people, the new plant reduced the cost of manufacturing parenteral solutions in PVC bags, and provided the capacity to manufacture sterile material for single use.

From 1995, the Murcia plant would manufacture and fill the PVC bags, and the Barcelona plant would produce solutions in glass containers. In the same year, the Quality Guarantee System for blood bag production at the Murcia plant obtained CE certification, the first to be granted to a Spanish pharmaceutical company. Some years later this certification would be extended to the two health product manufacturing plants.

In 2001, it was decided to extend the plant with the construction of a completely new building that would provide 27,000 square

Las Torres de Cotillas production plant. 2003.

1 **Fleboflex bag preparation lines. 2012.**

2 **Packing area. 2012.**

3 **Sterilization autoclave. 2012.**

4 **Visually checking Fleboflex bags. 2012.**

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Gri-fill: automating the preparation of intravenous mixtures

In the late 1980s, the Marqués de Valdecilla Hospital in Santander, in the Cantabria region of northern Spain, collaborated with Grifols on a project to study the use of a closed filling system for low-volume bags containing filter-sterilized medicines: the Gri-fill system. The instrument was developed to meet the hospital's need to fill bags with sterile ranitidine solution without sterilizing it in an autoclave. Ranitidine is used to protect the stomach from other medicines, and it has to be dissolved with saline solution if it is to be prepared in liquid form for infusion. Dr. Víctor Grífols Lucas designed a PVC bag incorporating a sterilizing filter in each bag's filling tube, which meant the solution could be sterilized by filtration while the bag was being filled. The doctor and his team developed a machine that filled six bags at a time, with the integrity of the filter being checked automatically. The method was found to be safe, and it was decided to offer the device to hospital pharmacy services to prepare intravenous mixtures.

The system, launched in 1993 with the name Gri-fill, allowed on-site preparation of sterile intravenous mixtures of pharmaceutical products, with the doses adjusted to reflect the bodyweight and needs of the individual patient. Gri-fill 2.0 was released in 2002, incorporating several improvements, including the replacement of the filling pump with a syringe and a disposable kit and obviating the need to wash and sterilize the whole circuit after each use. In 2003, the new system obtained an FDA license for sale in the United States. A new generation of the device permitted the safe preparation of chemotherapy treatment with drugs that are generally toxic. This product was validated by the University of California in 2005 and launched in 2006.

Closed sterile solutions volumetric filling machine with Gri-fill device. 2012.

meters of space (290,000 square feet), three times the size of the existing facilities. The project included a warehouse for raw material and finished product, a plant for plastic components, and an area for the manufacturing of bags.

After coming on line in 2003, the new plant produced 14 million bags of intravenous solution per year, destined primarily for the Spanish health system, in addition to 6 million bags for the extraction and conservation of blood, of which over 50 percent were exported.

In 2005, an automated warehouse with 5,200 pallet positions for the storage of raw materials, intermediate products, and finished product was opened. In the same year, the new Fleboflex bags were released, manufactured using polypropylene, an inert material suitable for the preparation of certain intravenous mixtures that were incompatible with other plastics.

Rising demand over the years that followed led, in 2009, to the automation of the production lines and the start of construction of a new plant for the manufacture of parenteral solutions in flexible polypropylene containers. The new facilities increased production capacity by 30 million bags per year, to a total of 44 million.

Computers and software as an incentive

Grifols' innovative spirit also manifested itself in the field of information technology. In 1981, the only software systems available were for management and administrative purposes. There were no suppliers of hospital software, and Grifols therefore decided to offer computers and software programs as an incentive for purchasers of its fluid therapy products. Between 1981 and 1995, Grifols used information technology as a key marketing tool. The success of this approach contributed to a significant increase in sales, and in 1987 the group created Logister, a company dedicated to the development of hospital software. Five years later, the situation had changed radically, as the Spanish Department of Health had computerized the hospital system, while the level of competition in the parenteral solutions market meant that margins were very tight. Logister was gradually scaled back, and in 1993 it ceased to exist as a separate company and joined Movaco, the sales and distribution company for Spain.

Improving the Quality of Care

Automating Hospital Pharmacy Services

Since the 1980s, the Spanish hospital pharmacy service had gone from being a mere supplier of medicines to playing a central role in their safe and efficient use, and in controlling expenditure in this area. It was not until the mid-1990s, however, that automation of the service

began, with Grifols at the forefront of this process. In this area, the company pioneered the introduction of control and unit dose dispensing systems in Spain, and subsequently exported this model to some Latin American countries.

Sometimes it was the Grifols technical team that presented logistical systems to hospitals, while on other occasions it was the pharmacy managers themselves who identified technology that they felt could be useful in their hospital. An example of the former was the adaptation of the Kardex automated warehousing system for use in a hospital supply warehouse and pharmacy environment, while an example of the latter was the introduction and adaptation of the Pyxis Automated Drug Dispensing System. The rotating arms and carousels of the Kardex system were adapted to store and dispense unit doses of drugs. The system was presented in 1997, and the company's engineers rose to the challenge by developing a tailor-made software package called Mercurio to control and manage drugs and other hospital supplies.

In 1999, Grifols was awarded an exclusive distribution contract for the Pyxis system, produced by North American firm Cardinal Health. Pyxis enabled the group to offer hospitals a system for controlling and dispensing medicines on the ward, and allowed pharmaceutical spending to be monitored on a patient-by-patient basis. The first of these systems in Europe was installed at the Vall d'Hebron Hospital in Barcelona in 1999. The reorganization of pharmacy and hospital supply services gradually became a priority for the Spanish health system, which had come to realize that management of these areas had a direct impact both on the quality of care provided to patients and on budgetary control.

In 2005, Cardinal Health renewed its distribution agreement for a further five years, and also decided to entrust Grifols with the task of introducing this hospital technology into Latin America. At the time, there were 300 Pyxis units operating in 44 hospitals in Spain. Six years later, in 2011, over 2,000 Pyxis units had been installed in Europe and Latin America, with 400 Kardex installations, and over 300 automated systems in hospitals in Argentina, Brazil, Chile, Italy, Mexico, Portugal, and Spain.

In 2006, Grifols presented Silicon, an electronic prescription and hospital pharmacy management application. This software enhanced safety by improving the flow of information between medical, nursing, and pharmacy professionals. The tool used the UNIX operating system and web technology.

The Grifols model for the integrated hospital logistics management of drugs and disposable hospital supplies continues to develop, and currently consists of a wide range of high-tech products that cover every stage of the medication process, from the central pharmacy all the way through to individualized recording of administration to patients. This model is designed to ensure maximum quality and safety of patient care.

From the blister pack to unit doses

Grifols' most recent contribution to hospital pharmacy is the BlisPack system, the world's first automated system for the cutting, repackaging, and electronic identification of blister packs of drugs for hospital use. Presented in 2010, the system reflects the needs of hospitals that generally receive drugs from the pharmaceutical industry in the form of blister packs and have to sort them into unit doses manually due to the lack of an automated alternative. BlisPack automates the process of cutting the blister pack and obtaining a unit dose of the drug while retaining the manufacturer's original packaging. It is a completely independent device capable of packing up to 1,500 units per hour. The system helps to minimize errors by applying a barcode identifier to each dose. As with other innovations, its design and features reflect the contributions and suggestions of a multidisciplinary group of professionals from the Hospital division and engineers from Grifols Engineering, who worked closely with a team of experts in hospital pharmacy.

Industrial Growth and International Expansion

Global Horizons

International Expansion and the First Subsidiaries

From the 1960s, alliances and relationships with companies in the United States gave Grifols an opportunity to expand internationally. In those days, it was very unusual for a Spanish company to be audited to meet international quality standards, but Grifols' links with multinational companies meant that the group's philosophy,

Prototype of Coombs centrifuge for automatic washing of red blood cells. Patented in 1966.

1 Grifols Portugal. 1988.

2 Grifols de CR s.r.o. Prague. 1993.

3 Pexaco International Corporation in Miami, Florida. 1990.

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language, and operating procedures all came to reflect a commitment to quality.

Its ties with the Green Cross Corporation (a company with a strong commitment to research and development and extensive knowledge of plasma products) and with Alpha Therapeutic Corporation (Alpha) gave Grifols access to the technology that would enable it to develop its double-inactivated factor VIII, Criostat SD-2. Subsequently, it would provide a basis for the transfer of the techniques that Grifols would use to manufacture its own liquid intravenous immunoglobulin, Flebogamma.

The strategy of internationalization implemented at the end of the 1980s soon began to bear fruit, and by 1994 sales in foreign markets accounted for 25 percent of total income, with exports doubling since 1993 and rising by a factor of four since 1992. The subsidiaries established during this first phase of international expansion are described below.

Portugal

This is where the first foreign subsidiary was established, in 1988, with its head office in Lisbon. It represented the first step in the process of internationalization and provided experience in keeping accounts in other currencies, and in the export of health and pharmaceutical products.

Czech Republic

Grifols began its activities in the former Czechoslovakia in 1990 through a local distributor, Coyco Farma S.A. A year later, Instituto Grifols—in partnership with Immuno Wien—won the tender from the Czech Department of Health to fractionate plasma collected in the Czech Republic. In January 1992, fractionation at the Parets del Vallés plant began, with the resultant products being supplied to hospitals in the Czech Republic. On December 15, Grupo Grifols de CR s.r.o. was established in Prague. The subsidiary was also responsible for other countries in the region, such as Albania, Poland, and Bulgaria.

Slovakia

Established in 1999 as a representative office, the Slovak subsidiary was based in Bratislava and was responsible for market research and the promotion of Grifols products. In 2001, the subsidiary began the fractionation of Slovakian plasma, following the example of the Czech Republic.

Central America

Pexaco International Corporation was created in Miami in 1990, at a time when the city was a major hub for flights connecting Europe and Latin America. That year, Hikosuke Yorihiro, President and Chief Executive Officer of Alpha, authorized Grifols to establish a distribution company

for the Latin American market. The group had been keen to be allowed to export to South America, a natural market for Spanish companies, and permission was finally granted for the whole of Latin America with the sole exception of Brazil; a country in which Alpha had its own operations. The firm was subsequently renamed Grifols America Inc., and was responsible for sales and distribution in Central America.

Chile

Established in 1990 in Santiago, its commercial activity grew rapidly in an expanding domestic market. It was one of the group's few subsidiaries to sell almost the whole portfolio of Grifols products.

Argentina

The subsidiary was established in Buenos Aires in 1991. The dramatic impact of the economic crisis of 2001 and the lack of stability meant that the subsidiary followed a cautious strategy. As a result, the business grew slowly. However, the subsidiary now sells all the group's main product lines (plasma derivatives, blood bags, and gel technology reagents for immunohematology cards). It also serves Paraguay and Uruguay.

Mexico

The Mexican subsidiary was established in 1993 following the purchase of 49 percent of Laboratorio Farmacéutico Rollán (a firm that had been founded in 1970). In 1996, Grifols raised its holding to 100 percent. Grifols continued to manufacture the Rollán product line, and also packed its plasma-derived medicinal products at the plant in Zapopan (just outside Guadalajara, the state capital of Jalisco), which holds a license from the Mexican Department of Health.

In 1997, the President of the Government of Catalonia, on an official visit to the state of Jalisco, inaugurated the expanded subsidiary, which also had branches in Mexico City and Monterrey to enable it to serve such a large territory. The Mexican subsidiary is responsible for distribution in Bolivia, Ecuador, and Venezuela, in addition to the Central America region.

Brazil

Grifols was unable to establish itself here until 1998, as the country was assigned to Alpha's distributors. The first office was established in Curitiba, capital of the state of Paraná, 250 miles south of São Paulo and 620 miles from Rio de Janeiro. Ten years later, in 2008, it employed 15 members of staff and had a commercial branch in São Paulo.

1 Grifols Chile. 1990s.

2 Grifols Argentina. 1990s.

3 Grifols México. 1990s.

4 Grifols Brasil. 1990s.

Miami: a family and business relationship

Grifols' link with Miami, the site of the company's first office in the United States, goes back a long way to when Dr. Víctor Grífols Lucas first traveled to the city in 1961 with the aim of spending three months working at the head office of Dade Reagents Inc. in order to learn more about the company. The visit gave rise both to personal friendships and to a professional project: the creation of a new company, Dade-Grifols S.A., which would distribute Dade's products in Spain.

Dr. Grífols returned to Miami in 1964, this time accompanied by his wife. In his luggage he carried the prototype of the Coombs centrifuge, the patent of which he would sell to Dade, who exploited it with great success for many years throughout the world. In 1969, it would be his son, the current President and Chief Executive Officer, Víctor Grífols, who would cross the Atlantic for a three-month placement at Dade. This would be an experience he would repeat at other American Hospital Supply (AHS) companies, such as Harleco, in Philadelphia, McGaw, in California, and at AHS head office, in Evanston, Illinois.

Dr. Víctor Grífols, Dr. Anido and Dr. Rutllán at the Merz & Dade Congress. Switzerland. 1981.

These experiences saw the start of new friendships and gave rise to new forms of business organizations based on close relationships and cooperation agreements that were underpinned by a spirit of understanding.

In 1979, Víctor Grífols, now the Chief Executive Officer, visited the company again with his senior management team, and such trips would become a regular occurrence. Many of the ideas that these managers would subsequently implement were the result of these experiences, which gave them the opportunity to learn about how a great company like AHS operated. In his speech at the opening of Grifols' new facilities in Miami in 1994, Víctor Grífols recalled "the best way for a partnership like ours to prosper is for it to be based on a personal relationship."

Dade Harleco Sales Meeting. Attended by Dr. V. Grífols and his son, Víctor. Munich. 1974.

Europe: Accessing New Markets

Alpha's European Subsidiaries and Grifols

In 1989, the group found itself obliged to seek alternative sources of plasma when the closure of its blood bank deprived it of the raw material from which it manufactured plasma-derived medicines. Grifols started to buy plasma from its partner Alpha Therapeutic Corporation (Alpha), who had a network of plasma donor centers in the United States.

In many ways, the association with Alpha was a positive one, although it was eventually marred by quality problems due to the lack of investment in manufacturing facilities and inadequate quality control procedures. Alpha's growth strategy was based on increasing production and sales, but without updating manufacturing processes to incorporate the latest safety advances that were so vital to these products. This lack of understanding of what Grifols saw as a vitally important issue prompted Víctor Grífols to resign his membership of the board of directors of Alpha.

In light of the difficult situation facing Alpha by mid-1997, the directors of Japanese firm, the Green Cross Corporation, decided to offer Grifols the option of purchasing its three European subsidiaries in Germany, Italy, and the United Kingdom, which were also in financial trouble. The proposal was not popular with the American directors of Alpha, who saw the direct relationship between Grifols and the Japanese company as a threat. However, Grifols accepted the offer, which provided it with a great opportunity to directly access these important

European markets that had previously been closed to it by Alpha's commercial interests in Europe.

Grifols organized what amounted to a miniature trade fair to welcome the three new subsidiaries, taking the opportunity to introduce the newcomers to the organization, its culture, and its identity. Held in the Mediterranean resort town of Sitges in July 1997, each of Grifols' departments and divisions explained what they did, and the members of the board of directors explained how the group would be restructured to incorporate the subsidiaries into the existing commercial structure. The holding group was reorganized into two major divisions: production, consisting of the four manufacturing companies, Instituto Grifols, Laboratorios Grifols, Biomat, and Diagnostic Grifols; and commercial, led by the newly formed Grifols International S.A. The new European subsidiaries are described below.

1

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1 **Grifols Italia staff celebrating St. George's Day. 2010.**

2 **Grifols Deutschland staff celebrating St George's Day. 2010.**

Italy

Established in 1993 in Pisa, it began trading in 1995 when Alpha issued its first invoice for the sale of albumin. At the time of its acquisition by Grifols two years later, it was exclusively focused on plasma derivatives, but only 15 percent of its turnover was generated by the sale of Instituto Grifols products. The Food and Drug Administration's (FDA) decision not to authorize the sale of Alpha products pushed the subsidiary to the brink of bankruptcy, but the enthusiastic response of customers to the company's new strategy and its success in obtaining the registrations for a number of Grifols products helped to turn its financial position around.

Germany

The tax and legal problems of Alpha's subsidiary in this country led to the decision to create a new company in May 1997. Grifols Deutschland progressively took over all the activities that had previously been performed by Alpha GmbH. At that time, the German plasma protein market was one of the most important in the world, and some years previously Grifols had manufactured anti-thrombin III (AT-III) for Germany, sold under the Alpha brand. The Chief Executive Officer of Alpha GmbH at the time had asked Grifols to manufacture the product because it was not possible to import it from Japan, and Alpha no longer manufactured it. As a result, Grifols studied the production method used by the Green Cross Corporation and added the product to its portfolio.

United Kingdom

Based in Cambridge and established in 1979 as a subsidiary of Alpha, it primarily sold factor VIII, factor IX, and intravenous immunoglobulin (IVIG). Early in 1990, it became the distributor of Grifols IVIG and factor VIII in the United Kingdom. Two years after joining Grifols, the U.K.

Strength, balance, courage, and common sense

One of the highlights of the Grifols meeting in Sitges was the construction of a human tower or *colla castellera*, in which delegates formed the base. As Grifols' corporate magazine *Cosmos* explained in 1997, this Catalan folk tradition, "summarizes the philosophy of teamwork: strength, balance, courage, and common sense. [...] And this philosophy is one on which we can build the Grifols project: working every day with the strength of a team, with the balance we need to withstand difficulties, with the courage to face new challenges, and with the common sense to act at all times in an ethical and responsible manner."

Staff of Grifols UK. 1997.

subsidiary began distribution of the Diagnostic division's products. It also offers a home delivery service for intravenous immunoglobulin, factor VIII, and factor IX.

Poland

Although the first registration applications for Poland were submitted in 1994, it would be another three years before direct commercial operations began. During this period, Grifols acted first through a local distributor and subsequently through an exclusive agent. Following Poland's entry to the European Union, the subsidiary was created in December 2003, and Grifols registered most of its plasma-derived products, in addition to blood extraction and conservation bags.

1

France

Established in 1999 in Montpellier, the subsidiary was then transferred to Meyreuil, near Aix-en-Provence. Its main activity was to promote sales of products for Diagnostic division, as France has its own publicly owned plasma-derived products company covering most of the country's needs.

2

United States

In March 2003, Grifols began to study the possibility of opening a distribution company on the East Coast, in addition to the Miami branch that primarily covered Central America. On the verge of obtaining FDA approval for its Flebogamma liquid intravenous immunoglobulin, Grifols opted for Boston, a city that boasted an excellent university sector with research activities in Grifols' own field. The subsidiary would only act as an importer of finished product, and a sales network would therefore have to be established. Three months later, Grifols faced a new challenge when it acquired the assets of Alpha. In June 2003, the head office of Grifols USA was transferred to Los Angeles, where Alpha had its central offices and manufacturing plant.

3

Asia-Pacific region

The first office in this region was opened in Singapore in 2000, with the intention that it should serve as a springboard for entering the markets of Southeast Asia. With the acquisition of the assets of Alpha in July 2003, three commercial subsidiaries were included in the sale. These were Singapore, which was merged with the existing office and established as the regional head office for the other subsidiaries: Malaysia, in Kuala Lumpur, and Thailand, in Bangkok. Grifols Asia-Pacific serves the markets of 15 countries in the region.

1 Staff of Grifols France. 2006.

2 New offices in Boston, United States. 2003.

3 Inauguration of Grifols Asia-Pacific. 2004.

Masters of their Own Destiny

From the Break with Alpha to the Purchase of its Assets

The relationship with Alpha Therapeutic Corporation began to run into problems at the end of 1997, after the retirement of the company's President, Hikosuke Yorihiro. His replacement focused on immediate economic results, while Grifols prioritized the safety of patients and products over the longer term.

Aerial view of Alpha Therapeutic Corporation in Los Angeles.

Managers of Grifols and Alpha Therapeutic Corporation at the negotiations in New York.

In October 1998, as a consequence of failings in the sterile water system at its manufacturing plant, Alpha had to withdraw some of its products from the market at the request of the Food and Drug Administration (FDA), and temporarily suspended distribution. This measure directly affected Grifols, as the company had to withdraw products distributed in the United Kingdom, Italy, and Mexico. In August 1999, the situation was further complicated when Alpha received notification from the FDA obliging it to cease manufacturing.

Three months later, given Alpha's poor prospects as a result of its failure to satisfy successive FDA inspections, its owners decided to sell their share in Grifols to raise the financial resources they needed to support the U.S. business. They met with Grifols' directors in New York to tell them that they had received an offer to buy the entire company for a value of 600 million dollars, a transaction that would produce a 300 million dollar windfall for the firm's Spanish shareholders. Financially, the offer was a tempting one, but also somewhat frightening as it would, in practice, mean the end of Grifols as a company. It was a difficult moment for Víctor Grífols Roura and the directors who had traveled with him, as they tried to weigh the financial arguments against the history of the company, the memory of Víctor's uncle, José Antonio, and the sacrifices of his father.

Head office of Alpha Therapeutic Corporation in Los Angeles.

During a break in the meeting, they glimpsed an opportunity in this unexpected situation. As on other occasions in the history of the company, it was decided not to sell, but rather to bet on the future. The directors of Grifols stunned the American directors by announcing their intention of purchasing the 50 percent of the company's shares that were held by Alpha, an offer that took the American management completely by surprise. Upon their return to Spain, the management of the group received Alpha's approval to go ahead with the operation, for which funding had to be raised immediately. Lengthy and difficult negotiations were required to close the deal, and at times the whole process teetered on the edge of failure.

As on other occasions, Grifols' legal firm, Osborne Clarke, played a key role, and the company also received valuable advice from American firm, Proskauer Rose. The final document was signed at four o'clock in the morning of December 22, 1999, beneath the famous clock in the lobby of the Waldorf Astoria Hotel in New York. The operation involved a payment of almost 200 million dollars, a significant sum of money that had to be obtained at short notice. The operation's success depended in no small part on the commitment of the directors of Grifols, who joined the rest of the company's shareholders in giving it their personal financial backing. The result of this joint effort was that the group was

Plasma donation center in Glendale, Arizona next to The Grifols Academy of Plasmapheresis. 2009.

once again the master of its own destiny. The buyout also added a new name to the list of Grifols shareholders: Morgan Grenfell Private Equity (MGPE), a member of the Deutsche Bank group, supported the operation and took ownership of 35 percent of the company.

In addition to its much-needed financial resources, this partner provided another valuable asset in the form of the financial know-how that would enable Grifols to prepare for its flotation on the stock exchange over the medium term. The process of laying the groundwork for an initial public offering of Grifols shares on the Spanish stock market within a maximum period of three years got under way, although in the end the process would take somewhat longer.

Víctor Grífols Roura, Chief Executive Officer of the group, explained the purpose of the operation at the start of 2001 in an article in the company magazine, *Cosmos*: "By breaking away from Alpha, we avoided being dragged down by that firm's situation, which has left it on the verge of bankruptcy and with the likelihood that it will be sold off." Grifols had severed its ties with Alpha, attracted a powerful financial partner, and was developing some of the most ambitious industrial and commercial projects in the plasma industry. In the words

of its President and Chief Executive Officer, "We are highly skilled and have a great team spirit. And that means that we hold the key to our own future."

New plasma suppliers

In addition to the buyout itself, the agreement also established technology exchange and plasma supply arrangements. While there were no problems during the first year, at the start of the second year Alpha introduced a sharp price rise. This increase in the cost of its principal raw material set alarm bells ringing at Grifols, and the company wasted no time in searching for an alternative supplier. Eventually, an agreement was signed with SeraCare in the United States in 2000.

The following year, Grifols decided to buy the firm for 140 million dollars, in an operation that set the seal on a relationship between Grifols and SeraCare that went back to 1997, when the company had first supplied Instituto Grifols. SeraCare was renamed Biomat USA, taking the same name as the group's Spanish company with responsibility for the control and safety of plasma for fractionation. This major operation was funded through an equity offering subscribed primarily by Banco Santander, who came on board as a new financial partner, and BBVA bank.

Hikosuke Yorihiro: a loyal friend of Grifols

Hikosuke Yorihiro, better known as Ike, began his career in the banking industry in the City of London. However, in 1981, Ryoichi Naito, the founder of the Green Cross Corporation, invited him to become Alpha Therapeutic Corporation's financial director. He was a key figure during the 1980s, when contact between Alpha and Grifols began and the latter was looking for a partner with technological and scientific experience in the plasma-derived therapies sector. Yorihiro supported the partnership from the beginning, clearly seeing that the arrangement could be to the benefit of both companies. As President of Alpha, he supported Grifols' decision to create a holding company and establish a new diagnostic division. This was because he believed that this was the best solution for the development and growth of the Spanish company, and further down the road he would not hesitate in opening the door to the creation of Grifols' first subsidiaries in Latin America, a market that had previously been reserved to Alpha.

His relationship with the company went beyond strictly business affairs, and he became a close friend of Dr. Víctor Grífols Lucas. He was a friendly, relaxed, hospitable man, with a wide variety of interests, including photography, fishing, music, and skiing. After his retirement in 1997, he lived in Los Angeles and continued to take a keen interest in the fortunes of both companies until his death in 2009.

The opportunity to buy Alpha

Following the split with Grifols, Alpha's situation deteriorated, and in 2002 the company was put up for sale. Its purchase would represent an opportunity for Grifols to consolidate its position in the U.S. market. Grifols continued to maintain excellent relations with the senior management of the Green Cross Corporation, who still controlled Alpha. Although the Japanese firm was in negotiations with Baxter, a leader in the plasma-derived therapies sector with an interest in acquiring Alpha's network of plasma centers and the license for alpha-1 antitrypsin, the executives of the Green Cross gave Grifols ten days to present an offer. Víctor Grífols Roura and his management team had to work around the clock to finalize a bid. There were only two days in which to evaluate how much investment was required by the Los Angeles manufacturing plant and to assess stock levels, but an offer for Alpha's assets was eventually submitted.

The operation, which had begun on March 15, 2003, was completed on July 7 for a value of 100 million dollars. Grifols acquired the assets of Alpha, with the exception of the product license for alpha-1 antitrypsin, and also gained three new subsidiaries: Malaysia, Thailand, and Singapore. In exchange, it had to make a major investment in modernizing the plant to bring it up to the standards required by the Food and Drug Administration. Funding came from the banks that participated in the syndicated loan, their willingness to support this ambitious project an expression of their confidence in the credibility, and transparency of the group.

Creating a team

The management and technical team tasked with modernizing the Los Angeles plant encountered an outdated facility that had been starved of investment and whose staff were demoralized. The day after the purchase had been completed, Víctor Grífols Lucas addressed the 600 employees. He explained that Grifols needed to focus all of its efforts on reorganizing and modernizing the plant, and made no secret of the hard work that would be required to turn around an unsustainable situation. The workforce responded enthusiastically, and the staff were quick to make the company's principles their own.

Industrial Infrastructure

Constant Growth

Being awarded a Food and Drug Administration (FDA) license in 1995 was a milestone in the history of the Parets del Vallés facilities, with approval for the manufacture of albumin being followed by licenses to market other plasma products, and authorization for further improvements and extensions to the group's manufacturing plants.

Although plasma accounts for 50 percent of the volume of blood, only 7 percent of plasma consists of proteins. Of this, some 60 percent is albumin, 15 percent antibodies, and a mere 1 percent clotting factors. This means that thousands of liters of plasma must be obtained via plasmapheresis to provide a hemophiliac with the factor VIII needed to treat their condition for a year.

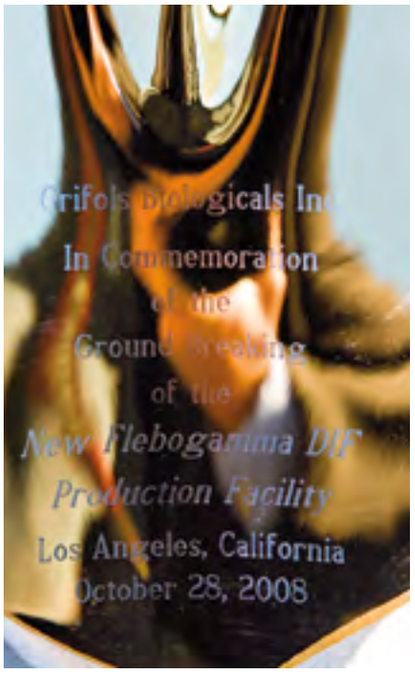
At its Barcelona plants, Grifols re-engineered the plasma fractionation process by completely redesigning the clean areas. This search to optimize space and reduce energy consumption led to a decision to isolate the zone controlling access to the interior of the reactor to reduce the volume of the areas requiring air treatment, so that most of the reactor would be excluded from these zones. This innovative concept, implemented in 1992 and subsequently patented, delivered a drastic reduction in the plant's maintenance costs by reducing the area that had to be kept 'clean'. An additional advantage was that it gave workers free access to the technical zone housing the machinery associated with the reactors, without interfering with or restricting production. Despite the initial reluctance of Alpha's engineers, the FDA inspectors validated the installation and recognized the ingenuity of an application that made it possible to double fractionation capacity by maximizing use of the available space.

After obtaining an establishment license from the FDA in 1995, Grifols began to expand its fractionation capacity with the aim of doubling output to 1 million liters of plasma by 1997. In June 2000, the initial establishment license was revalidated, with validation also pending for the group's new albumin production plant, which had


COLUMNA 150 L
AT-III

been designed in its entirety by Grifols and incorporated innovative technological solutions. In the third quarter of 2002, the plant that produced parenteral solutions in glass containers was transferred to a new building, and the space freed up as a result was allocated to the new Flebogamma DIF plant to meet rising demand for this product. That same year, the Spanish Department of Health approved the expansion of the facilities to enable it to process 2 million liters of plasma per year, making it one of the largest in Europe and one of only four to hold an FDA license. The new facilities manufactured a range of new plasma products, and 2003 saw the launch of Trypsone on the Spanish market, indicated for the treatment of alpha-1 antitrypsin deficiency.

In 2005, plasma-derived products generated almost 70 percent of Grifols' sales revenue, with the three main products (liquid intravenous immunoglobulin, albumin, and factor VIII) accounting for almost 90 percent of this, due to consolidation of the company's manufacturing, and sales and marketing structure in the United States. The strong performance of sales of Flebogamma, the group's intravenous immunoglobulin, was also helped by the fact that it was now indicated in the treatment of two more diseases: Kawasaki disease and Guillain-Barré syndrome. Another development saw the commercial release of Anbinex, an anti-thrombin III concentrate manufactured using two specific viral elimination phases.



Plaque commemorating the groundbreaking of the new Flebogamma DIF plant in Los Angeles, United States. 2008.

The challenge of relaunching the Los Angeles plant

The acquisition of Alpha's assets in 2003, which included its Los Angeles manufacturing plant, represented a new challenge for Grifols' technical team, as the plant had been under an FDA consent decree since 1998 due to quality problems. A lot of hard work would be required to bring the facilities up to the same level as the plant's Spanish counterpart, and it was decided to reduce manufacturing volume by 25 percent for almost an entire year while processes were reviewed, adapted, and modified. This reduction was possible thanks to Alpha's product inventory, which meant that sales levels could remain unaffected.

In October 2007, a new investment plan worth 400 million euros until 2012 (535 million dollars) was announced, and one of its key objectives was to increase plasma fractionation capacity. The Los Angeles facilities received a major cash injection to complete the sterile clotting factor purification and filling plant, and were granted an FDA license in May 2008. They had been designed to ensure maximum safety in the dosing, sterile filling, and lyophilization of the clotting factors: factor VIII, factor IX, and prothrombin complex. This authorization completed the first stage of investments for the

Los Angeles plant, which would also house a sterile albumin filling line that would receive FDA authorization in December 2009. In the same year, the Minifrac fractionation plant obtained the approval of the U.S. authorities. This facility had been inherited from Alpha and had never been put into operation, but the FDA gradually removed the precautionary measures that had applied to the plant, until the most important of all, the consent decree, was lifted at the end of 2012.

The new Flebogamma DIF

Two thousand and six was a year of special significance for Grifols because, in March, the FDA granted a license to the Barcelona manufacturing plant that produced the latest generation of intravenous immunoglobulin, Flebogamma DIF. At the end of the same year, the FDA granted a license for the sale of this product in the United States. This was the culmination of Grifols' most ambitious project, one that had lasted almost ten years. The manufacturing process patented by the company and developed at its Barcelona plant incorporated two separate pathogen inactivation processes,

Managers at the groundbreaking ceremony for the new Flebogamma DIF plant in Los Angeles, United States. 2008.

Minifrac installation. Los Angeles. 2007.

in addition to a 20-nanometer filtration stage, which significantly increased the safety margins of the product, making it possible to obtain a high-purity solution.

In 2006, total plasma fractionation capacity reached 3.6 million liters per year, with a capacity of 2.1 million liters at Parets del Vallés and 1.5 million liters at Los Angeles. However, the fact that Grifols only actually fractionated 1.8 million liters of plasma that year, employing only 50 percent of the firm's capacity, showed it had plenty of capacity to grow. The long-term investment plan provided for a further

PediGri: guaranteeing the traceability of all plasma derivatives

PediGri is an innovative program designed to ensure the traceability of all Grifols plasma-derived products from plasma donation through to the finished product. By entering the batch number, health professionals can access specific information for each plasma donation used in the production process, and can view the product batch analysis certificate and fact sheet. This commitment to transparency goes back to 1996, when Logister and the IT systems department worked together to develop the PediGri system.

Specialists in hospital software development. Logister. 2010.

Grifols Engineering: experience at the service of biopharmaceutical engineering

The knowledge that Grifols had acquired over the years in the fields of engineering and manufacturing led to the creation of Grifols Engineering in 2000. The tradition inherited from Gri-Cel of developing instruments–combined with subsequent experience of developing manufacturing equipment–formed the basis for the creation of this company that would serve all the manufacturing areas of the group, and would also offer its expertise to other biopharmaceutical companies. Its portfolio includes sterile filling systems, automated opening of plasma units, and the development of high-tech manufacturing facilities.

doubling of plasma fractionation capacity at Parets del Vallés to 4 million liters by 2013, together with investment in the construction of a new immunoglobulin purification plant to complete the modernization of the Los Angeles site. That year, Grifols also obtained authorization in Spain and Italy to market Niuliva, an anti-hepatitis B intravenous immunoglobulin whose main indication is the prevention of reinfection by the hepatitis B virus in patients undergoing liver transplants as a result of hepatitis B.

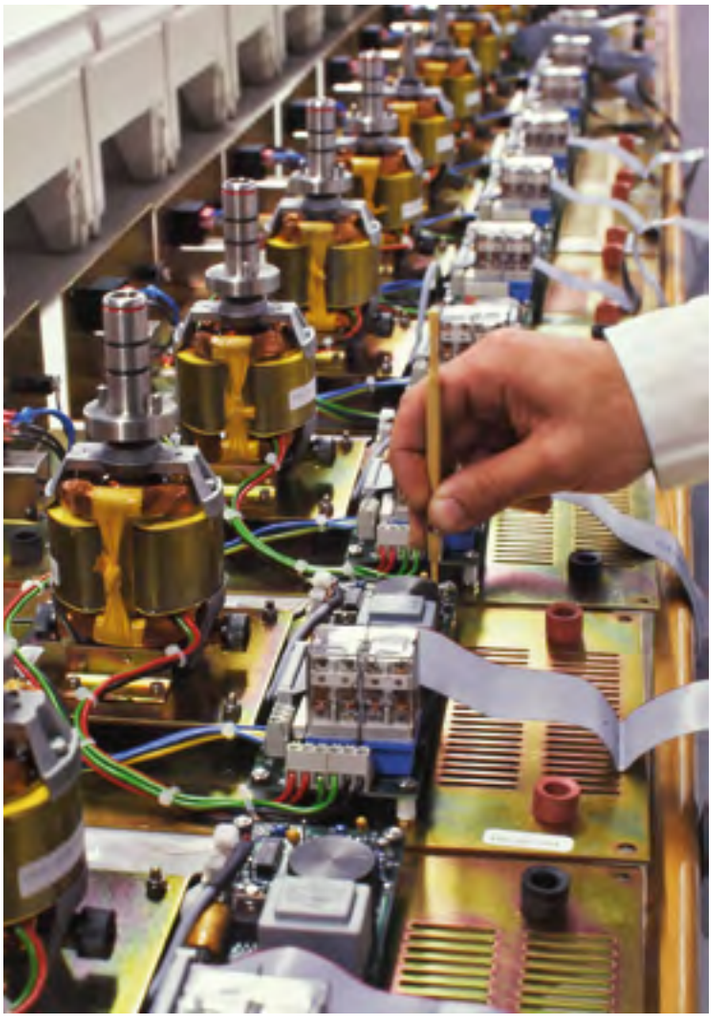
At the end of 2009, sales of plasma-derived products generated almost three quarters of the company's income, with the division doubling its turnover in the preceding five years. Sales of intravenous immunoglobulin, albumin, and factor VIII accounted for almost 90 percent of income, with 50 percent generated in Europe and 35.7 percent in the United States. That year, marketing authorization was granted for Flebogamma DIF 10 percent in the United States, offering health professionals the choice between 5 percent and 10 percent concentrations of the product, depending on the patient's needs. By the end of 2010, Grifols had facilities for the manufacture of plasma products in both Parets del Vallés and Los Angeles.

Flebogamma DIF plant, Los Angeles, United States. 2013.

The Automation of Blood Typing

New Instruments and Reagents

Grifols' involvement with analysis and diagnostics goes all the way back to 1909 and the foundation of the Central Institute of Clinical, Bacteriological, and Chemical Analysis by Dr. José Antonio Grífols Roig, grandfather of the current President and Chief Executive Officer. This activity was continued by Gri-Cel, the company created by Dr. Víctor Grífols Lucas and Dr. Guillermo de Celis, which in 1961 went into partnership with U.S. firm Dade; specializing in reagents and instruments in order to add new products to its range and gain access to new markets.



Diagnostic Grifols Diana processor assembly line. 1990s.

The subsequent purchase of Dade by Baxter in 1985 and the division of Dade-Grifols led to the creation of the Grifols holding group and a new company, Diagnostic Grifols, in March 1987. In the search for new products, Grifols contacted Swiss firm, Diamed, a manufacturer that had launched a new type of reagent for blood typing. Its innovative gel agglutination technique had already been well received in international markets, and the group obtained the distribution rights for Spain and Portugal. In addition, the sales potential of these reagents led the research and development team at Diagnostic Grifols to develop two instruments to semi-automate the new technique, designed to support the introduction of the reagents of gel cards into the market. The results were an incubator and the Diana processor (the name formed from a contraction of 'diagnostic analyzer'), both of which were presented to Diamed.

Initially, the Swiss were somewhat skeptical as to whether a company from a country

with no tradition or reputation in the clinical diagnostics sector could make any useful contribution in this area. However, they were forced to overcome these prejudices when they saw just how effective the Diana processor could be in automating the technique. The result was a global distribution contract under which Diamed sold the processor with the name ID Sampler II.

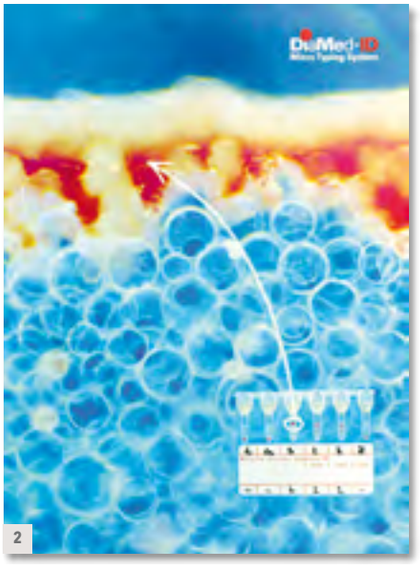
Total automation of the analysis process required a number of other elements that Grifols also developed. For example, to read the card wells where the reaction occurred, the company developed the Diamed Reader, a reader using artificial vision that had been developed in cooperation with the Polytechnic University of Catalonia. Again it was presented to Diamed and, despite some reluctance on their part, the international distributors of the cards included it in their portfolio of immunohematology products.

The next development was to automate the pipetting of reagents and other dilutions, even though Diamed did not believe this to be necessary. However, through their contacts with analysis laboratories, the Grifols sales network had identified this requirement, as the automation of the pipetting process would minimize human error.

1 Diana processor assembly. 1990s.

2 Diamed Micro Typing System poster. 1990s.

3 Twin Reader with tray and card. 1990s.



The company pioneered this innovative, cost-effective solution that also incorporated direct piercing of the seal.

Use of the Diana processor to identify blood groups and perform transfusional compatibility studies saved time and reduced errors and the risk of sample contamination. It also offered over 200 different pre-programmed techniques to cover all the needs of clinical laboratories. What was more, its small footprint meant that it could be accommodated in the limited space available in the typical immunohematology laboratory.

The sales figures speak for the success of the Diana system: in the year of its launch, ten units per month were exported to Switzerland, from where it was marketed globally, with a further eight units per month being installed in Spain. One year later, Diagnostic Grifols manufactured 200 units, of which 50 were in use in Spanish laboratories. This success led to the

Celebrating the manufacture of the 500th Diana processor. 1998.

expansion of the premises of Diagnostic Grifols, and in 1995 the division moved its instrumentation manufacturing area to a new building at Parets del Vallés, giving it almost five times as much space as it had previously enjoyed.

Six years after its launch, in 1999, in a simple ceremony in the production assembly area, Dr. Víctor Grífols Lucas pressed the Enter key that would start the manufacture of the five-hundredth unit. The Diana processor was the basis of the models that came after it, which have positioned Grifols as one of the leaders in the immunohematology diagnostics sector, as a producer both of reagents and of instrumentation.

The first Grifols reagents

Despite the healthy sales performance, the relationship with Diamed came to an end in 1996 due to commercial differences. The break left Grifols in a weak position, and contact was rapidly made with Diagast, a French company linked to the Lille Transfusion Center that manufactured a similar gel card reagent. This led to an agreement to distribute the cards under the Diana gel brand, which differed from the Diamed version in having eight reaction columns instead of six. In addition, Diagnostic Grifols redesigned the format of the reaction column to deliver clearer, more reliable results.

1 DianaGel reagent card. 1990s.

2 WADiana, blood typing device. 2000.

3 Performing quality control on the WADiana. 2000.

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Due to a patent issue, Diagast was forced to suspend its activities, and Grifols purchased the technology that, after improvement, provided the basis for Grifols' own gel card. The development of reagents was the second step in creating a portfolio of integrated diagnostic solutions. This involved months of hard work and experimentation to study the behavior of gels, and to analyze errors in blood group typing. Even Dr. Víctor Grífols Lucas, who was now retired, contributed his experience as a clinical analyst to help perfect the new reagent. The result was the DG Gel card, which became a standard in blood compatibility tests.

In 1999, the next generation of the Diana processor, the WADiana (which automated typing and transfusional compatibility tests) was launched. The WA stood for 'walk away,' as this was a fully automated system. The innovative WADiana autoanalyzer aroused the interest of Ortho Clinical Diagnostics, part of the Johnson & Johnson group, and of Olympus; both of whom wished to add the analyzer to their range of immunohematology laboratory products.

In 2010, the next generation of the automatic immunohematology analyzer was presented: Erytra, a high-capacity blood typing device aimed at transfusion services and blood banks that processed large volumes of tests on a daily basis.

Elisa reagents

During the long association with Dade, as part of its immunochemistry line, Grifols' had distributed a microplate-based Elisa (enzyme-linked immunosorbent assay) analysis kit, manufactured by U.S. firm Diamedix. However, the product ceased to be available when the company that manufactured it changed hands. Some time later, in 1996, a group of former Diamedix employees offered Grifols similar kits through a new start-up. And in response, Grifols decided to buy a 25 percent stake in the new firm, Quest International Inc., a share that would increase to 35 percent the following year. This gave the group access to the manufacture of reagents and the sale of immunology instrumentation for these reagents in the United States. The Grifols device was named Triturus, and was an open, flexible autoanalyzer for Elisa techniques that permitted the use of a wide range of reagents. It was launched simultaneously in Spain and in the North American market.

Triturus carousel for Elisa techniques. 2006.

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Hemostasis

Now coagulation was the only diagnostic specialty for which Grifols did not have proprietary instrumentation, instead distributing a device manufactured by Amelung. Despite the delay in its development due to the need to dedicate resources to the WADiana and Triturus projects, the Q hemostasis analyzer was launched in 2005. The new instrument determined clot formation times, an essential piece of information when operating on patients, and was aimed at emergency departments and hemostasis labs.

Like the WADiana system, the commercial strategy for the new instrument was based on consumption of the associated reagents, and in 2009, the group launched its own hemostasis reagents that had been specially developed to work in the Q analyzer. At the same time, the range of products was gradually expanded to make it more competitive.

1 Celebrating manufacture of the 1000nd Triturus device. 2009.

2 Q hemostasis autoanalyzer. 2010.

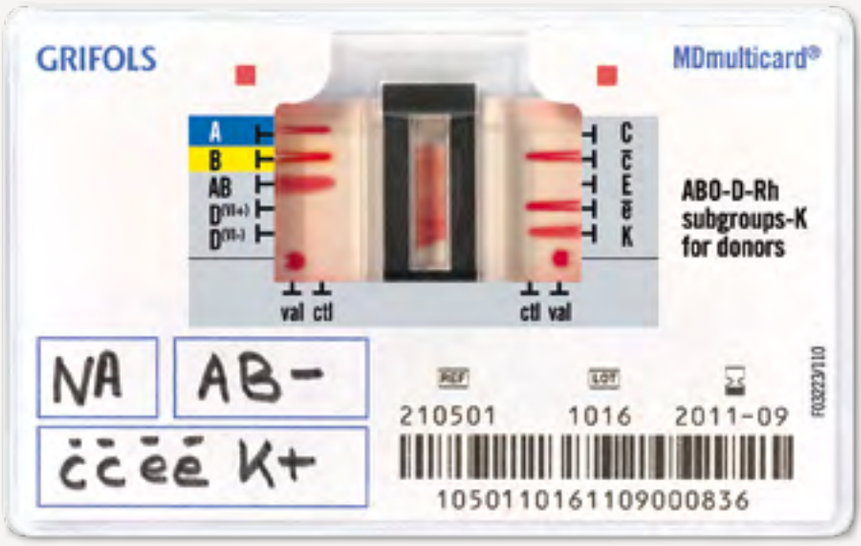
3 *In vitro* diagnostic instruments manufacturing area. 2013.

Technology diversification

As part of its strategy of expanding its immunohematology range, in 2009 Grifols acquired 49 percent of Australian-Swiss group Lateral-Diagnostic, the owners of Swiss firm Medion, specialized in the development and manufacture of immunohematology reagents. This company had developed new technology for the rapid performance of blood typing tests, the MDmulticard test.

One year later, in September 2010, Grifols opened a new MDmulticard manufacturing plant in Düdingen, Switzerland. Two new lines for the production of DG Gel cards were also opened in Melbourne, Australia. The purpose of these investments was to significantly increase production of both cards, in order to ensure greater product availability in the new markets, where the group was also seeking to consolidate sales of other items.

In the immunohematology line, Grifols completed its product range with an agreement with Progenika Biopharma, based in Bilbao, for the international distribution of that company's new blood genotyping test, BLOODchip. In contrast with the DG Gel card, which uses a blood sample to perform a serology blood test, BLOODchip uses a DNA sample to perform much more extensive tests, enabling it to deliver an exhaustive analysis of all the subject's blood groups.



3

One Step Ahead

A History of Research

Dr. Walter Oppenheimer in the laboratory of the Central Institute of Clinical Analysis. 1930s.

Research has always been a central part of Grifols' activities, and as far back as the 1940s the Central Institute of Clinical Analysis had its own research department. The investigations conducted by this department led to the first lyophilized plasma in 1943, and the development of the plasmapheresis technique by Dr. José Antonio Grífols Lucas in 1951. Since then, the search for new therapeutic proteins and the study of new manufacturing processes have been part of Grifols' ongoing commitment to society; a commitment that has also found expression in the development of diagnostic instrumentation, and new products in the areas of fluid therapy and hospital logistics.

During the 1940s and 1950s, in the difficult times that followed the end of the Spanish Civil War, the lack of material and economic resources limited research, and the partnerships with North American companies such as Dade, American Hospital Supply (AHS), and Alpha Therapeutic Corporation (Alpha) in the 1960s gave the group access to advanced knowledge and new technologies. The results of this transfer of technology and knowledge included Flebogamma intravenous gammaglobulin and success in obtaining Food and Drug Administration authorization for albumin, an achievement that built on the previous experience of Alpha.

In the mid-1980s Grifols decided to strengthen its own research capacity so that it would no longer be dependent on the research and development strategy of Alpha and the Green Cross. These years saw the development of Criostat SD2, the first factor VIII concentrate with

double viral inactivation using both the solvent-detergent method and heat treatment, as a response to the threat of HIV.

In the mid-1990s, an initial team of 15 researchers belonging to the process development and biochemical laboratory departments was recruited to work on a range of research projects. Until 2000, they worked primarily on product safety issues, evaluating and establishing nucleic acid amplification techniques to screen for the presence of viruses in plasma units for fractionation. They also conducted research into the group's own products, demonstrating the benefits of plasma products over the recombinant products that had been released at the start of the 1990s.

Instituto Grifols R&D laboratory. 1990s.

These studies were important in comparing plasma-derived factor VIII with the recombinant product. In the hemophiliac community there was a perception that recombinant products were inherently far safer, as they were not primarily of human origin. It is not difficult to understand the reasons for this belief, given the devastating impact on the hemophiliac community of the side effects of treatment with plasma-derived products, as a result of which the community had been

ravaged by HIV and hepatitis during the 1970s and 1980s. The studies and their subsequent publication in specialist journals were essential in demonstrating that plasma-derived products had the highest levels of safety and efficacy, in addition to offering the advantage of lower inhibitor rates than recombinant factors, one of the major complications of the new products. The publication of various studies of this issue in scientific journals earned the company international prestige and established its reputation in the scientific sphere. Grifols thus became a participant in the process of globalization in the widest sense of the word, and not solely at the economic level. It was not just an international company with manufacturing facilities and employees in countries across the world, but it also contributed to the dissemination of medical knowledge and health technology. Being in the vanguard of the economic growth and expansion of the preceding decades also meant cooperating with the international scientific community to improve health care.

Reagents R&D team. 2009.

Grifols Scientific Awards

Grifols' commitment to supporting the scientific community in its search for medical advances that affect people's health and quality of life finds expression in the Grifols Scientific Awards. Over the years, Grifols has established a number of prizes to promote and recognize research in disciplines linked to our areas of activity.

Martín Villar. Hemostasis Prizes. To recognize young researchers engaged in activities related to clinical research in hemostasis, with the aim of promoting studies in this field.

SPIN. Awards for scientific progress on the use of immunoglobulins in neurology. To develop novel concepts in immunoglobulin research in neurology, by encouraging the research of novel therapeutic options for patients with neurological conditions.

ALTA. Alpha-1 Antitrypsin Awards. To identify and support clinical and scientific research into alpha-1 antitrypsin, offering researchers the opportunity to study this protein in greater depth.

Albus. Albumin Awards. To recognize studies that extend our knowledge of the role of albumin as a therapeutic product.

GATRA. Scholarship program. To promote research on antithrombin therapy.

Industrial improvements

One of the main lines of research and development activity focused on industrial improvements, and particularly on improving the production process for the world's first pasteurized liquid immunoglobulin, Flebogamma, with the result that yields increased by 25 percent. In partnership with Alpha, Grifols had developed alpha-1 antitrypsin, a product for patients suffering from a deficiency of this protein. The company also implemented the PediGri program, giving health specialists information about each unit of Grifols plasma-derived product.

As these research and development projects grew, so the clinical trials department was expanded to meet the need to determine the safety and efficacy of new products. Another development was the design of a new model of blood bag that included a filter to remove leukocytes from red blood cells in order to prevent contagion with bovine spongiform encephalopathy, better known as mad cow disease.

In the diagnostic field, Grifols was the first company to automate the column agglutination technique, something that had never been done before. The automation of laboratory routines for pretransfusion tests improved the speed, standardization, and safety of transfusional diagnostics.

The level of resources allocated to research and development activity continued to grow as the years went by. At the end of the 1980s, Grifols allocated the equivalent of 4.5 percent of income to this area, a figure that had risen to 6 percent by the end of the 1990s; a proportion that has remained stable since then. This increase is particularly impressive if we recall that it occurred at a time when the company was involved in major investments such as the purchases of Alpha, SeraCare, and PlasmaCare, and leaves no room for doubt as to the group's commitment to research.


TELSTAR
BioUltra
BIOHAZARD

Research activity

Research activity has been one of the drivers of the company's growth, helping it to become a global leader in its field. In Spain, the authorities have repeatedly classified Grifols' research program as 'excellent,' recognizing the company's major research effort. The firm's longstanding commitment to research and development led to its inclusion in 2007 in the European Union's classification of Europe's top 1,000 companies for investment in research and development, a list that only features 23 Spanish firms.

Evidence of the benefits of this commitment are the almost 700 patents held by Grifols in 2010, of which 65 percent pertain to the Bioscience division, 20 percent to Diagnostic, and 15 percent to Hospital. The last decade has seen further increases in the research effort, with the number of patents almost tripling in this time. The fact that 70 percent of these patents have a remaining life span of ten years or more means that the group's intellectual property enjoys a high level of protection. This is reinforced by the fact that the group has not licensed any of its patents to other companies. The importance of these assets led to Grifols' decision to establish a specialist department dedicated to managing and maintaining patents and brands, and monitoring possible infringements.

Another aspect of the company's commitment to research is its policy of recruiting staff with a background in academic research and with experience in planning, managing, and implementing complex projects. These employees are the human capital that has enabled Grifols to pursue new lines of research in fields such as Alzheimer's disease and cirrhosis.

In addition, in 1999 Grifols renewed its tradition of scientific publication, a defining feature of the company since its foundation and one that was strongly encouraged by Dr. Víctor Grífols Lucas. The company undertakes research both on an independent basis and in partnership with public and private entities, with publication in a range of scientific journals making the results of these studies available to the wider medical community as part of the exchange of knowledge between scientists across the world.

Research laboratory. Araclon Biotech. 2008.

A Dream Come True

Becoming a Listed Company

In 2000, after buying out Alpha Therapeutic Corporation's (Alpha) share in Grifols, it was decided to explore the possibility of floating the company on the stock exchange. This influenced the decision to choose Morgan Grenfell Private Equity, a member of the Deutsche Bank group, as a partner on the basis of its financial experience.

The first step was to create a new parent company for the holding group. As a result, Probitas Pharma was established in June 2001 to replace Grupo Grifols S.A. The name change was intended to project the image of a global health company, with the name Probitas connoting the core values of life and honesty. That year, the general meeting of shareholders approved an equity offering of 90 million euros, subscribed in its entirety by Grupo Santander Central Hispano through its subsidiary, Secuoya Capital Privado. The banking group, the biggest in Spain and one of the largest in Europe, thus became a Grifols shareholder, owning 11.3 percent of the company's equity. This equity offering—together with

other funding sources—was allocated to the acquisition of SeraCare Inc., an operation that was completed in March 2002 and led to the incorporation of one of the leading plasma collection companies in the United States, with a workforce of more than 800 employees. This strategic acquisition ensured the company's supply of plasma.

The attack on the World Trade Center in New York in September 2001, and the subsequent world stock exchange crash, made it advisable to postpone the launch. However, the initiative would be resumed in 2003 with the aim of consolidating the company in the U.S. market. The prospectus submitted to the Spanish stock exchange regulator expressed the long-standing aspirations of the Grifols family as follows: "Achieving the necessary financial flexibility would enable the company to consolidate its presence in the United States." By 2004, the United States already accounted for 20 percent of sales, with Europe generating 40 percent, excluding Spain, which generated a further 20 percent.

The operation provided for the Grifols family to retain 30 percent of the company. Víctor Grífols Roura explained this presence with reference to the family's own history, one that had always eschewed speculation in favor of a responsible business philosophy. As Chief Executive Officer at the time, on July 7, 2004, he explained his reasoning to Spanish financial daily, *Cinco Días*: "For us, it is a dream come true, not the sad end of a family business."

Probitas Pharma's debut on the trading floor was scheduled for July 16, 2004. The media described the planned launch as 'complicated,' because the business of manufacturing and selling biological products derived from human plasma was something of an unknown quantity both for the general public and for institutional investors. "It lacks sex appeal," wrote one financial journalist. To address this lack of knowledge, the company's directors held meetings with market analysts and institutional investors explaining their business plan and their strategy for expanding in Latin America and Europe, their manufacturing capacity in the United States as a result of the assets they had acquired, and the opportunity to increase income on the basis of synergies within the group.

The Spanish stock exchange regulator approved the launch for July 16, 2004, and this consisted of offering up to 50.02 percent of the equity at a price of between 2.7 and 3.3 euros per share, thus valuing the business at between 550 and 700 million euros. The operation was coordinated by Santander Central Hispano (SCH), Banco Bilbao Vizcaya Argentaria (BBVA), and Deutsche Bank, and consisted in a subscription offering of 15.4 percent of the equity and an initial public offering (IPO) of 28.11 percent. In this way, 10 percent of the total was set aside for small investors; 25 percent was allocated to Spanish institutional investors, with the remaining 65 percent for international investors.

Víctor Grífols Lucas. President and CEO of Grifols. 2000.

Grifols makes its debut on the Barcelona Stock Exchange. 2006.

Company managers during the roadshow to promote the launch. 2006.

The financial partners of Probitas Pharma would sell part of their shares in the IPO, while Capital Riesgo Global, a Santander Central Hispano company, intended to dispose of half of its holding (21.7 percent of the total). Morgan Grenfell Private Equity, the Deutsche Bank fund, would reduce its holding from 37.7 percent to 4.6 percent, with the result that—upon completion of the operation—the Grífols family would hold 30 percent of the capital. The IPO proved to be a tricky affair, with the plasma-based therapies sector failing to attract investors, and the low level of demand registered during the subscription period led to the decision to call the process off at short notice.

"The money people are scared," the analysts explained. The wariness of investors combined with the bursting of the dot-com bubble, and with so many companies selling their future without having

a viable business model for the present, gave no choice, but to cancel the launch. Despite this, the company managed to raise sufficient financial resources to consolidate its presence in the United States, reduce its debt, and absorb Alpha, thanks to internal adjustments and the strict control of spending and investments, an effort to which every member of the Grifols workforce contributed.

In a letter addressed to employees in December 2004, Víctor Grífols Roura recalled the events of the summer: "It was a heavy blow for all of us." In a delicate financial situation, a number of measures were considered, the most dramatic of which (not least for symbolic reasons) was the sale of Laboratorios Grifols, the parenteral solutions company that suffered most from the delays in payment by the Spanish authorities. However, the improved performance in the United States, with the start of sales of Flebogamma, together with spending controls and other measures, allowed the disposal of Laboratorios Grifols to be avoided, and in 2005 Probitas Pharma changed its name back to Grifols.

2006: successful stock exchange flotation

In August 2005, the group's shareholding structure underwent significant changes, with the exit of Santander Central Hispano and Deutsche Bank and the entrance of three investment funds managed by Morgan Stanley: one of the world's leading financial institutions, and one with a thorough knowledge of the plasma-based therapies industry. The entrance of these new partners, debt reduction, and positive annual results in 2005 enabled the company to resume its plans for trading its shares on the stock exchange.

The 2006 launch was designed to raise financial resources for three key objectives: to buy back non-voting shares created as a result of the restructuring process, to fund the company's business plan, and to gradually increase investment in research and development. In addition, it also sought to provide the principal shareholders with liquidity. The hopes on which the previous attempt had been built had now become a reality: the company had had a direct presence in the United States for three years, sales had grown exponentially, as had profits, and the shortcomings of the Los Angeles manufacturing plant had been addressed.

The subscription offering was coordinated by Morgan Stanley, with the guideline price ranging between 4 and 4.5 euros per share, and with 71 million shares initially on offer. The process began on April 5 following approval by the meeting of shareholders, and in the same month the Spanish stock exchange regulator approved the prospectus. One week earlier, Grifols had made a splash by purchasing 100 percent of PlasmaCare, a company with 14 donor centers in the United States

Dr. Víctor Grífols rings the bell marking the start of trading. 2006.

and a plasma collection capacity of 500,000 liters, thus ensuring the supply of raw material for the manufacture of plasma products.

This time, the management held an extensive round of presentations with local investors in different cities and countries across the world. In addition to these roadshows, the company improved the communication of its business strategy by using other formats, such as promoting meetings between investors and health professionals with a knowledge of plasma products.

At the end of the subscription period on May 15, Grifols and Morgan Stanley set the starting price at 4.4 euros, slightly below the upper limit, and representing a total stock exchange valuation for the company of 937 million euros. The next day, Morgan Stanley confirmed that the demand for Grifols shares was more than ten times the number of shares on offer, amply demonstrating that the group had achieved a high level of credibility with institutional investors.

Despite this, there was still a lot of uncertainty as to how the shares would perform once trading began, primarily due to the poor results of Renta Corporación and Parquesol, the companies that had preceded Grifols in making their stock exchange launch, and whose shares were at that time trading at below their launch price.

On Wednesday May 17, 2006, on the Barcelona stock exchange, a satisfied Dr. Víctor Grífols rang the bell to start the day's trading. However, before he did so, Víctor Grífols, his son and the current President and Chief Executive Officer, welcomed the new shareholders on board and remembered his uncle, José Antonio Grífols Lucas, who had died prematurely in 1958: "I know that this moment would have filled him with pride."

That day, the Ibex 35, the main Spanish stock exchange index, recorded its largest fall since 2004, dropping by 3 percent. Despite this, Grifols shares rose by more than 15 percent on their debut, to hit 5.09 euros per share, valuing the company at 1,084 million euros (1,345 million dollars). The main shareholders were the four branches of the Grífols family (36.1 percent), Morgan Stanley (13.9 percent) and Scranton Enterprise, the company that represented the group's management (10.9 percent). Following the subscription offering, the equity traded on the stock exchange represented 33 percent of the

total, with plans to allocate 15 percent of the annual net profit to dividends.

The group had achieved one of the historic ambitions of its oldest shareholders: trading on the stock exchange in order to be able to compete on equal terms with the two leading plasma-derived medicinal products companies when it came to accessing financial resources.

By the end of 2006, Grifols had achieved the best performance of a newly launched company since 2001; gaining 218 percent in one year, with its shares being included in the list of the 50 most frequently traded stocks. A year later, on December 11, 2007, the technical advisory committee of the Ibex 35 decided to include Grifols in this select listing, with effect from January 2, 2008, making it the youngest company to feature in the index. The value of the group had risen by a further 57.13 percent during the preceding year. In less than two years, then, the company had posted a spectacular performance and been included in Spain's leading share index; something that few would have predicted after the problems of 2004. The markets knew much more about Grifols, they had seen how it met its forecasts and implemented its plans, and they responded by backing the company.

Grifols head office in China. 2013.

The third international expansion

Its successful stock exchange launch gave Grifols the boost it needed to become a global company, enabling it to expand its presence in a number of foreign markets.

Japan

In March 2006, Grifols established a representative office in Osaka, Japan, to promote and generate its clinical diagnostics business, in particular the immunohematology product line.

China

Grifols' commercial relationship with China went back to the 1980s, with the first imports of intramuscular immunoglobulin thanks to its partnership with the Green Cross Corporation, the owner of Alpha. These imports have continued, although with some interruptions, for more than 30 years. Grifols' representative office in Shanghai was established in 2009, prior to which the Shanghai subsidiary handled activity that focused primarily on the distribution of the products of the Diagnostic division. China has been one of the largest markets for Erytra and WADiana autoanalyzers, and this trend is expected to continue in the near future.

Switzerland

In 2009, Grifols acquired Australian-Swiss company, Lateral Diagnostic, which had a presence in Switzerland through its subsidiary Medion (formerly Merz-Dade), a company specializing in reagents for blood group typing.

This acquisition expanded its portfolio of blood typing products by incorporating a new technology owned by Medion, the MDmulticard, for the rapid determination of blood groups, capable of delivering results in five minutes on the basis of a single drop of blood. Its Düdingen plant held Food and Drug Administration approval for the manufacture of reagent red blood cells.

Australia

Lateral Diagnostic (see above) had a strong presence in the country, and was a longstanding distributor of the Grifols immunohematology instrumentation line. The acquisition enabled the Diagnostic division to expand into new markets.

1 Facilities in Switzerland. 2013.

2 Building housing Grifols' Stockholm office. 2013.

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Dr. Víctor Grífols Lucas retires

Between the break with Alpha in 1999 and the purchase in 2003 of Grifols' former partner, an important event took place: the retirement of Dr. Víctor Grífols Lucas, who had been the company's President since 1976 and was its Chief Executive Officer until 1985. As President he had replaced his father, Dr. José Antonio Grífols Roig, following his death. As Chief Executive Officer, he in turn was replaced by his son, Víctor Grífols Roura, the company's current President and Chief Executive Officer.

Born in Barcelona in 1919, Víctor Grífols Lucas belongs to the second generation of the Grífols family. At the age of 12, under his father's supervision, he was assigned his first task in the laboratory: collecting mercury from broken thermometers so that it could be sold. He combined business vision (which led him to seek out contact with foreign firms) with a thorough knowledge of analytical techniques, learned from his father, and a solid university education in chemistry and pharmacy.

After a professional career spanning more than 60 years, Dr. Víctor Grífols Lucas

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Grifols Nordic AB

Founded in 2010 as a platform for the sale of Grifols products in the Nordic countries of Denmark, Finland, Iceland, Norway, and Sweden, Grifols Nordic commercializes products of the Diagnostic and Bioscience divisions.

Grifols Colombia Ltda.

Grifols Colombia Ltda. was established in Bogotá in 2010, although Grifols had operated in the country since 2000 via Grifols International. The subsidiary is responsible for importing, supporting, and marketing the products of the Bioscience and Diagnostic divisions, and also for identifying new distributors for other product lines the company wishes to launch in the country.

presented his resignation to the general meeting of shareholders. To mark his retirement in 2001 and in recognition of the loyalty shown by the company's employees, the general meeting of shareholders decided to distribute 1 percent of the company's equity among those members of staff who had been with the company for at least one year.

On July 25, 2011, he said goodbye to his former colleagues at an event held at the company's first manufacturing facilities in Parets del Vallés, the factory that he had helped to design with his father and whose growth and expansion he had witnessed over the years. During the event, Dr. Víctor Grífols Lucas unveiled a sculpture titled Vigor, by Clemente Ochoa, which reproduces the two interlinking Gs of the Grifols Group and is located at the entrance to the premises, where it ensures that the memory of this exceptional man and his work will live on.

In 1998, he promoted the creation of a foundation for the study of bioethics that bears his name and has become a leader in this discipline, reflecting the company's commitment to an ethical approach to business that combines quality and safety. As Dr. Víctor Grífols Lucas always reminded people, "One should never put financial interests above the safety and health of the patient."

He has also been blessed with a wonderful memory, and helped document and describe the majority of the items in the Grifols Museum in Barcelona, of which he was an enthusiastic supporter.

Like his father, he believes that there is always room for improvement, and that the world of business is like riding a bicycle: "If you stop moving forward, you fall over." At the age of 81, he retired with the satisfaction of a job well done, surrounded by grandchildren and having achieved one of his greatest ambitions: the company he had inherited from his father and that he had had to take charge of due to the early death of his brother was now listed on the stock exchange. He retired with the same discretion and humility that he had shown every morning when he went to work at the Parets del Vallés factory.

Coming to America

Entering the World's Largest Plasma-derived Products Market

Following the break with Alpha Therapeutic Corporation (Alpha) in 1999, Grifols explored the possibility of establishing a subsidiary to distribute its products in the United States. A year after its acquisition of SeraCare (later to be renamed Biomat USA) and with authorization to market its liquid intravenous immunoglobulin Flebogamma DIF in the United States about to be granted, the group established a subsidiary on the East Coast in Boston. The acquisition of SeraCare, completed in March 2002, saw Grifols absorb one of the leading plasma collection companies in the United States, with a workforce of more than 800 employees. This was a strategic move, as

Plasma donor center, Glendale, Arizona, U.S. 2009.

Plasma donors at the Terre Haute center, Indiana, U.S. 2012.

the network of collection centers would ensure supplies of Grifols' key raw material: plasma.

Three months after the subsidiary had started up in Boston, the opportunity to purchase the assets of Alpha arose. As a result, in June 2003 the group's head office was transferred to Los Angeles, where Alpha had its central offices and manufacturing plant. This acquisition would enable Grifols to manufacture in the United States, an essential prerequisite for any serious attempt to enter the U.S. market, while the network of plasma donor centers provided a key element in the company's strategy of creating a vertically integrated business that would be strong enough to face the future with confidence.

Biomat USA embarked upon a policy of increasing its network of centers to keep pace with rising production volumes. By the end of 2006, Grifols had 73 plasma donor centers supplying almost 2 million liters per year, making it the world's second-largest supplier of plasma. Two years later, the volume of plasma collected was 2.6 million liters, supplying more than 85 percent of the firm's fractionation needs. Biomat USA and its centers had over 150,000 repeat donors, each of whom underwent a detailed initial examination and regular checks to confirm their health, with the center keeping up-to-date records for individual donors. By 2010, the network consisted of 80 donor centers.

The purchase of Talecris: Grifols leaps to third place in the plasma industry

On its seventieth anniversary, on June 7, 2010, Grifols announced an agreement to purchase United States company Talecris Biotherapeutics. Six years before, in December 2004, private investment fund Cerberus had acquired Bayer's plasma products unit and renamed it Talecris Biotherapeutics, with the intention of selling it once it reached the desired value.

In August 2008, Australian firm CSL Ltd., also specializing in plasma derivatives, had reached an agreement with Cerberus-Plasma Holdings LLC. However, one year later CSL announced that it was withdrawing its proposal in light of the objections of the United States competition

Plasma derivatives production plant at Clayton, North Carolina. 2012.

authority, the Federal Trade Commission (FTC), who took the view that the operation posed a threat to competition.

The report of the FTC commissioners suggested that a company with a smaller market share might be a valid candidate. The legal team at Osborne Clarke had no hesitation in suggesting to Grifols that they seek to reach an agreement with Talecris, even though, if the commission refused to sanction the move, it could leave the group facing a bill for 375 million dollars. The FTC took over a year to approve the operation, one of the biggest ever seen in the pharmaceutical industry. On June 2, 2011, the company received permission to buy all of the shares in Talecris for 3,400 million dollars, with the total value of the transaction, including the net debt of Talecris Biotherapeutics, standing at 4 billion dollars. This purchase brought together the innovative spirit and business vision of both companies.

For Víctor Grífols Roura, the purchase of Talecris was, "one of the most important decisions of the decade," with the hope that the combination of the two companies would accelerate growth by

promoting diversification and generating major synergies across the business. "We are completely complementary and, united, we will be able to respond better and on a larger scale to the needs of millions of patients across the globe, with the safety, quality, professionalism, and ethics that are our hallmark."

The operation made Grifols one of the three largest manufacturers of plasma products in the world, with a diverse product range, and it was also a leader in plasma collection with a network of 147 donor centers and a fractionation capacity of 8.5 million liters per year.

Grifols' research and development program was also strengthened by the purchase, with resources being allocated to complementary projects. Talecris had a highly skilled and experienced team of staff in its clinical trials department, with extensive knowledge of the U.S. market and of local regulations. The combination of their know-how with the expertise of Grifols' existing research team has enabled the group to increase the number of clinical trials it conducts.

Fractionation plant at Clayton, North Carolina. 2012.

Osborne Clarke: the legal team that advises Grifols on its corporate operations

In 1982, legal firm Osborne Clarke began to provide the Grifols group with business and legal advice in the context of the tax implications of the purchase of 50 percent of Grifols by Alpha. This marked the beginning of a long and fruitful relationship at both the professional and personal level. The firm played a key role in the development of the company. Its legal and tax advice underpinned the international expansion of Grifols, and its guidance helped protect the company from exposure to tax or commercial liabilities. Its staff, specializing in a wide range of areas, have provided advice and guidance during the major corporate operations, which enabled the group to expand and grow stronger.

Víctor Grífols Lucas and Tomás Dagá, Managing Partner in Osborne Clarke.

Osborne Clarke played a key role in designing these operations and in identifying the best financial structure for them, which in some cases was technically complicated, and ultimately all of them have delivered impressive results.

The practice and its staff enjoy the full confidence of Grifols' senior management, and this is why Grifols has not created its own legal department.

Parets and Clayton: two plants with parallel histories

Grifols and Cutter Laboratories are two companies on opposite sides of the Atlantic who, over 70 years ago, embarked on parallel paths in pursuit of a single goal: to use plasma-derived products to save and improve the lives of people with rare or serious diseases. In 1972, at a time when America was still involved in the Vietnam War, Cutter Laboratories, with subsidiaries in Japan, Mexico, and Australia, decided to open a production plant in Clayton, North Carolina. At the same time, Bayer AG, one of the world's largest chemical-pharmaceutical companies, was particularly attracted by Cutter's potential contribution to its strategy of expanding into the U.S. market. Finally, after lengthy negotiations, Cutter was purchased by Bayer, who acquired the manufacturing plant when it was still only half completed. In September 1974, almost two years after Cutter's arrival in Clayton, Plasmate was launched. This was the first product to be manufactured at the plant, with the production of albumin, immunoglobulin, and tetanus immunoglobulin following shortly afterward.

In 1984, the Clayton plant was modernized and expanded, enabling it to produce intravenous immunoglobulin for the North American market. In 2005, the plant was bought by Talecris as part of an expansion program that also included the acquisition of 58 plasma donor centers, and saw sales exceed 1 billion dollars by the end of 2006. Three years later, the company had 5,000 employees and was preparing its stock market launch. And a mere nine months after that, Talecris announced that a definitive agreement had been reached for its purchase by Grifols.

A Company for People

People Power: Grifols' Strength

A Multicultural Company

Grifols is a company that has been forged by the commitment of its employees, and one that sees the people who work for it as the true source of its value. The group may be somewhat unusual in the business world: it is a company that is listed on the stock exchange, has a presence in 25 countries, and employs almost 13,000 people,

The Grifols workforce encompasses a wide range of professional profiles.

but that, nevertheless, continues to be seen as a family firm with a distinctive personality and culture that made it what it is. This spirit is, quite simply, a way of doing things that has been transmitted by Dr. Grífols and his son.

For the management team at Grifols, the best way to keep alive the traditions and values that have characterized the company during the first 75 years of its history is to recognize that this success has been built on the growth and development of its staff. The company

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1 Monitoring autoclaves used to sterilize solutions at the Parets del Vallés plant. 1990s.

2 Intravenous solution tanks at the Parets del Vallés plant. 1990s.

is committed to a policy of equal opportunities with regard to the recruitment, training, remuneration, promotion, and professional development of staff, as a means of ensuring that it has professionals capable of researching, developing, manufacturing, and marketing products designed to deliver health and well-being on the basis of the highest levels of quality, efficacy, and safety.

A growing workforce

The companies that constituted Grifols in the 1960s (Laboratorios Grifols, Gri-Cel, and Dade-Grifols) employed a total of 145 members of staff. In 1975, three years after the inauguration of the new manufacturing plant in Parets del Vallés, the workforce had risen by over 300, and between 1979 and 1987 the workforce remained stable at 455 employees.

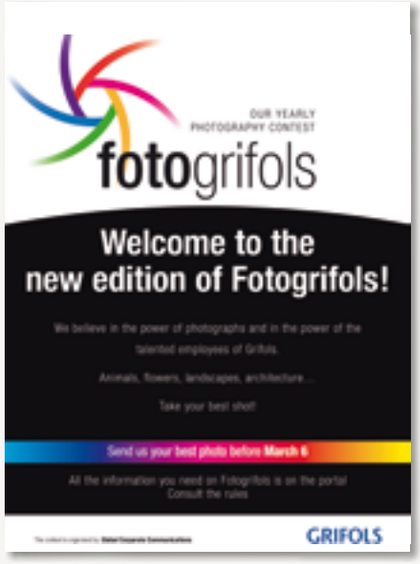
The following table shows how this growth is linked to the key events in the company's history.

Year	Average workforce	Historical event
1960s	145	
1975	300	
1979	354	
1980	354	
1981	340	
1982	342	
1983	353	
1984	300	
1987	455	Creation of the Grifols holding and Laboratorios Grifols, Instituto Grifols, Diagnostic Grifols, and Movaco.
1988	466	Creation of Movaco Portugal.
1989	475	
1990	441	Opening of Miami office. Subsidiaries in Chile and Argentina.
1991	569	
1992	655	Subsidiaries in the Czech Republic and Mexico.
1993	704	
1994	785	Inauguration of Murcia plant.
1995	915	
1996	1,021	
1997	1,155	Purchase of Alpha subsidiaries in Germany, United Kingdom, and Italy. Grifols International founded.
1998	1,347	New subsidiary in Brazil. Creation of the Víctor Grífols i Lucas Foundation of Bioethics.
1999	1,507	Subsidiaries in France and Slovakia.
2000	1,651	New Grifols offices in the USA and Singapore. Grifols Engineering created.
2001	1,770	Purchase of SeraCare.
2002	2,912	
2003	3,397	Purchase of Alpha Therapeutic Corporation. Creation of Grifols USA and subsidiary in Poland.
2004	3,509	
2005	3,443	
2006	4,199	Purchase of PlasmaCare.
2007	4,749	
2008	5,505	New corporate HQ at Sant Cugat del Vallés.
2009	5,984	Purchase of Australian-Swiss company Lateral Diagnostic.
2010	5,968	Grifols Nordic AB and Grifols Colombia created.
2011	11,230	Purchase of Talecris Biotherapeutics.
2012	11,108	

Opportunities for talent and creativity

Since 1994, the corporate calendar has featured photographs taken by employees participating in the *Fotogrifols* competition, held annually as a way of showing the diversity and skills of the people who make up the Grifols team.

Since 2005, the Environment Department has organized the Children's Art Competition, open to the children of employees and designed to promote respect for the natural world among the citizens of the future.



The importance of continuing professional development

Grifols believes that training is one of the most important aspects of the professional development of its staff, helping to mold a team with the personal attitudes and professional skills needed to implement projects anywhere in the world. The rapid growth of the network of plasma donor centers in the United States and its geographic dispersion revealed the need to find new ways of providing this team of more than 4,000 people with a suitable framework within which to share knowledge of the specialist activities that underpin the plasma industry.

The response was the creation of the Grifols Academy of Plasmapheresis in the United States, and Academia Grifols in Spain. The term 'academy' originally referred to a body of experts whose aim was to protect, develop, and promote progress in a specific field of knowledge, such as literature, art or science, through debate, work, and the exchange of experiences between its members. This definition captures the spirit of the academies and their training programs, which aim not solely to educate, but also to create an active environment for the exchange of the knowledge and experiences that

Celebrating Saint George's Day, the patron saint of Catalonia

Saint George's Day, which commemorates the patron saint of Catalonia, falls on April 23 and has always been an important date in the Grifols calendar, traditionally celebrated by presenting a rose to each of the company's female members of staff. In a parallel Catalan tradition, men are given a book on the same day.

In 2001, to celebrate the first 60 years of the company, Grifols published *A Passion for Life*, a book that told the story of three generations of the Grífols family and the origins of the group. And in 2010, to mark the company's seventieth anniversary, all employees were presented with a copy of the memoirs of Dr. Víctor Grífols, *With a Cork and a Piece of String: the experiences of an entrepreneur in post-war Spain.*

Opening the Grifols Academy in Barcelona. 2011.

are specific to the plasma industry; something that simply does not exist in conventional training centers.

The Academy of Plasmapheresis opened its doors on January 28, 2009, in Glendale, Arizona, in order to provide plasma center staff with advanced, standardized training in the processes relating to the donation, analysis, and control of plasma, and the manufacture of plasma-derived medicines. With the purchase of Talecris, a second center was acquired based in Indianapolis, Indiana. Two years later, Academia Grifols opened in Barcelona, close to the site of the company's first manufacturing plant, which dated back to the 1970s.

Committed to Society

Philanthropic Endeavor

Ever since it was created, Grifols has been committed to society: to plasma donors and patients; to its workforce; and to the environment. This has been reflected in actions such as the creation of a corporate museum, the Grifols Museum (1994); the establishment of the Víctor Grífols i Lucas Foundation for the promotion of bioethics (1998); work to support people with hemophilia in the United States; and, more recently, the Probitas Foundation (2008), dedicated to humanitarian projects.

Grifols Museum exhibition gallery, Barcelona. 1994.

A company museum

In 1994, inspired by the intellectual curiosity and thirst for knowledge of Dr. Víctor Grífols, the company began to keep and classify laboratory devices, administrative documents, reports, photographs, product catalogs, scientific publications, and any other material relating to the history of the company. Thanks to the extraordinary memory of Dr. Víctor Grífols Lucas, it was possible to classify and document this material, and a curious collection of scales, microscopes, devices

Grifols Museum exhibition gallery, Barcelona. 2008.

manufactured by the company, and photographs on glass plates, among other items, found a home in the Museu Grifols, which opened its doors in May 1997. During the first ten years, the exhibition received over 3,000 visitors, including customers, suppliers, and employees. Coinciding with the renovation of the company's symbolic home, at Jesús i Maria street, Barcelona, the museum underwent a major refit, and the presentation and layout of the exhibition were improved. In 2012, the Grifols Museum in Los Angeles was inaugurated, telling the story of the company in the United States and its links with various North American firms, such as Courtland, Dade Reagents, American Hospital Supply, and Alpha Therapeutic Corporation.

Foundation seminar, attended by specialists in bioethics. 2009.

Víctor Grífols i Lucas Foundation

Since its foundation, a concern with ethics has always been at the core of the Grifols business philosophy. This concern was given concrete expression by Dr. Víctor Grífols i Lucas in 1998 with the creation of a foundation that bears his name, and whose mission is to promote bioethics through dialogue between specialists in different areas of expertise. The Foundation also seeks to encourage an ethical approach in organizations, companies, and individuals whose activities are linked

to the health sciences and human health. It focuses on bioethics, a discipline that studies the ethical dilemmas that arise as a result of scientific and technological progress. The Foundation's board consists of leading specialists in the area, and its President is Victòria Camps, Professor at the Autonomous University of Barcelona.

José Antonio Grífols Lucas Foundation (United States)

The mission of this foundation is to provide educational and health support to promote the well-being of people who donate plasma at Grifols' donor centers. It is named after Dr. José Antonio Grífols, the developer of the technique of plasmapheresis, and it recognizes the value of the donors whose plasma enables the manufacture of life-saving products. The foundation's objectives include promoting the study of plasmapheresis and identifying potential new applications for the technique. It has conducted studies to identify the effects of this technique on the cholesterol levels of donors, and found a reduction of cholesterol levels—in particular, levels of LDL or 'bad cholesterol'—in people with a high baseline level of cholesterol.

Probitas Foundation

Probitas Foundation traveling exhibition for employees. 2012.

In 2010, Grifols decided to establish the Probitas Foundation to improve health care in countries with limited resources, drawing on the company's experience and knowledge of the health sector. The company allocates 0.7 percent of its net profits to this foundation. It acts in partnership with a range of non-governmental organizations and institutions already working on projects in the field. The main purpose of its programs is to create basic health infrastructure in the most disadvantaged regions, to provide local staff with training and education, and to ensure the sustainability of these projects. Its main project, Global Laboratory Initiative, seeks to break the vicious cycle of poverty and disease by providing vulnerable communities and populations with basic diagnostic laboratories in order to improve the prevention, diagnosis, and treatment of the most common diseases in each region.

The Grifols Values

The Grifols spirit is a way of understanding and performing our work that captures the essence of the group. "It is a way of thinking about our business, a way of doing things, a way of relating to each other and to the outside world that has made the company what it is today," in the words of the 2010 document setting out the group's corporate values. This philosophy finds expression in the following values:

Safety

Grifols products are of vital importance for the health and quality of life of many patients. This is why safety is more than just a regulatory requirement; it is an attitude that supports the quality of the company's products and the thoroughness of its internal processes.

Effort

Grifols' position today is based on a history of major achievements that have been the result of the efforts of individuals and teams who strive to achieve new goals, overcome problems, and search for solutions.

Excellence

Healthy ambition and the desire to excel mean that the company and its employees use all the resources available to achieve their goals and deliver the greatest possible benefits.

Teamwork

The history of Grifols is the history of a team that has grown as new members have joined the project. The final outcome is the result of the cooperation and teamwork of everyone.

Innovation and improvement

The ability to plan ahead, invest in improvements, and strive for innovation are key factors in caring for people's health. Grifols' efforts have made it a leader in society and the market, but Grifols remains committed to the continuing improvement and innovation of its products and processes.

Pride

Everyone who works at Grifols is proud to form part of a company where decision-making is based on honesty, and where staff identify fully with the company. Grifols' good reputation in society and the market is a reflection of the sense of responsibility that is central to every decision.

Commitment

Grifols maintains the trust of customers because of its firm commitment to quality. They trust the group because it responds to their needs, and puts them at the core of its activities. And they rely on Grifols because they see that it is a company that is committed to them and is eager to find solutions.

Supporting patients

Grifols supports the activities of patients' associations. For example, employees at plasma donor centers enthusiastically participate in the Blue Jeans for Healthy Genes campaign to raise funds for patients with immunodeficiencies, organized by the Immune Deficiency Foundation in the United States. This campaign also raises awareness among donors and local communities about the importance of donating plasma to obtain medicines to treat primary immunodeficiencies. The company, as part of a joint effort to help these associations, matches any funds that are raised.

Since 2006, Grifols has supported the PatientCare program, which supports treatment for patients suffering from hemophilia and primary immunodeficiencies and who are temporarily without medical coverage in the United States. To qualify for this support, the only requirements patients must satisfy are diagnosis with the disease and a minimum of three months of treatment with Grifols products.

Each year, donors, employees, family members, and supporters of the group participate in the Hemophilia Walk, organized by the National Hemophilia Foundation (NHF) of the United States and designed to increase awareness of this disease, as well as raise funds for research into new treatments. The company is one of the sponsors of this event, confirming its commitment to the people who suffer from this disease.

Víctor Grífols

The Architect of a Great Project

Víctor Grífols Roura (Barcelona, 1950) is the current President and Chief Executive Officer of the Grifols group. He succeeded his father, Víctor Grífols Lucas, as President in 2001, and represents the third generation of the family to lead the business. More than any other individual, he has been responsible for driving the internationalization of the company and its conquest of global markets. He is a great admirer of Konrad Adenauer, the first Chancellor of West Germany after World War II, who rebuilt his country after the war and established a stable democracy, bringing West Germany back into the international system. He likes historical fiction and opera, and is a fan of new technologies, while his hobbies include sailing, photography, and motorbikes (even though they have given him the occasional scare!). He has shown dedication, passion, a firm belief in the company's mission, and a driving ambition to ensure that it realizes its full potential.

Víctor Grífols Roura studied Business Science at the University of Barcelona, and joined the firm

in 1974. In his youth, before joining the company, he helped his father move furniture and archives to the new plant at Parets del Vallés. "That factory was a dream come true," he explained in an interview with the corporate magazine, *Cosmos*. "When its construction was complete, it seemed as if the place went on forever. It was difficult to imagine that one day we would fill those huge warehouses. But within nine years we had run out of space!"

With his strong business vision, Víctor was given responsibility for the company's commercial department in 1979, and one of his first moves was to organize a sales network that could drive the business in Spain. He has always stressed the importance of professional and human dignity when dealing with customers, an approach that came to characterize the new sales network. In 1985, he was made executive director and, in this role, was responsible two years later for the reorganization that laid the foundations for the Grifols group holding company.

When he was at university, Víctor spent many summers working at American Hospital Supply. In his view, the Grifols group owes a lot to those times, "because it was there that we learned how to organize what would become the business of today." He argues that American Hospital Supply was nothing less than a 'business school' for the group's management team, and he always encouraged them to visit members of the U.S. multinational group.

Now the President of the company, he sees the link with Alpha Therapeutic Corporation in 1982 as a particularly important one, and has fond memories of Ike Yorihiro and Samuel Anderson: the two people who most strongly supported the growth and internationalization of Grifols, and with whom he established strong ties of friendship and trust. Víctor Grífols is interested in people and dedicates a lot of time to them.

Corporate HQ at Sant Cugat del Vallés, Barcelona. 2013.

"I like meeting people, particularly those who work in the donor centers, because they are the ones who can feel most isolated. I also like visiting our manufacturing plants and offices, because I want our facilities to be comfortable. I spend 70 percent of my time explaining to our staff where

we come from; I like them to know the history of our company, and learn about how we managed to do research and development with barely any resources. These values should never be allowed to die in a family firm, even one that is listed on the stock exchange."

The memory of this research and development conducted by his father "with a cork and a piece of string" during the period following the end of the Civil War in Spain, left Víctor Grífols convinced of the vital importance of investing in research, development, and innovation, and in staff training. He likes to joke that he's not scared of the competition; what terrifies him is incompetence.

Víctor Grífols thinks it's important to remember history. When he gave that interview to the company magazine, *Cosmos*, back in 1999, he was 49 years old, and recalled one of the most difficult decisions he had been called upon to take: the sale of Dade-Grifols to the North American firm, Baxter. Time has shown that this was the correct decision, but it involved taking a risk and convincing shareholders to reinvest the proceeds of the sale to create the Grifols group. At the time, he set an ambitious goal: "In ten years, we need to double in size." This goal was achieved and indeed surpassed: the company's sales grew by a factor of four; its net profit was twelve times higher; and its workforce was ten times larger. In 1999, his aim was to build a company that would be confident in its ability to face new challenges, "proud of its past, respectful of its present, and full of hope for the future."

Board of directors of Grifols in 2007.

In 2011, he was selected as Business Leader of the Year by the Spain–U.S. Chamber of Commerce in recognition of his efforts to double the size of his company as a result of the purchase of U.S. firm, Talecris. On that occasion, he identified the importance of ethics, and stressed that the company worked with donors and employees, for the benefit of patients and shareholders.

He defines a leader as someone who, "is not afraid of intelligent people, and is keen to surround himself with them." For this reason, "it is important that managers surround themselves with people who are capable of flourishing," a belief that found expression with the creation of the board of directors in 1987. The board takes decisions on a collective basis, and as the company has grown so the size and composition of the board have changed to incorporate the needs of the expanded company. Víctor Grífols has his own recipe for successful leadership. "The most important thing is to be decisive, and to stay ahead of the competition," he explained in a session for the Alumni Association of ESADE Business School in Barcelona in 2012, and this is exactly what he has done since he took over the reins of the family firm in 1985.

A businessman among doctors and chemists

In a family of scientists, Víctor Grífols Roura chose to study Business Science. His great-grandfather had been a homeopathic doctor who was very popular with his patients, and his grandfather kept up the family tradition, taking a degree in Medicine before going on to study Clinical Analysis and Transfusion in Germany.

The laboratory, founded in 1940, grew with the help of his sons, José Antonio, doctor and pharmacist, and Dr. Víctor (father of the current President and Chief Executive Officer), who was a chemist and pharmacist.

Víctor Grífols' brother, Albert, and sister, Núria, also work for the company. Raimon is a member of the law firm, Osborne Clarke, which provides the group with legal advice, while Enrique is a doctor. With various members of the fifth generation of the family already working in different departments across the company, it appears that the future is assured and that the next generation of the Grífols is ready to take up the baton.

If the first thing he did was direct the restructuring process that converted the group into a holding company to provide a basis for its international expansion, the new millennium saw the company preparing to launch on the stock exchange, realizing his father's longstanding ambition. Six years after the group made its debut on the trading floor, its senior executive continues to advise medium and large-sized companies to seek funding from the stock market. In the opinion of Víctor Grífols, the luck the company has enjoyed at some of the key points in its history has gone hand in hand with the philosophy of "a job well done; effort, commitment, and innovation; and a desire to excel," supported by "quality and the search for innovative solutions that help improve people's health."

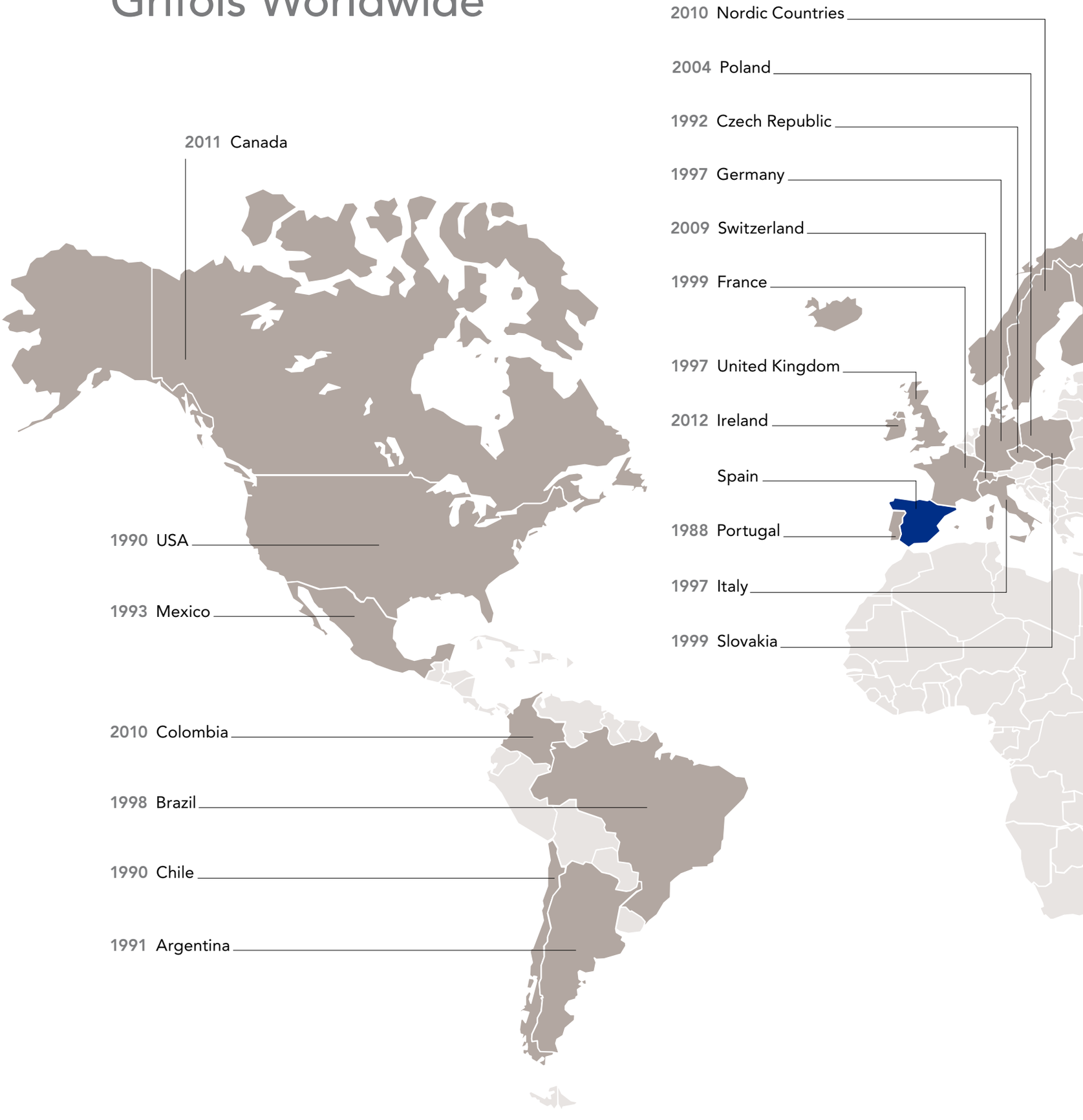
The Dream Lives On

As we have seen, the early years of this family business were closely linked to the development of plasma-derived therapies, at the time a new and even controversial method of treating illness. Now, at the start of the twenty-first century, with huge progress in regenerative medicine and genetic therapies, Grifols cannot ignore the opportunities that this field offers.

With the same pioneering spirit that marked its beginnings, the group has in recent years focused on the research and development of these disciplines, a field with great potential to treat illnesses that lack effective treatments. And in doing so it has paid homage to the pioneers of those early days, reviving the Gri-Cel brand, the company founded in 1957 by Dr. Víctor Grífols to manufacture diagnostic instruments and reagents.

Today Gri-Cel coordinates research in gene therapy and cell therapy, undertaken by a number of spin-off companies in which Grifols has invested. In this way, the group remains faithful to its origins, working to find innovative solutions that help to improve people's health, and without ever losing sight of its commitment to patients. In its daily activities, it is guided by the values that have made it great: a job well done, effort, commitment, and a desire to excel. This is the spirit that three generations of the Grífols family have communicated to the people who work for the company, making dreams come true and converting Grifols into one of the leading players in the plasma protein therapeutic industry. Far from being a goal, leadership is a constant challenge because, as the company's code of conduct states, achieving a dominant market position is not just an advantage, it is—above all—a responsibility.

Grifols Worldwide




2009 China
2014 Hong Kong
2006 Japan
2003 Malaysia
2013 Dubai
2003 Thailand
2000 Singapore
2009 Australia

Timeline

1940 Laboratorios Grifols established on November 18 as the successor to the Central Institute of Clinical Analysis, which had operated since 1909 under the leadership of Dr. José Antonio Grífols Roig, a pioneer of blood transfusion and clinical analysis. He establishes Laboratorios Grifols with his sons, José Antonio and Víctor Grífols Lucas, with the aim of performing clinical and biological research, and developing reagents and therapeutic products.

1943 Dr. Víctor Grífols produces the first lyophilized plasma in continental Europe.

1944 Laboratorios Grifols moves to a new building in Jesús i Maria street, Barcelona, where it focuses on hematology and hemotherapy.

1945 Foundation of the first private blood bank in Spain, and first steps in the development of plasmapheresis.

1951 Dr. José Antonio Grífols Lucas develops the plasmapheresis technique, destined to become the standard technique for plasma collection.
- Dr. Víctor Grífols and Dr. Guillermo de Celis found Gri-Cel, a company dedicated to the manufacture of laboratory instruments.

1958 Untimely death of José Antonio Grífols Lucas.
- Grifols establishes the first industrial plasma fractionation plant in Spain to obtain immunoglobulins and purified albumin.

1960 New building opened at the Grifols site at Jesús i Maria street, designed by architect Miquel Ponseti to house the private blood bank.
- Partnership with U.S. firm, Reagents Corp., to create, Dade-Grifols, a jointly owned company selling reagents and instrumentation.

1968 American Hospital Supply Corp. absorbs Dade and acquires 50 percent of the two Grifols companies: Laboratorios and Gri-Cel. Shortly afterwards, Gri-Cel is merged with Dade-Grifols.

1972 Inauguration of new manufacturing facilities at Parets del Vallés, a municipality of Barcelona. The plant has the capacity to fractionate 60,000 liters of plasma per year and to fill 16,000 bottles of parenteral solutions per day.

1976 Death at the age of 91 of José Antonio Grífols Roig, the founder of Laboratorios Grifols.

1978 Launch of integrated processing of hospital plasma program (AIPH) for the collection and processing of hospital plasma in Spain.

1982 Laboratorios Grifols goes into partnership with Alpha Therapeutic Corporation, owned by Japanese hemotherapy conglomerate The Green Cross Corporation.

1983 First exports of plasma-derived products to China.

1985 Baxter-Travenol acquires American Hospital Supply Corp. and takes control of 50 percent of Dade-Grifols.

1987 Remaining share in Dade-Grifols is sold to Baxter.
- The Grifols holding group–consisting of Laboratorios Grifols, Instituto Grifols, Diagnostic Grifols, Movaco and Logister–is created, with the support of Alpha.

1988 Creation of Movaco Portugal, first international subsidiary.

1989 Registration and marketing of Criostat SD-2, the first factor VIII concentrate in the world to include double viral inactivation in its manufacturing process.
- Laboratorios Grifols blood bank closes after over forty years of service in Barcelona.

1990 Grifols begins its expansion in Latin America, establishing Pexaco Internacional and Grifols Chile.

1991 Biomat is established to certify the quality of plasma for fractionation.
- Grifols Argentina established.
- Purchase of Laboratorios Hypnos, a manufacturer of blood bags based in Murcia.

1992 Start of European expansion, with the establishment of a new subsidiary in the Czech Republic.
- Registration and market launch of Flebogamma, the first pasteurized, intravenous immunoglobulin in the world.
- Laboratorios Grifols starts the sale of blood bags.

1993 New Latin American subsidiary, Grifols México, is established.
- Development and manufacture of the Gri-fill system, parenteral solutions sterile filling device.

1994 Release of Fanhdi, high-purity, double-inactivated factor VIII.
- Laboratorios Grifols obtains CE certification for blood extraction and storage bags.

1995 The U.S. Food and Drug Administration (FDA) grants an Establishment License to the Parets del Vallés plant, and issues a product license for the albumin produced there.
- Inauguration of the Laboratorios Grifols plant in Las Torres de Cotillas, Murcia, for the manufacture of parenteral solutions in PVC containers.
- Diagnostic Grifols releases the Diana processor, which automates blood group typing.

1997 Grifols distribution company, Grifols International, is founded.
- Grifols acquires Alpha Therapeutic's three European companies. The firms in Italy, the UK and Germany become commercial subsidiaries.
- Biomat launches its IPTH service (hospital transfusion plasma inactivation) for Spanish hospitals.
- Grifols opens its corporate museum, telling the company's story in the field of hematology and transfusion medicine.

1998 Grifols Brasil established.
- Laboratorios Grifols' manufacturing plants in Murcia and Barcelona obtain ISO 9001 quality certification.
- Establishment of the Víctor Grífols i Lucas Foundation to promote bioethics.
- Commercial release of WADiana, an instrument for automated blood typing using gel technology.

1999 Creation of Grifols subsidiaries in France and Slovakia.
- Diagnostic Grifols obtains ISO 9001 quality certification. Launch of Triturus autoanalyzer, using Elisa techniques for serological testing.
- Laboratorios Grifols starts manufacture of parenteral nutrition products and registers Soyacal lipid emulsion.
- Start of sales in Spain of the Pyxis system, manufactured by U.S. firm Cardinal Health, for the automated dispensing of medicines in hospitals.

2000 New internal organization based on three business divisions: Bioscience, Hospital and Diagnostic.
- Singapore subsidiary established.
- Logister becomes part of Grifols International and shifts its focus towards hospital logistics.
- Grifols Engineering established to develop biopharmaceutical engineering projects.

2001 Grupo Grifols changes its name to Probitas Pharma with the aim of floating on the stock exchange. Secuoya Capital Privado, a subsidiary of Banco Santander Central Hispano, comes on board as a major shareholder.

2002 Acquisition of SeraCare and its 43 plasma donor centers in the United States. In July the company changes its name to Biomat USA.

2003 Purchase of assets of former partner, Alpha Therapeutic Corporation.
- Market launch of Trypsone, a plasma-derived product for alpha-1 antitrypsin deficiency.

2006 Acquisition of PlasmaCare and its 14 plasma donor centers in the United States.
- Successful stock exchange debut of Grifols, with the share price rising by 15.7 percent on the first day of trading.
- The FDA licenses the plant that will manufacture the new double-inactivated, filtrated intravenous immunoglobulin.
- Representative office established in Japan.

2007 Grifols included in the Ibex-35 index.
- New Flebogamma DIF released in Spain and the United States.
- New "Q" hemostasis analyzer presented.
- Representative office established in China (Shanghai).

2008 Redesigned Grifols Museum opened, with more exhibition space.

2009 Creation of The Grifols Academy of Plasmapheresis in the United States to support staff in acquiring specialist knowledge related to the plasma products industry.
- Purchase of Australian-Swiss company Lateral Diagnostic.

2010 70th Anniversary of Grifols. The company announces agreement to purchase 100 percent of the shares of Talecris Biotherapeutics, Inc.
- Release of Erytra high-capacity automatic blood typing analyzer.
- Establishment of Grifols Nordic AB, the commercial subsidiary to serve Sweden, Norway, Denmark, Iceland and Finland.
- Grifols Colombia established.
- Commercial launch of BlisPack, an automated, robotic system for the preparation of unit doses of drugs supplied in blister packs.

2011 Grifols completes the purchase of Talecris and becomes the world's third-largest manufacturer of plasma-derived products.
- Inauguration of the company's new corporate HQ at Sant Cugat del Vallés, Barcelona.
- Opening of the Grifols Academy in Barcelona to encourage employee training and development.

2014 Acquisition of the Novartis transfusion diagnostics business unit. This operation is part of a strategy to strengthen the Diagnostic division and its transfusion medicine line of products. Grifols incorporates NAT (Nucleic Acid Amplification Technology) to its line of products; this is one of the most innovative techniques for analyzing samples from blood donations.

GRIFOLS