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REVISIÓN

Innovation *vs.* tradition: the election of an european way toward pharmaceutical industrialisation, 19th-20th centuries

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ABSTRACT

This paper discusses the scientific and technological factors that coincided in the beginning and in the initial development of the pharmaceutical industry in Europe. Having pointed out the reasons that favoured the initial success of the German chemical pharmaceutical industry, we evaluate the efforts of other countries to occupy the leadership of this industrial sector: from the British trials of business concentration to all the strength of the Swiss as a neutral nation in conflicts of war; a special tractor will be dedicated to the study of the penetration of German industry in France, in particular, in the systems invented by German manufacturers to violate the French protectionist legislation. In concluding, we describe the two industrialization models followed by the pharmaceutical industry during the decades of change of the 19th-20th centuries. We evaluate and explain the social, economic, cultural and, above all, scientific-technical reasons that defined both and discuss the motives that led to the current situation of leadership of the central European model in the pharmaceutical sector.

Keywords: Pharmaceutical industry; history; Europe.

RESUMEN

Innovación *vs*. tradición: la elección de un modelo de industrialización farmacéutica en la Europa de los siglos XIX y XX.

Analizamos los factores científicos y tecnológicos que confluyeron en el inicio y primer desarrollo de la industria europea del medicamento. Tras señalar las razones que favorecieron el auge inicial de la industria químico-farmacéutica alemana, pasamos a valorar los esfuerzos de otros países por ocupar el liderazgo de este sector industrial: desde los ensayos británicos de concentración empresarial hasta la potencialidad de Suiza como nación neutral en los conflictos bélicos; un capítulo especial queda dedicado al estudio de la penetración de la industria alemana en Francia, en particular, a los sistemas ideados por los fabricantes alemanes para violar la legislación proteccionista gala. Para concluir, caracterizamos los dos modelos de industrialización seguidos por la industria farmacéutica durante el gozne de los siglos XIX y XX; se valoran y explican las razones sociales, económicas, culturales y, sobre todo, científico-técnicas que les definen y se discuten los motivos que condujeron a la actual situación de liderazgo del modelo centroeuropeo en el sector farmacéutico.

Palabras Clave: Industria farmacéutica; historia; Europa.

1. INTRODUCTION

The stages that define process of industrialisation in Europe are not uniform; their differences have their roots, as wisely pointed out by the German sociologist Max Webber at the beginnings of the 20th century (1) in the 'spirit of capitalism' which defines the countries of the centre and north of Europe, with the 'traditionalist' temperament of the Mediterranean Europe. The different mentality and the different rent *per capita* with which the countries of the centre and north of Europe (the 'Protestant Europe') faced the 'industrial revolution' as opposed to those washed by the Mediterranean (the 'Catholic Europe'), is undoubtedly.

The genesis of the European pharmaceutical industry is not indifferent to this situation as a whole; even though, together with the social factors, economic or political definers of any type of industrial activity others of a scientific and technological character should be considered as well. Among the most important is the appearance of the active principles of synthesis and semi-synthesis as well as the arrival of new pharmaceutical forms, more adaptable to the requirements of large-scale elaboration demanded by the new pharmaceutical industry.

From the middle of the 19th century, the industry of active principles and, above all, those relative to chemical synthesis of medicines from carbon, were dominated by Germany, thanks to the hegemony in the field of organic chemistry of industrial application. Other countries in central Europe, such as Switzerland, or those of Anglo-Saxon culture such as England, also tried to get a look into this market, principally after the outbreak of the First World War.

The Mediterranean Europa —France, Italy or Spain— could never compete with the large pharmaceutical chemical industries established in 'Protestant Europe'; their contribution to the development of the drug industry would come with the adaptation of pharmaceutical tradition to large-scale elaboration, principally through the creation of new services of forms of drugs and the industries for their commercialisation.

The modernisation of pharmaceutical technique came about in the last 30 years of the 19th century as a result of the efforts of the pharmacy collective at an attempt at compatibility with the traditional *modus operandi* and the new scientific doctrines. With the exception of injectable vials, invented in 1886 after the development of asepsis, the new pharmaceutical forms which would revolutionize the therapy and the professional habits of medical and chemists professionals, came into being throughout the long period between 1833 and 1853. During this time, the principal forms of oral administration were invented: gelatine capsules (1833), pills (1843) and amylaceous capsules (1853).

The perfection of these preparations was intimately linked to the birth and development of the drugs industry as their elaboration was undertaken with the use of specific machinery. The existence of forms for the drugs is therefore, necessary for their industrial development. However, and although this seems paradoxical, these were not invented by the large pharmaceutical laboratories but by the chemists, in

an attempt to resolve old pharmaceutical problems and to adapt the dispensary tactics to the new sciences of health. This modernisation of the professional collective of pharmacy was made use of by the drugs industry for its own development. In effect, both traditional pharmaceutical preparations as well as the modern pharmaceutical forms appearing in the last 30 years of the 19th century would be subjected to a profound technological recycling in order to accelerate and make the process of production profitable (2, 3).

In the following pages we will try to discern and typify most models of industrial development. We shall endeavour to define what the characteristics are that, from a technical option, define both models. The drugs industry presents some of its own characteristics that differ from the chemical industry, to which they tend to be united conceptually. It is certain that both have in common —although more so today— the use of processes of similar production, but they differ —more so in the past— in the finality itself of the finished product. The drug is not always of chemical origin and for this its industrialisation process is not strictly comparable with that of the chemical industry in general. The specificity of the pharmaceutical industry is closely related to the final aspect with which the drug is presented, the pharmaceutical dosage form (4).

The European chemical industry has been the object of a great number of studies, some of which have centred on strictly technological aspects or of industrial projection (5, 6), others have attacked the problem from an economic or political viewpoint (7, 8), although others have compared the models of industrialisation followed by different European countries (9, 10). Our work attempts to deal with the peculiar characteristics of the pharmaceutical industry, whose origin resides in the existence of a professional group dedicated, previous to the appearance of manufacturing processes, to the artisan elaboration of medicines. The models of compliance of these professionals, to new industrial techniques, is the object of this paper.

2. THE INNOVATION: THE CENTRAL-EUROPEAN MODEL

From the last quarter of the 19th century, chemical industries began to take on an importance in the consolidation of the European

capitalist system, which until then had been limited to textile manufacture, the iron and steel industry and mining.

At the beginning of the First World War, German predominance in the chemical sector was unquestionable; no other world power was able to compete with the German giant. German leadership was evident from 1871 on, dating from the end of the Franco-Prussian war and the commencement of German unification. The main field of action was that of dyestuff industries, appearing in the middle of the 19th century, due to the reuse of residues originated in the operations of distilling bituminosus coal distillation. With reference to the organic chemistry industry in particular, more than half the total of the chemical production exported by Germany in 1912 corresponded to dyestuffs, perfumes or drugs, and the sales abroad of these products exceeded the total figure of exports in the rest of the world (11). This was, without doubt, the golden age of the German chemical industry, after which the figures descended gradually due to competition of other countries such as the United States, France or England. In 1916, there were 4.000 chemical remedies synthesised in Germany (more than 200 were the most used and exported), representing the greater part of those existing in the world and which were produced in no less than 20 large factories (12). In 1924 the German contribution to the world market of synthetic dyestuffs was barely 40% of the exports, although still the highest in the world, they had dropped considerably (13). This productive centres basing their activities on the tars obtained from diversity was not capricious. They were coaltar, residues from other industries and at the same time raw materials for the elaboration of these articles and others, as important for national defence as the explosives. This concept of integrated chemical industry is especially useful for the understanding of the tentacular scheme of enterprises in the cleaning industry.

The devastating advance of the German chemical industry would have repercussions especially in those countries which, until then, had been leaders in this market. The most representative case perhaps is that of England; leader of this industry during the central decades of the 19th century, it underwent a progressive deterioration, almost inversely proportionate to German growth, and would acquire almost critical overtones during the change of the century. The conflict of 1914 would oblige them to carry out a profound examination of con-

science, aimed at analysing and attempting to meet the enemy, with both the arms of science and industrial progress.

The British effort was worthy of praise, although not as productive as would have been wished; the self-critical analysis of the causes that provoked industrial weakening and the possible recipes for trying to palliate their disadvantageous situation with respect to Germany, were amply debated subjects in scientific, commercial and political forums throughout the first quarter of the 20th century. The key to their failure was the same that had propitiated the German triumph: namely, industrial scientific training at high level and development of applied research. The solutions to overcome this situation lay, obviously, in the emulation of the only possible model, that followed by Germany, eg., the design of an *ad hoc* educative infrastructure, and entrepreneurial investment in chemical research.

The manufacture of dyestuffs is a paradigmatic example of this situation. This industry, born in England after the discovery of mauveine by William Henry Perkins, was soon to be snatched from them (14). In 1913, England imported 17.000 tonnes of artificial dyestuffs, of which 90% corresponded to operations in which Germany was the remittent and the remainder came from Switzerland. In an attempt to lift this dependency, at least partially, possibly for motives of national pride, the British government became involved in a project to create a national industry of dyestuffs with state capital. This project took the form of *The British Dyes Co. Ltd*., which, after its fusion (1918) with other factories, became known as *British Dyestuff Corporation*. With a very strong protectionist policy against colouring materials made outside England, this Society started off its career in the difficult market of derivates of coaltar (15). The British effort was to produce an important increase in these products and a descent in importations, although at the cost of an important deficit originating from multiple factors, among which an insufficient domestic market and the rather weak uncompetitive export resources can be highlighted, precisely, associated to the protection measures laid down by the British government.

Following in the footsteps of Germany, England attempted to resolve these problems by means of business concentration. The results of these efforts were an integrated *British Chemical,* formed by the merger of the *United Alkali Co.,* the *Nobels Co.* and the *Brummer Mond*,

capable of assuming not only the production of dyestuffs but also fertilisers, explosives, sulphuric acid, etc. (13, 16). In spite of all the difficulties, more so, if we compare them with the Mediterranean European countries, England continued to be an important power in the chemical pharmaceutical industry and drug sector.

Chemical drugs also sustained a considerable development in Switzerland especially in Basle, one of the most important nuclei of the world chemical pharmaceutical industry (12). The upsurge of Swiss dye industries during the first 15 years of the 20th century, a specially negative period for this type of activity in France and England, can be explained by a cumulous of circumstances of synergistic effect: specialisation in the fabrication of products, some of which were authentic monopolies; quality of the commercialised products, partly due to acceptable research planning; permissiveness and collaboration with the German dying industry; and greater facility for the sale of its production due to its condition of neutrality.

The typical pharmaceutical dosage forms used by the pharmaceutical industries in the Central-European countries was tablets. We owe the invention of tablets to the Englishman William Brockedon who, on December 1843, patented this product in his country under the domination of "Shaping pills, lozenges and black lead by pressure in dyes". His intention was to eliminate from the pill formulation all the excipients, generally of a glutinous cohesion nature which made the later desegregation dissolution and internal absorption of these preparations more difficult. On general lines, the idea of Brockedon was formed by a cylindrical compressor, a matrix and mortar, which the author himself would describe exhaustively in the text corresponding to the patent of his invention (17, 18). The operation that characterises this pharmaceutical form and allows the preparation to be converted in the most adaptable way for the requirements and the technology of the new medicinal industry. The fabrication of tablets is, essentially, industrial. If at any time dispensary elaborations were carried out, principally in the countries of the European Mediterranean area, these were made possible thanks to the adaptation of manufacturing technology to the necessities of the chemist.

The pharmaceutical form invented by Brockedon remained inert for nearly 30 years. During the period 1843 to 1872, work relative to

this invention, and possibly its improvement, was little and of scant relevance. The year 1872 can be considered as the real takeoff of the elaboration of tablets, with the presentation by the German Isidor Rosenthal of a new system of manual compression, based on the action of a screw press which supplied the compression force (19). These machines opened a new page in the history of drugs, and began a process of improvement and popularisation unknown till then by any pharmaceutical preparation.

If Germany became one of the principal suppliers of this new technology to the pharmaceutical world, the other was the United States. The Americans, in the same way that the teutons had done, developed their own procedures of compression, competing directly, in space and in time with German technology and, contrary to what happened with the latter, taking into account the first English patents. North American research in this field gave fruit and this time the technological innovation would be truly original; on the one hand the manual lever press (1879) and on the other, the excentrical and vertical tableting compressor machine (1874) also activated manually but with the vocation of being able to transform itself or influence in future automatic inventions. Two technological proposals that would compete during the last quarter of the 19th century, with the German screw press, in an endeavour to achieve hegemony which was exclusively based on criteria or parameters of mechanical origin. The German-North American competition in this field should not be understood to be based on reasons or postulations of a strictly pharmaceutical type, focused on obtaining a final product of formulation, desegregation, solubility and optimum stability but rather on arguments of technological basis, more concerned with engineering than pharmacology (20, 21).

The tools used to carry out the elaboration of tablets respond essentially to one same reason, sustained on two premises which, in our opinion, are fundamental for understanding the success of this pharmaceutical form and its excellent industrial implantation: the tendency towards the unification of all the procedures of pressure and the search for processes of continual function, capable of achieving a total automation of the machinery (17, 22).

Another pharmaceutical dosage form used by the Centro-European industries was a rebirth of the french capsules, adapted in the 1870s

for dealing with large-scale elaborations. The North American pharmacist, Frederick A. Hubel was probably, the first to prepare, around 1874, hard gelatine capsules on wholesale scale using a mechanical device, manufactured by himself, which would be subject to successive improvements until finalising in the first patent for an apparatus of this type (1877). The period 1877-1883 was the most fertile time as regard to patents for capsule making machines, and the years immediately following these are those of final consolidation of the great industry of hard gelatine capsules (23, 24). At the beginnings of the 20th century machinery had already displaced the manual worker. There were those who gave 'objective' reasons for choosing mechanical procedures in detriment of the artisan, based on criteria of uniformity, appearance, solubility, stability and profitability. The success of the procedures for manufacturing hard gelatine capsules among the main drug industries resides on the suitability of the different stages that this type involves and the technological possibilities of the machinery used. The great achievement is separating the phases obtained by the capsular support and the closed filling in two totally independent industrialised processes. Given the difficulty of agglutinating these operations in the same machine, it was decided to give the elaboration of empty capsules to firms specialised in this matter.

3. THE TRADITION: THE EUROPEAN-MEDITERRANEAN-MODEL

The fragility of the French chemical pharmaceutical industry compared with that of Germany was evident, mainly in reference to organic chemistry. On the reverse, both the inorganic chemistry industry as well as that relative to pharmaceutical specialities were perfectly competitive, and on occasion, free. As we have commented, the scientific and commercial imbalance of Germany in the drugs sector was constructed on approaches of global chemical development, quite the contrary to the French case, where the drug industry held its own identity. The global results gave an advantage to Germany, making it capable of invading the world with new active pharmacological molecules and, the ability to adapt these industrial formats, both classic and modern. The experience and tradition of French pharmacy only gave it a certain *chance* in the market of finished products and in

those of inorganic basis. It showed deficits however and was dependent on their German 'enemies' for all the necessary raw materials with which to elaborate their chemical drugs.

The imbalance in this speciality is translated into the existence of a single factory of artificial dyestuffs, of French capital, capable of working from basic raw materials. We refer to *Société anonyme des matières colorantes et produits chimiques de Saint Denis*, founded in 1881, by merger of the *Poirrier* (1830) and *Dalsace* (1843). The rest of the French establishments could only deal with the manufacture of dyestuffs using intermediate products of Germanic origin; this is the case of *Fabrique de Couleurs d'aniline et Raffinerie de Beuzines Victor Steiner*, the *Fabrique de Produits chimiques et Matières colorantes Mabboux et Cammel* and the *Manufacture de Matières colorantes Laroche et Juillard*. To these four companies, we should also add the *Compagnie nationale de matières colorantes et de produits chimiques*, a national project, promoted by the *Syndicat national des matières colorantes*, in the same line as the *British Dyes* and with similarly ambitious aims.

Faced with a scarcity of purely French manufacturers, others were able to find a place, either by means of acquisition, or through implantation in French soil acting as subsidiary or branch of the large German and Swiss firms. They were only finalisation factories in which intermediate products were used coming from Germany, and susceptible to conversion into dyes with a simple chemical operation of transformation. In this way, the large German houses of dyestuffs obtained a double profit: outwitting customs norms which prohibited the entrance of any supposedly medicinal product either undeclared or not included in the pharmacopoeia, thus enabling the payment of reduced tariffs, applicable to raw materials not existing in French territory. Also, they continued to maintain their privileged situation by retaining, confined and protected, the procedures and techniques of fabrication in Germany.

But German colonisation was even more evident in the case of drugs ready made for consumption. In this case, the system used was that of the *prate-nom*, i.e French pharmaceuticals established in the country who prepared and/or sold drugs supplied by their German associates (25). The mechanism consisted in elaborating pharmaceuti-

cal specialities prepared from German associates, on French territory, thanks to the existence of these figureheads. These would then be sold in France and Germany as if they had been French prepared, in accordance with the Convention of Bern. The results were much more beneficial for the German industrialists, as they managed to export their merchandise and avoid their own pharmaceutical legislation which prevented them from selling drugs ready for consumption at another price other than the official tariff. Despite a notable expansion, in the form of chemical subsiduaries established in French soil and through *prête-noms* pharmaceuticals, France continued to carry an important weight in the drugs industry.

Contrary to what had happened with the German chemical drug industry, the French laboratories were, for the greater part, specifically pharmaceutical either in specialities or in chemical products and their qualified personnel included many medicals, biologists and pharmacists as well as the chemists and chemical engineers, also present in German industry.

As an answer to the triumphant apparition of tablets in the drug industry, French pharmacy was to concentrate its interest on another two new pharmaceutical forms: the soft gelatine capsules and the *cachets*. While the former responded to a pure industrialised model, which in the end would not last due to be unstoppable rise in hard gelatine capsules, the *cachets* arise as the most modern banner of the traditional pharmacy (26). With the advance of technology and the establishment of procedures of large scale drug manufacture in full swing, this pharmaceutical form, clearly homemade, and poorly adapted to wholesale production, appears.

Gelatine capsules were invented by the French pharmacist François Achille Barnabe Mothes in 1883, with the aim of disguising the medicinal substances of disagreeable organoleptic propieties. The method invented by Mothes, was based on the immersion of ovoid metallic moulds in baths of liquid gelatine, a troublesome process, which required great manual skill and was not very productive. These limitations facilitated the development of new systems of encapsulation, more in accordance with industrial imperatives that began to be in vogue in most developed countries. The proposal of the French pharmacist Viel (1844) was in this context and constituted the first

really interesting variant since the invention of the new format. The basis of his technique relied on obtaining medicinal capsules by means of a simple mechanism, capable of elaborating cylindrical hollow bodies of gelatine by sliding them into a mould and in whose interior the medicinal substance was kept. These cylinders of gelatine could be submitted to capsular division thanks to the use of a cutting instrument specially designed for this operation. The perfection of the technique of capsular elaboration meant a truly gigantic step forward with the validation of a new French patent presented by Lavalle and Thévenot in 1846. The basis of this new method, clearly influenced by the procedure carried out two years before by the Italian Pegna, was the fabrication of capsules by interposition of the medical substance between two plates of solidified gelatine, fused by pressure of metal plates with holes (capsular moulds).

Parallel to the proposal of Thévenot was another developed and defended by yet another Frenchman, Jules César Lehuby; a new invention self-denominated as *Mes enveloppes médicamenteuses*, which would later be patented in France in October of 1846. Lehuby would describe these 'envelopes' as similar to the cocoons of silk worms, formed by two adjustable compartments one within the other until making a form like a cylindrical box capable of containing the required medical substance in its interior. The revolutionary invention of Lehuby, at that time known by the name of hard gelatine capsules, was modified by its author three consecutive times (1847-1850) with the aim of improvement. Despite the fact that Lehuby was really the inventor of the double compartmental gelatine capsules, other authors, principally from the Anglo-Saxon area, would concede the privilege of invention to the British James Murdoch, responsible for a patent for "an improved capsule or small care for protecting matters enclosed therein from the action of air, and an improved material to be used in their manufacture" (May 1848). Murdoch himself recognised, in the preamble to the text of his patent, that his contribution was not totally original: "it was communicated to me from abroad" (24). One of the possible reasons to explain this error of attribution, maintained by the greater part of the texts on the subject of gelatine capsules written at the end of the 19th century, and even today (27), was the scant repercussion that this type of preparation had during nearly 30 years following the publication of the first patents. The cap-

sules of hard gelatine were specially indicated as a support of solid medicines, which were less used at this time than the liquid forms and, therefore, only needed moderately high productions in order to profit from the construction of capsular moulds.

The amylaceous capsules made their appearance in France in the middle of the 19th century as a pharma-technical answer to certain problems of solubility that some covered pills represented. In 1853, the French man André Alexandre Guilliermond proposed a new pharmaceutical form which he called *enazyme*, as a result of closing a previously flattened pill, between two discs of unleavened bread approximately two centimetres in diameter and hollowed in the centre, which were then soldered by pressure after moistening the discoidal edges. The *enazyme* of Guilliermond did not have much repercussion in the pharmaceutical world until 20 years later. In 1873, Stanislas Limousin, also French, presented, first to the *Societe de Pharmacie de Paris* and later to the *Académie Nationale de Médecine*, a new pharmaceutical form, basically very similar to that proposed in 1853 by Guilliermond, which he named *cachets médicamenteux* (28). The Limousin's *cachets* were capable of hiding the disagreeable odours and tastes of some drugs, by avoiding the interactions of drug and excipient due to the absence of the latter. They could be used in a great number of drugs, due to the possibilities offered by the technical proposals for filling, closing and sealing that he had elaborated. The success of Limousin lay in generalising the elaboration of amylaceous capsules by the previous establishment of technological keys that would propitiate their existence, that is, while the *enazyme* of Guilliermond is only the final result of our specific pharmaceutical operation, the essential in the Limousin's idea is the pharmaceutical form, the *cachet*, usable, generally speaking, for any drug. The evolution of traditional pharmacy towards the drug industry had already begun.

Injectable vials was a particular and integrated pharmaceutical dosage form; the inyectable were invented in 1886, by the French chemist Stanislas Limousin (29). Their magnificent reception among european pharmacists of the Mediterranean area was due to the handmade character of this pharmaceutical form and the artisan manner of carrying out this type of preparation. Perhaps for this, the name that has lasted has been that of the Latin root *Ampullae* and not that of *Amphiolen* or *Einschmelzgläser*, proposed by the German Pharma-

cy. The bottling and filling process of the medicinal liquid in the glass vial constitutes the most characteristic and definitive stage in the manufacture of injections, at least from the pharmaceutical point of view. We are faced with an operation, or group of operations, which are totally innovative for pharmaceutical procedure. We believe that the implantation and evolution of the different systems of filling marked a point in the progress of this pharmaceutical form, going from totally artisan practices to industrial procedures (30, 31).

4. CONCLUSION

The therapeutic revolution of the 19th century was not lived in the same way in all countries; the economic social and cultural tradition, was key for interpreting the conceptual change that the discovery of natural active principles and the preparation of new synthetic remedies from bituminosus coal, supposed. The Central European countries were very involved in the mechanisms and in the philosophy of the industrial revolution. Soon they were to control the fabrication of new drugs. The industry of alkaloids and that linked to organic synthesis of pharmacologically active molecules was very soon dominated by the countries of this area, especially by Germany, although other nations also played a part, namely Switzerland and England.

Although it is certain that with the synthesis of alkaloids, the launching of industrialised medication took off, the definitive backup was produced with the development of organic chemistry of pharmaceutical application. In the first case, the research protagonist is obviously therapeutic: the extraction of active principles is no more than an optimisation of classic medicinal material. In the second case, the drug is only a secondary product obtained or attainable from the procedures used in any chemical industry.

The 'innovative' scheme for drugs, generalised in Central European countries, follows general industrialisation guidelines; specific factories do not exist for their attainment but they are integrated into much more viable commercial and technological units such as those responsible for the elaboration of artificial dyestuffs. The chemical industry functions as a whole; each raw material used in a specific process may not be more than the product or waste of another. In these conditions,

the elaboration of chemical drugs cannot be improvised and has to be subject to a general industrial flow chart.

In this model, the pharmaceutical industry does not exist, at least understood as an easily identifiable sub-sector; the preparation of drugs is carried out in factories in which, in addition, explosives, dyestuffs, perfumes, photographic material are also elaborated. The birth of German or Swiss pharmaceutical industries is chemical; only those laboratories created as a result of the breakthrough with alkaloids, the cases of *Merk-Darmstad* or *Schering* are two good examples, originating in apothecaries, the rest proceeded from the evolution of other less specialized fabrication centres (*Agfa, Bayer, Hoescht, Ciba, Geigy, Sandoz*, etc.). The break through of new pharmaceutical forms and the application of French machinery would come later, when chemical infrastructure had already been consolidated, favouring the development of the pharmaceutical speciality more linked to the great chemical laboratory than to the professional collective of pharmacists.

The fundamental axis of the 'traditional' model is pharmacy, understood as a highly qualified profession but also as a scientific discipline on its own. This premise is extremely useful for understanding the principal characteristics of the pharmaceutical industry in the countries of southern Europe; its objective is medicine and this can never be a sub-product attainable as a result of ordinary processes of industrial chemistry. In these factories the drug is the protagonist and its preparation is, generally, the only line of possible activity in this type of laboratory.

For the large factories of German dyestuffs, medicines appear as the result of general chemical planning or as another object in a diversified superstructure in need of an adequate covering, of pharmaceutical form, for its commercialisation. For the French industries the covering is the final aim and the chemical substances are no more than raw materials with which to elaborate the end product. While the medicine industry in Central European countries is essentially, pharmaceutical chemical, that of the European Mediterranean countries tends towards pharmaceutical specialities and while the former depends on organic chemistry, the latter depends on pharmaceutical technology.

Laboratories of pharmaceutical specialities are born from the super-production of the chemist's shops at a time marked by the prescrip-

tion of specific generalised remedies for pathologically homogeneous populations. This would explain the movement of the Mediterranean pharmaceutical industry towards exclusively inter-professional capitalisations. The structures of their laboratories do not derive from Limited Companies, but family enterprises with pharmaceutical capital or arising from chemist's shops and directed commercially and technically by professionals of the drug business.

The decisive implication of the chemist in the Mediterranean area in the construction of the pharmaceutical industrial framework was key to the conformation of a model with its own identity, strongly participated by professional corporations and with the industrial solutions or recipes, exportable to modest pharmaceutical laboratories as well as proceeding from these, a mechanism of reciprocity which reminds us how originally the laboratory of pharmaceutical specialities was no more than a prolongation of the dispensary.

The industrialisation of medicines has been effected by two different models. Central European countries, involved themselves in the manufacture of large-scale pharmaceutical specialities taking advantage of the important advances in Chemistry and Technology. On the other hand, the Europe nations around the Mediterranean area, tried to accelerate and benefit from their traditional procedures of manual elaboration, using apparatus and machinery that, in general, only permitted the mechanisation of some of the productive stages.

The triumphant model was that of the Central European countries, essentially for its capacity to respond to the principal industrialisation criteria: mechanisation, re-productivity, profitability, wholesale elaboration, tendency to the implantation of a single productive process and the use of machinery of continuous function. Their most important innovations, tablets and hard gelatine capsules are today, two of the predominant pharmaceutical forms.

The model of the European-Mediterranean countries, although, on occasion, complying with some of the necessary conditions for large-scale fabrication, was never able to compete with the powerful English or German manufacturers. The idiosyncrasy itself of the French, Spanish or Italian pharmaceutical collective, more prone to individualised elaboration, would gag, limit and even cause the failure of its own industrialisation prospects. Its two main contributions, the soft

gelatine capsules and the amylaceous capsules disappeared from the therapeutic map. Only the injectable vials, due to the hybridisation of technologies between both models, have been able to survive.

The 'innovative' model: Centro-European area	**The 'traditional' model: European-Mediterranean area**
• Countries: Germany, England, Switzerland.	• Countries; France, Spain, Italy.
• Basic chemical industry very developed, especially organic ones.	• Chemical industry little developed and the organic even less.
• Highly capitalised firms and with great quantity of labour.	• Few highly capitalised firms and abundance of labour.
• Inclusion of highly qualified salaried personnel.	• Deficient training in industrial chemistry: lack of qualified personnel.
• Clear separation between the property (limited companies) and the technical management.	• Tendency towards inter-professional capitalisations: pharmaceutical capital. Separation between the owner of the productive centre and the technical management did not exist.
• Integrated chemical industry: manufacture of dyestuffs, explosives photographic material, perfumes and medicines.	• Typical industry of consumer goods: exclusive manufacture of drugs. Inexistence of a global industrial organigram.
• Inexistence of a pharmaceutical industry with own identity. Exception: the industry based on vegetable active principles.	• Pharmaceutical industry with own identity. Place of manufacture: dispensaries, dependent and independent laboratories.
• The essential of the drug is its active pharmacological molecule; pharmaceutical form, the finished product, is no more than a covering.	• The 'covering' of the drug is the primordial aim, the active pharmacological substances are no more than raw materials.
• The execution of the hegemony through the industrial property: manufacturers brand marks for the chemical substances.	• Industrial protection is effected through the trademark of the establishment or pharmaceutical speciality.
• Secondary role of the pharmaceutical in the global industrialisation process. Principle protagonists: the investors and chemical engineers.	• The pharmaceutical is the protagonist of the industrialising process.

Continuous

The 'innovative' model: Centro-European area	**The 'traditional' model: European-Mediterranean area**
• Use of high-performance machinery.	• Use of pseudo-industrial machinery.
• Adaptation of drugs to large-scale manufacture: tablets and gelatine capsules.	• Adaptation of the machinery to drugs.
• Tendency towards the mechanisation of all the productive stages and the implantation of machinery of continuous working.	• Mechanization only of some productive stages, discontinuity in the global process of manufacture.

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6. REFERENCES

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