

**‘The American ‘model’ and the British and French pharmaceutical industries in
the twentieth century’**

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THIS TEXT IS ONLY THE FIRST DRAFT OF A STUDY WHICH IS DEVELOPED FOR THE HELSINKI CONFERENCE OF
AUGUST 2006, BUT WHICH WILL BE SUPPLEMENTED FOR THE FUTURE PROCEEDINGS.

About twenty years ago, historians coming from business history and sciences studies began turning their attention towards the pharmaceutical industry¹. As a result, the history of pharmaceutical R&D, of the relationship between academic and industrial research, and of the growth of science-based companies, is quite well documented². The relationship between the industry and the State in different countries has also become the subject of historical analysis³. The American pharmaceutical industry in particular has attracted a great deal of attention. At first sight, the history of American pharmaceutical firms appears to be the ultimate success story: a number of small or medium-sized firms expanded, and became the largest drug companies in the world. After WWII, American firms set up subsidiaries in several countries, including in Europe, usually for the purpose of manufacturing penicillin. Many books tell such a story⁴. Thus, WWII helped to transform what until then was a relatively small-scale industry into a major, competitive industry. Historians have therefore attempted to analyze the reasons for the growth of American, and other pharmaceutical firms, especially during and after WWII. The success of American companies have led them to ponder whether there might not have been an ‘American Model’, which, when it was emulated, led to a successful industry in other countries as well⁵.

Our study of the influences of the American pharmaceutical industry in Britain and France is inspired by what can be observed about the wealth and internationalisation of American companies. Our hypothesis is that American subsidiaries participated in the diffusion of this ‘American Model’, and influenced the development of the pharmaceutical industry in Britain and France. If our hypothesis is correct, then *how* did American pharmaceutical firms influence their British and French counterparts? Does the ‘American Model’ help to explain

¹ “Industries du médicament et du vivant”, *Entreprises et Histoire*, 36, octobre 2004, see the editorial for a bibliographical review.

² Jonathan Liebenau, *Medical Science and Medical Industry: the formation of the American Pharmaceutical Industry*, London, MacMillan Press, 1987; Jean-Paul Gaudillière, *Inventer la biomédecine: la France, l’Amérique et la production des savoirs du vivant, 1945-1965*, Paris, La Découverte, 2002; Viviane Quirke, *Experiments in Collaboration: the changing relationships between scientists and pharmaceutical companies in Britain and France, 1935-1965*, PhD, Oxford University, 1999, and forthcoming with Routledge.

³ Peter Temin, *Taking your medicine: drug regulation in the United States*, Cambridge, Harvard University Press, 1980, Arthur A. Daemmrich, *Pharmacopolitics. Drug Regulation in the United States and Germany*, Chapel Hill, University of North Carolina Press ; Sophie Chauveau, *L’invention pharmaceutique. La pharmacie française entre l’État et la société au XXe siècle*, Paris, “les empêcheurs de penser en rond”, 1999.

⁴ See for example: Jeff L. Rodengen, *The Legend of Pfizer*, Fort Lauderdale, Write Stuff Syndicate, 1998.

⁵ Japan Business History Institute (ed.), *Medicine for the People. The First 85 Years of Banyu Pharmaceutical, 1915-2000*, Banyu Pharmaceutical Co., Ltd., 2001; Michael L. Burstall, *The Community’s Pharmaceutical Industry*, Luxembourg, European Communities, 1985; Lacy Glenn Thomas, “Implicit industrial policy: the triumph in Britain and the failure of France in global pharmaceuticals”, *Industrial and Corporate Change*, 1994,3, p. 451-489.

the development of the pharmaceutical industries of Britain and France after WWII? Our two papers, and their different approaches, reflect the contrast that existed between the French and British experiences in pharmaceuticals, at least until the 1980s, after which they show greater resemblance as part of a more globalized industry.

I. The French pharmaceutical industry (S. Chauveau)

To begin, I shall say a few words about the ‘American model’: the 2nd WW was a turning point, after which the American pharmaceutical industry became part of a biomedical complex. We may ask ourselves whether there were American influences (and even more, a ‘model’) in the way of carrying out R&D, marketing drugs, gathering funds and investments, creating subsidiaries, and negotiating with the State the rules and regulations governing the marketing of new drugs. These questions are important because many of the firms that dominate the world’s pharmaceutical industry today are American: does this leadership constitute the end of a long process of Americanisation of the pharmaceutical industry? Is there another way, for example the way of European “big pharma”? The analysis of American influences on the French pharmaceutical industry leads to a number of remarks. First, let’s consider business organisation: American firms are part of a biomedical complex, with R&D divisions, relationships with hospitals or physicians and with government.⁶ Such an organisation may function as a model, as these firms market the most innovative drugs, and gain a competitive edge on the market as a result⁷.

However, French firms were somewhat different: R&D was less well developed, although industrial chemists and pharmacists entertain relationships with physicians working in hospitals⁸. Since the end of the 1940s, State intervention on drug prices prevented firms from increasing their profits on safe conditions. As French State set drug prices at a very lower level, French firms could not reach a turnover that allowed to spend enough to get a competitive R&D and to develop innovative drugs. Consequently, they tended to market me-too drugs and drug innovation remained an exception⁹. We may therefore ask ourselves if the concept of an ‘American Model’ is useful for describing French firms and for the French market. When American firms set up subsidiaries in France after WWII, these subsidiaries often tended to be manufacturing plants, without R&D, and with a small but aggressive commercial organisation. However, the French firms that had connections with these subsidiaries may have been influenced by American methods, for example in marketing.

Although French companies did not create big R&D divisions, foreign subsidiaries or marketing divisions, they were influenced by American methods nonetheless. Many of them bought American licences (for antibiotics, corticosteroids, beta-blockers), while others tried to rationalize their advertising (but advertising was already important for the French pharmaceutical industry, even before WWII). American influence and the ‘American Model’ may have played a more important part when American firms controlled French firms’ capital. The analysis of the influence of American model gives rise to a number of questions about “Americanisation”. Such a concept implies that the ‘American Model’ functions in a similar manner in different contexts. Is it also possible for such a model to develop in the same ways in America, where there aren’t price controls as in France, where such controls

⁶ J-P. Gaudillière, *Inventer la biomédecine...*op.cit.

⁷ J. Liebenau, *Medical Science...*op.cit; Peter Temin, *Taking your medicine...*op.cit.

⁸ J-P. Gaudillière, *Inventer la biomédecine...*op.cit, V. Quirke, *Experiments in collaboration...*op.cit.

⁹ S. Chauveau, *L’invention pharmaceutique...*op.cit., p. 337 et sq.

exist. The historiography on Americanisation¹⁰ shows that the model changes within different contexts. The model is not unique, and different firms will borrow different elements: one would be influenced by commercial organisation, another one by manufacture organisation. For example, if we consider the French pharmaceutical industry, we observe that marketing influences are few and far between: French firms have already developed advertising. Marketing introduces change in organisation and in the conceptualisation of commercial activity. Influences in R&D appear more striking: French firms try to develop their own antibiotics, doing screening like American firms. The comparison with British industry also reveals different patterns of development. The French and British pharmaceutical industries were not influenced in the same way by the ‘American Model’: those differences set boundaries on the American model and show the strength of national models (which together can create other regional models, like the European one).

I would like to review the influence of ‘American model’ on the French pharmaceutical industry through the following aspects: the R&D organisation, the marketing, the relationship with State, the creation of American subsidiaries and the acquisition of French firms by American ones. My analysis focuses on the 1950s-1970s, after which I argue that a new dynamic, that of globalisation, stimulated change in the French pharmaceutical industry, even if the influence of the ‘American model’ was a main aspect of this globalisation.

1. Drug innovation

The manufacture of antibiotics at an industrial level: that is the representation of American industry that French pharmaceutical manufacturers would have.

WWII is a turning point: American firms succeeded in the organisation of the manufacture of antibiotics, with the help of the Government and the Army. For many enterprises, the war provokes a main change: industrial plants were built up, or R&D organisations set up. The standardisation of products introduces new habits. The R&D begins also to adopt new methods like screening. What was new was the methods, the standardisation and the machines and scientific apparatus. The change occurs in several parts of the drug discovery and manufacture. The new drugs are innovative and efficient: this is also important for the success of the ‘American model’.

French scientists travel in America since 1944, as Jean-Paul Gaudillière recalls us, and they look for help: how to manufacture some of the new drugs in France, like penicilline? How to organise research, with new scientific instruments or methods? At the end of the 1940s, some French firms and academic research laboratories begin to introduce ‘American’ methods, but this did not give birth to a biomedical complex. The case of penicilline is a first example. French government offers to firms and to a national company to manufacture antibiotics that will be reserved for the Army, later it could be sold to civilians. A national company, the “*Société des produits chimiques*”, is set up: it will drive research on biochemical and manufacturing processes. The society is also an issue to the management of relations between industry and academic research. “*La mise au point et le perfectionnement de cette technique [penicilline manufacturing processes] exigent la collaboration de chercheurs dégagés de toutes préoccupations étrangères à la science et disposant de puissants moyens d’investigation: la nécessité s’impose donc de prévoir, à cet effet, la création, sous l’égide de*

¹⁰ Jonathan Zeitlin, *Americanization and its limits: Reworking US technology and management in post-war Europe and Japan*, Oxford, Oxford University Press, 2004; Dominique Barjot, Isabelle Lescent-Giles et Marc de Ferrière Le Vayer, *L’américanisation de l’Europe au XXe siècle: économie, culture, politique*, Lille, Université de Lille 3, 2002.

l'État, de laboratoires qui poursuivront leurs travaux, tant dans le domaine de la science pure que dans celui de l'exploitation industrielle des découvertes nouvelles, en liaison étroite avec l'Institut Pasteur et le Centre National de la Recherche Scientifique. L'absence d'une telle liaison ne peut, en effet, dans l'état de choses actuel, que compromettre l'efficacité des recherches, et ce fait apparaît d'autant plus regrettable que l'on ne peut se dissimuler que, du fait de l'occupation, la science française accuse, dans ce domaine, un retard appréciable, mais qu'elle ne manquera pas de surmonter dès que les moyens nécessaires seront mis à sa disposition."¹¹

But the society does not succeed. In 1949, French Government decided the dissolution and the main plant was offered to the French Blood organisation. The collaboration between academic scientists and military did not work; the aim of a public society manufacturing for the Army needs was criticised. Lastly, the price of antibiotics decreased so quickly that it's better to buy antibiotics than to manufacture¹². The organisation of medical research in France borrowed some elements of the 'American biomedical complex', mainly if we consider the relationships between scientists and hospitals, the development of statistics and randomized trials or the use of scientific machines. But, till the end of the 1970s, the pharmaceutical industry remained quite apart from this organisation, except of the relationships with hospital for the driving of clinical trials. Change in the 1980s should be linked with the internationalisation of the firms and the beginning of an European regulation¹³.

Other American influences appeared if we consider the French firms. First, the licences were one of the main issues to distribute the innovative drugs. Joint ventures help also to the spreading of the new drugs. Clin-Byla had a joint venture with Pfizer for the manufacturing of terramycine in France, and another joint venture with Wyeth for the manufacturing of tranquillisers¹⁴. Fifty French firms had agreements with American firms for the manufacture of antibiotics during the 1950s¹⁵. The licences and the joint ventures were the issues for two different objectives. The first one was the prohibition of drugs importation in France, till 1972: if an American or any foreign firm wanted to market in France, the drug had to be manufactured in France; if raw materials and active components might be imported, the preparation and packaging had to be done in France. Even if the American firms looked for the increase of their foreign market shares and their internationalisation, it was easier, in a first time, to do so in Great Britain: people spoke the same language and, as V. Quirke shows it, the links were early. Patents right and prices policy restrained also American direct investments in France: drugs were marketed at a very lower price in France since the end of the 1940s¹⁶; and till 1960, there were no right on drugs patents¹⁷. In the point of view of French firms, licences and joint-ventures offered an access to innovative drugs, without high investments in R&D. As there was any patent right in France on these American drugs, French firms also could manufacture me-too drugs: this an other way of innovation.

¹¹ Exposé des motifs de la loi du 23 mai 1946 créant la *Société des produits biochimiques*. Cette loi n'est suivie d'aucun texte d'application et dès 1949, il est projeté de céder le siège de la société au CNTS.

¹² Jean-Paul Gaudillière, *Inventer la biomédecine...* op.cit., p. 58-60.

¹³ Boris Hauray, *L'Europe du médicament: politiques, expertises, intérêts privés*, Paris, Sciences Po les Presses, 2006; Philippe Urfalino, *Le grand méchant loup pharmaceutique*, Paris, Textuel, 2005.

¹⁴ "Comment s'est constitué le groupe Clin-Byla ? ", *Entreprise*, 16 décembre 1961.

¹⁵ "Les antibiotiques ", *Actualités pharmaceutiques*, octobre 1961.

¹⁶ S. Chauveau, *L'invention pharmaceutique...* op.cit., p. 321 et sq.

¹⁷ Maurice Cassier, "Brevets pharmaceutiques et santé publique en France : opposition et dispositifs spécifiques d'appropriation des médicaments entre 1791 et 2004 ", *Entreprises et histoire*, 36, octobre 2004, p. 29-47.

In the 1950s, some French firms introduced new organisation of R&D and imitate American firms. The most famous case was Rhône-Poulenc who created a big R&D department and set it up in new buildings in Vitry, where is the main plant of the firm. In the documents published about this new R&D department, the author suggests comparisons with American firms¹⁸. But even if this R&D department might be the biggest in French pharmaceutical industry, as it gathered about 300 persons, including 60 chemists, physicians or pharmacists, it remained a little department: Merck research department employed about 800 persons at the same time. Nevertheless, Rhône-Poulenc succeeded in the 1950s in the marketing of new antibiotics (*Rovamycine*) and the well-known *Largactil*, the first anti-depressant. The new research organisation helped to a greater collaboration between biochemistry, chemical synthesis, biology and pharmacology¹⁹. Shall we consider that such a change occurred under the influence of an ‘American model’? or shall we think that the change in drug discovery, and the emergence of ‘chemotherapy like a paradigm’ induced such research organisations?

2. Advertising and marketing

The same question arises when we look about the marketing: if we can say that there were some American influences, which were not bound to the only pharmaceutical industry, we must recall a French experience in drug advertising. In the 1950’s, the American marketing captivated French managers: the methods appeared as “scientific” or “rationalised” and should be more efficient than the usual advertising. The change was not about advertising that is yet an important business in French pharmaceutical industry²⁰: what was new was the market inquiries, the analysis of the sales or the physicians prescription. The change was also a cultural one: the choice of investments and the choice of R&D programs would be more and more influenced by the market and the demand of patients and physicians. If such a strategy was well-documented in England (see Viviane about the ICI cardiovascular program²¹), French examples of research programs influenced by market analysis are not known yet. But we may suppose that such strategies occurred since the 1960s and the 1970s if we consider the development of me-too drugs and the main therapeutic orientations of the firms production.

The marketing was discovered at the beginning of the 1950’s : “*Dans notre métier [...] le marketing en est, du moins en France, à ses tout débuts. La présence d’un directeur de marketing dans un laboratoire est une initiative récente; la pratique des études de marché également. Cependant, nous pouvons dès à présent faire des études de motivation de prescriptions. Ceci est très important, car il importe de déterminer si nous allons commercialiser le produit sous la forme d’une injection, d’une pilule ou d’une dragée. Nous avons également beaucoup étudié les techniques du conditionnement*”²², as explained the marketing manager of the French-American firm Clin-Pfizer, who is ancient student of HEC (*Hautes Études Commerciales*) business school. J. Neukirch, who had the same task in Roussel, defined the marketing as the analysis of the outlets of new drugs and the examination

¹⁸ J. Marteret, “ Le centre Nicolas Griollet de la société Rhône-Poulenc ”, *L’industrie nationale*, 1956.

¹⁹ See Viviane PhD or book.

²⁰ S. Chauveau, “ Marché et publicité des médicaments ” in Christian Bonah et Anne Rasmussen (dir.), *Histoire et médicament aux XIXe et XXe siècles*, Paris, Éditions Glyphe, pp. 189-213.

²¹ Viviane Quirke, “ From evidence to market : Alfred spink’s 1953 survey of new fields for pharmaceutical research, and the origins of ICI’s programme ”, in Virginia Berridge and Kelly Loughlin (ed.), *Medicine, the Market and the Mass Media. Producing Health in the twentieth century*, London, Routledge, 2005, p. 146-171.

²² Bernard Meyer-Warnod cité in “ Comment consolider la réussite d’un produit ‘vedette’ ? ”, *Entreprise*, 25-décembre 1965, p. 41-44.

of what physicians and patients would like²³. Articles about pharmaceutical marketing are first published in reviews about enterprises or marketing, like *Entreprise* or *Hommes et Commerce*. *La pharmacie industrielle*, the organ of the pharmaceutical industry organisation (and lobby) did not publish articles about marketing before the 1960s. And these articles were more informational one, about what was DOREMA or IMS, but nothing about the use of marketing in French firms. In the French industry, even if the advertising expenses remained very high, there was an inability to express how the market cares for the success of the drugs, and how the marketing might help, since the 1960's (I suppose), the choice of R&D programs.

In 1967, a pharmacist, Georges Salsarulo published his PhD: *Introduction aux études des marchés pharmaceutiques*. As the marketing became an object of analysis, we may suppose that the pharmaceutical firms yet developed it. In the 1960s, IMS and DOREMA helped to the development and the use of marketing by the firms. Foreign subsidiaries used to do market enquiries and their setting up in France was driven by such enquiries. In countries like the USA, where there was no prices control, marketing played an important part. But it could be also an interesting tool in countries like France, where drugs prices were fixed by French government and drug innovation remained more difficult to get than in the USA: competition would be the differentiation between quite the same drugs that are me-too²⁴. IMS (*Information Médicale et Scientifique*) counts drugs selling on French market and DOREMA (*Documentation sur Recherche et Marketing*) collected the observations made by 400 physicians about their prescriptions, the occurrence of several disease, the motivations of drug consumption and the wishes of patients and physicians about drugs.

Last, another indication of the use of marketing is the increase of the expenses for marketing and advertising compared with the whole turnover. At the beginning of the 1960s, marketing and advertising were about 10 per cent of the whole turnover, in 1974 their part reaches 16 per cent²⁵. The part of R&D is below: 9,5 per cent in 1975. If we consider the competitiveness of the firms, that is more and more defined since the 1960s by their ability to get foreign market shares, we observe that more the R&D investment is high, more the exportations are also. So the increase of advertising and marketing expenses is perhaps, in a first time, a need to get a better conception of research program, and then, the firm must also increase its R&D expenses to get competitiveness.

3. State intervention

In the French context, where State intervention is stronger than anywhere in pharmaceutical industry, such strategies remain difficult to adopt. We may also observe that, if the choice of investment in the 1970s was characterised by a higher increase in marketing than in R&D, it did not offer to the firm great successes and helps only to keep market shares in France. State intervention in France increases since the end of WWII. Two main directions characterised this State influence: an economic one, dealing with prices and reimbursement by Social Insurance; a technical and scientific one, dealing with the safety and therapeutic interest of drugs. We do not intend to tell how this intervention was created and developed, as several historians do it, we would like to stress some similarities with the Food & Drug Act. We think that some of the change of drugs control, in 1941 and in the 1960's is somehow influenced by

²³ J. Neukirch, paper in *Hommes et Commerce*, 1954.

²⁴ S. Chauveau, *L'invention pharmaceutique... op.cit.*, p. 610.

²⁵ Rapport Boulin, *Pour une politique de la santé, L'information médicale*, Paris, Documentation française, 1975.

what happens in the US, but not at all. We must be cautious: in the US, the drugs control was driven by the need to inform and educate patients, and the rules of this control were negotiated with the pharmacists, who were influential lobbyists²⁶. The tradition was very different in France: the State used to offer a protection with the “sanitary policy”, which was a kind of police, prohibiting the quacks; the State took the role of the market: it assumed the evaluation of the innovative character and the therapeutic interest of new drugs. We may refer to Arthur Daemmrich and the “therapeutic culture” to define such national differences. “Therapeutic culture” refers to the relationships between State, firms, medical professions and patients associations²⁷, and therapeutic culture helps to understand the way the patient is conceived. For example, in the US, the patient was dependent from the physicians in the first part of the 20th century; then, the patient needed to be protected by the State —this was a main consequence of the *Thalidomide* affair —; nowadays, the patient is an active and self-aware consumer.

What could we say about France? We observe a kind of parallelism if we consider legislation about drugs and foods and safety. The 1902 and 1906 Food & Drugs Act (FDA) established that manufacturers of adulterated drugs would be sued, as they did sell products that were not identical to the formulary. The legislation was voted after several enquiries published by muckrakers and the scandal of the book *The Jungle*. In France, a law about fraudulent practices was also voted in 1905, after several scandals about adulterated wine and meat²⁸. If we consider the case of drugs, the American and the French legislation introduced the principle that a good drug is identical to its formula. This rule remained in the following laws: 1938 FDA in the US, 1941 “visa” in France. We suppose that even if there was no direct influence from the US to the France, there were common preoccupations when those two countries reinforce drug regulation. In 1938 the New Drug Application (NDA) was adopted: the manufacturer must provide documents about the drug safety, its formula, how it is manufactured and controlled. The NDA was adopted after the death of several patients who had taken syrup made up of sulphonamide and glycol, which is highly toxic. In France, no affair occurs before the promulgation of 1941 law, but there was a care of the safety of drugs. We may consider that such change in drug regulation was an issue to the marketing of new active principles that may be dangerous or toxic. The regulation was reinforced at the beginning of the 1960's in France and the US: manufacturers must present documentation about different trials (toxicology, pharmacology, clinical). In France, the new rules were adopted after the *Stalidon* affair: the drug provokes several death in 1954; in the US, the first reform about drug regulation should be about drug prices and trusts but the *Thalidomide* affair obliged to reinforce the rules to get a NDA²⁹.

What we may say about those changes in drug regulation and State intervention is not that the US should have strongly influence France. In the two countries, the traditions of State intervention were two different. But as the two States had to manage the same difficulties, which were the marketing of more dangerous (and more efficient drugs), they finally choose the same tools and very similar rules. This was important as it might have contributed to the development of the relationships between pharmaceutical firms, as they had to manage the same difficulties and to apply to very similar rules. It may help to the development of

²⁶ Peter Temin, *Taking your medicine: Drug regulation in the United States*, Cambridge, Harvard University Press, 1980.

²⁷ Arthur A. Daemmrich, *Pharmacopolitics. Drug Regulation in the United States and Germany*, Chapel Hill, University of North Carolina Press, 2004, p. 3-4.

²⁸ Alessandro Stanziani, *Histoire de la qualité alimentaire. France, XIX-XXe siècles*, Paris, Le Seuil, 2005.

²⁹ A. A. Daemmrich, *Pharmacopolitics, op.cit.*

American subsidiaries in France and more generally, the influence of American pharmaceutical industry.

4. American subsidiaries and American influence on French pharmaceutical industry

The very first links between American and French pharmaceutical firms were mainly licences agreement and joint-venture, as we have seen below, about the R&D organisation. With the time, as licence became a joint-venture, and the joint-venture the main share of the French firm shareholding, many French enterprises became American subsidiaries. In 1964, there were 36 foreign subsidiaries in France, including 15 American, 5 English and 4 German. In 1972, only eight years later, there were 82 foreign subsidiaries including 32 American, 19 German, and 10 English. These 82 foreign subsidiaries held 41,86 per cent of the whole turnover of French pharmaceutical industry. At the end of the 1950s five firms with foreign shares belonged to the group of the 35 first ones; in 1973, 19 firms with foreign shares belonged to the same group, so half of the biggest French pharmaceutical firms had foreigners in their shareholding. These subsidiaries manufactured and marketed 70 per cent of the antibiotics, 60 per cent of the cardiovascular and 80 per cent of the hormones marketed in France³⁰.

The “subsidiarisation” of the French firms was not only an issue to reach competitiveness for these French firms, or to get innovative drugs. Many little or medium firms did not have the means to increase their business and remain reluctant to take out loans. The debt ratio in French pharmaceutical industry was the lower one of the whole French industry in the 1960s. But this kind of management increased the ‘risk’ of a buying out by foreign firms, and mainly American firms. Not all the French firms had to become subsidiaries: they might be medium size, with R&D (even applied research), a good manufacturing plant and good network of medical representatives. In 1969, half of the firm doing a turnover of at least 10 million francs (medium sized firms, about the third part of the whole French pharmaceutical industry) had half of their shareholding belonging to foreign firms³¹.

French government was aware of the threats of such a ‘subsidiarisation’: French industry could disappear, but more worrying is the fact that drugs manufactured by foreign subsidiaries were sold at a higher price than French products (4,51 francs for French drug, 6,23 francs for foreign drug in 1974): the cost for the Social Insurance would be higher and higher. Several times, when a foreign pharmaceutical group, and mainly an American one, undertook to buy out a French firm French government tried to stop such a process and suggested that a French pharmaceutical enterprise would do the buy out³². Another issue was to encourage the emergence of French pharmaceutical groups: Sanofi, Synthelabo, Roussel-Uclaf and Rhône Poulenc became the four first pharmaceutical groups in France during the 1970s. Each one developed R&D, marketing organisation, several manufacturing plants and abroad subsidiaries³³. The growth of those pharmaceutical groups was not only the enforcement of the strategies or the model of American groups, it belonged also to a more general change which is globalisation.

First conclusion

³⁰ Travaux préparatoires au *Rapport Guinard* commandé par le ministre de la Santé — document de travail pour réviser les procédures de fixation des prix —, AN CAC 19780529/1.

³¹ S. Chauveau, *L'invention pharmaceutique... op.cit.*, p. 584 et sq.

³² S. Chauveau, *Ibidem*.

³³ S. Chauveau, *Ibidem*, p. 574 et sq.

The superiority of American firms, and therefore of the American model, was mainly related to the organisation of R&D. Such an organisation did not succeed in France, as collaboration between academic scientists and industry remained secondary in importance, except in the case of large firms such as Rhône-Poulenc and Roussel-UCLAF. However, from the 1980s onwards, this kind of collaboration became better developed. When and where American influence existed, it was made possible by the weakness of the French pharmaceutical industry, a weakness that was to a large extent the consequence of intervention by the French State. However, one must be careful when considering foreign ‘influences’ on a science-based sector such as the pharmaceutical industry. This industry had developed much in the same way in many different countries, relying as it did on scientific discoveries and innovations that did not remain national for long. The British case illustrated this point particularly well.

II. The British Pharmaceutical Industry (V. Quirke)

More than any other European country, Britain’s pharmaceutical industry has benefited from the transfer of American scientific knowledge and technological know-how³⁴, as well as the diffusion of American marketing practices since the 2nd World War³⁵. This was in part due to the greater openness and liberal nature of the British economic and political system³⁶. However, little has been said about the part played by Anglo-American relations in the diffusion of knowledge and practices across the Atlantic. In this paper, I therefore propose to explore the role of Anglo-American relations, and of the American ‘model’ in the growth of the British pharmaceutical industry in the twentieth century. The traditional view - such as that expressed by Jonathan Liebenau - has been that, after a period of lagging behind, it ‘caught up’ with its competitors (after the Second World War the American sector, which had taken over the position of world leaders in pharmaceuticals from Germany), by finally adopting their tools and methods³⁷. Through a study of Anglo-American relations, their impact on the British pharmaceutical industry, and of key post-war innovations, such as corticosteroid drugs or the beta-blockers, I believe that it is possible to challenge such a view and present a more accurate, as well as a more balanced picture, in which the ‘Americanisation’ of the British pharmaceutical industry can be seen to be a dynamic, two-way process.

1. Defining the ‘American ‘model’’ and the ‘British pharmaceutical industry’

But first of all, I need to define what is meant by ‘American’ and ‘British’, and then what characterized the pharmaceutical industry in the 20th century.

A. American vs British

Although the pharmaceutical industry retained its national characteristics until after the 2nd World War, the distinction between British and American firms may appear more problematic than between firms of other nationalities. This is partly because of common language and

³⁴ S. Chauveau, ‘Entreprises et marchés du médicament en Europe occidentale des années 1880 à la fin des années 1960’, *Revue Histoire économique et sociale*, pp. 49-81.

³⁵ J. Slinn, ‘A cascade of medicines’: the marketing and consumption of prescription drugs in the UK, 1948-2000’, in L. Curth (ed.), *From Physik to Pharmacology* (London: Ashgate, forthcoming in 2006).

³⁶ This point has been made by Lacy Thomas in his comparison of the French and British pharmaceutical industries. L.G. Thomas, ‘Implicit industrial policy: the triumph of Britain and the failure of France in global pharmaceuticals’, *Industrial and Corporate Change*, 3 1994, pp. 451-489.

³⁷ For instance, J. Liebenau, ‘The British success with penicillin’, *Soc. Stud. Sci.*, 17, 1987, pp. 69-86; *idem*, ‘The rise of the British pharmaceutical industry’, *BMJ*, 301, 1990, pp. 724-730.

cultural inheritance. Burroughs Wellcome, founded by two Americans, Silas Burroughs and Henry Wellcome at the end of the 19th century, is generally seen as an exceptional company, which played an important part in the growth of a modern, science-based pharmaceutical industry in Britain³⁸. It was, therefore, an early vehicle for the transfer of the American ‘model’ in pharmaceuticals (itself inspired by German chemical-pharmaceutical companies – as in the case of the American offshoot of the German firm Merck of Darmstadt): this was a laboratory-based industry, which as well as improving on existing drugs aimed to develop novel medicines, and relied on good relations with academic scientists and government agencies in order to do so.³⁹ In addition, it had a large sales force, with adopted distinctive, often aggressive sales practices⁴⁰. An interesting question is at what point in time Burroughs Wellcome became truly ‘British’. Perhaps in 1906, when it was decided to set up an ‘associated company’ in America⁴¹, or in 1925, when a chemical plant and pharmaceutical lab were created at Tuckahoe, N.Y. City⁴²? In any case, by the 1950s, Burroughs Wellcome’s innovative centre had moved from Britain to Tuckahoe, where George Hitchings and Gertrude Elion carried out their research on nucleic acid analogues, which led to their Nobel Prize for Physiology or Medicine, awarded jointly in 1988 to James (now Sir James) Black for his discovery of the first clinically useful beta- and H₂-blockers⁴³.

American companies started setting up subsidiaries in Britain earlier than elsewhere, no doubt in order to gain access to the British Empire, as well as the rest of Europe. Parke Davis was one of the first⁴⁴, in 1888. Others followed, for instance Abbott Laboratories⁴⁵ in 1937. However, note that in the same period, i.e. in the inter-war years, May & Baker became a subsidiary of the French group Rhône-Poulenc. It was largely under its influence that the British company acquired its science base, and became innovative in its own right, developing drugs such as *M&B 693*, a sulpha-drug famous for saving Winston Churchill’s life⁴⁶ during the WW2. The numbers of British subsidiaries of American companies greatly increased after the conflict, not only to gain access to the old Empire, but to also to the emerging European Community, and to what was recognised as a high-quality British scientific and medical

³⁸ E.M.Tansey and R.M.C.E. Milligan, ‘The early history of the Wellcome research laboratories’, 1894-1914’, in J. Liebenau, G.J. Higby and E.C. Stroud (eds), *Pill Peddlers: essays on the history of the pharmaceutical industry* (Madison, Wis.: American Institute of the History of Pharmacy, 1990), pp. 91-106. See also J. Liebenau, ‘The 20th century British pharmaceutical industry in international context’, *ibidem*, pp. 123-133; *idem*, ‘Ethical business: the formation of the pharmaceutical industry in Britain, Germany and the US before 1914’, in R.T.P. Davenport-Hines and G. Jones (eds.), *The End of Insularity: Essays in comparative business history*, London, Cass, 1988, pp. 117-129; and J. Slinn, ‘Research and development in the UK pharmaceutical industry from the nineteenth century to the 1960s’, in M. Teich and R. Porter (eds.), *Drugs and Narcotics in History*, Cambridge, Cambridge University Press, 1996, pp. 168-186.

³⁹ J. Liebenau, *Medical Science and Medical Industry: the formation of the American pharmaceutical industry*, Basingstoke, MacMillan, 1987; J.P. Swann, *Academic Scientists and the Pharmaceutical Industry: cooperative research in twentieth-century America*, Baltimore, 1988; J.-P. Swann, ‘Universities, industry and the rise of biomedical collaboration in America’, in Liebenau (*et alii*), *Pill Peddlers*, pp. 73-90; N. Rasmussen, ‘The Moral Economy of the Drug Company-Medical Scientist Collaboration in Interwar America’, *Social Studies of Science*, 34, 2004, pp. 161-185.

⁴⁰ Slinn, ‘A cascade of medicines’.

⁴¹ G. Macdonald, *One Hundred Years Wellcome, 1880-1980*, London, Wellcome Foundation, 1983, p. 29.

⁴² *Ibidem*, p. 74.

⁴³ K.H. George, ‘George H. Hitchings, 1905- : American pharmacologist’, *Notable Twentieth Century Scientists* (1995), volume 2, pp. 933-934; L. Marshall, ‘Gertrude Bell Elion, 1918- American biochemist’, in *ibidem*, volume 1, pp. 583-584; A. Giner-Sorolla, ‘The excitement of a suspense story, the beauty of a poem: the work of Hitchings and Elion’, *Trends in Pharmacological Sciences*, 9, Dec. 1988, p. 437-438.

⁴⁴ T. Deeson, *Parke, Davis in Britain: the first hundred years*, Park, Davis & Co., Ltd., 1995.

⁴⁵ J. Slinn, *Abbott Laboratories in the UK: celebrating 60 years of commitment to health care*, Cambridge, Granta Editions, 1999.

⁴⁶ J. Slinn, *A History of May & Baker, 1834-1984*, Cambridge: Hobsons Ltd., 1984, esp. chs. 5 and 6.

system⁴⁷. When in 1955 Smith Kline & French (SK&F) took over the British company A.J. White, with which it had had close relations since the 1920s, Glaxo's managing director Herbert Palmer commented: 'now... all our American friends have arrived and settled in the UK and we may expect even severer competition than we are now experiencing'⁴⁸.

At the same time, the nature of these subsidiaries changed. Increasingly, as well as manufacturing and sales activities, they encompassed R&D operations, which were more likely to lead to the diffusion (in both directions) of scientific knowledge and technological know-how. After SK&F had acquired A.J. White, they set up a research facility in Camberwell, which became known as 'the British Research Operation', and which moved to a new research centre built in Welwyn Garden City in 1959. It was there that, after he had left Imperial Chemical Industries (ICI) in 1964, James Black developed the H₂-antagonist cimetidine (*Tagamet*) for the treatment of peptic ulcers.⁴⁹

In addition to the creation of American subsidiaries, there were alliances and cross-licensing agreements between American and British companies in particular therapeutic or technical areas, such as corticosteroids, for instance between Glaxo and Merck, and Boots and Upjohn⁵⁰. In the 1970s, in the burgeoning new field of biotechnology, these were becoming so numerous and of such complexity that the companies' different interests were blurred, and their national boundaries began to dissolve.⁵¹ In the same period, British firms bought up smaller American companies in order to gain a foothold in the American market, the largest medical market in the world. For example ICI acquired Stuart Pharmaceuticals, and Glaxo Meyer Laboratories⁵².

Since the 1980s, the growing wave of mergers between American and British companies has contributed in large part to the global pharmaceutical industry we know today. In parallel with these developments, government officials and representatives of pharmaceutical industry have made efforts to standardize drug testing procedures and the regulatory process. However, as Arthur Daemmrich has shown, this is an area in which different 'therapeutic cultures' (defined as 'the historical evolution of a distinctive set of institutionalized relationships among the state, industry, physicians, and disease-based organizations') are likely to remain⁵³. Nevertheless, the importance of the American market to the global pharmaceutical industry has ensured that relationships with the FDA have tended to dominate the efforts by foreign firms to penetrate this market, and that the FDA has served as a model for regulatory agencies abroad. In Britain, although created in response to local circumstances and specific events, the Therapeutic Substances Act (TSA) of 1925, the Committee on Safety of Drugs (CSD) in 1963, and its successor the Committee on Safety of Medicines (CSM) in

⁴⁷ J. Slinn, 'The growth of the pharmaceutical industry', in S. Anderson (ed.) *Making Medicines: A Brief History of Pharmacy*, London, Pharmaceutical Press, forthcoming in 2005.

⁴⁸ Quoted in G. Jones, *The Business of Medicine*, London, Profile Books, 2001, p. 367.

⁴⁹ See L. Finucane, *SK&F: from Camberwell to Welwyn Garden City, 1956-1989* (Welwyn Garden City: Smith Kline & French Laboratories Ltd., 1989), chs. 1, 2 and 10.

⁵⁰ On corticosteroids, see V. Quirke, 'Making British cortisone: Glaxo and the development of corticosteroids in Britain in the 1950s and 1960s', in special issue of *Studies in History and Philosophy of Biology and Biomedical Sciences*, 2005, 36, pp. 645-674.

⁵¹ On biotech, see L. Galambos and S. Sturchio, 'Pharmaceutical firms and the transition to biotechnology: a study in strategic innovation', *Business History Review*, 72, 1998, pp. 250-278.

⁵² Jones, *The Business of Medicine*, p. 364.

⁵³ Daemmrich, *Pharmacopolitics: drug regulation in the United States and Germany*, Chapel Hill, UNCP, 2004, pp. 3-4.

1969 were based, albeit loosely, on the Food and Drug Administration (FDA)⁵⁴. However, in other areas, such as pricing policy, the British system has remained quite unique, relying on a voluntary arrangement between industry and the Ministry of Health, which was introduced in 1957, the Voluntary Price Regulation Scheme (VPRS), followed in 1978 by the Pharmaceutical Price Regulation Scheme (PPRS)⁵⁵.

Because much of the history of the American and British industries is a shared history, the products of this industry, i.e. the drugs themselves, offer us a privileged angle from which to examine how the American ‘model’ has been transferred and transformed in a British context. Therefore, the next section gives an outline of the history of drug development in the twentieth century⁵⁶.

2. Drug discovery and Anglo-American relations in the twentieth century

Not surprisingly, this history coincides with the rise of chemotherapy, which is usually traced back to the German bacteriologist and immunologist Paul Ehrlich, and the development of *Salvarsan* in the first decade of the twentieth century. However, there is another strand in our story, which became very important after the WW2, and has been an important aspect of Anglo-American relations in the pharmaceutical industry: the history of replacement therapy (vitamins and hormones). This is a vast topic, therefore I shall only be able to summarize the history of some key drugs.

A. Before 1939: vitamins and hormones

The interwar period is often considered as a low point in the history of drug discovery. Until the development of *Prontosil* in 1932-1935, chemotherapy appeared to have failed to fulfil its early promise, other than the occasional success against protozoal diseases, for instance *Germanin* against sleeping sickness, and *Plasmaquin* and *Atebrin* against malaria⁵⁷. Nevertheless, the interwar years saw important achievements in the field of replacement therapy, against deficiency diseases caused by a lack of vitamins or hormones. In this area, many significant developments occurred in Britain and North America, partly because of a shared strength in physiology in these two countries’ medical traditions.

The word vitamin was coined by a Polish chemist, Casimir Funk, when he was a guest worker at the Lister Institute of Preventive Medicine in London in 1912. The Lister Institute later joined the Medical Research Council (MRC) in a study of rickets in post-war Vienna. This led to the identification of the anti-rachitic factor, vitamin D. Other vitamins followed, and by the 1930s most of them had been isolated, their structures worked out, and their chemical synthesis realized, which enabled some companies, such as Glaxo, originally a firm of New-Zealand traders that became baby-food manufacturers, to enter the pharmaceutical sector.

⁵⁴ Liebenau, ‘The 20th century British pharmaceutical industry’, pp. 126-8; E.M. Tansey and L.A. Reynolds, ‘The Committee on Safety of Drugs’, *Wellcome Witnesses to Twentieth-Century Medicine*, vol. 1, April 1997, pp. 103-35.

⁵⁵ J. Slinn, ‘Drug Guzzlers or medicine junkies? Regulating the cost and consumption of prescription pharmaceuticals in the UK, 1948-1967’, *Business History*, 47, 2005.

⁵⁶ For general histories of drug development, see Weatherall, *In Search of a Cure*; W. Sneader, *Drug Discovery: the evolution of modern medicines* (Chichester: John Wiley & Sons, 1985). For shorter summaries see V. Quirke, ‘From alkaloids to gene therapy: a brief history of drug discovery in the twentieth century’, in Anderson (ed), *Making Medicines*; also J. Goodman, ‘The pharmaceutical industry’, in R. Cooter and J. Pickstone (eds.), *Medicine in the Twentieth Century*, Amsterdam, Harwood Academic, 2000, pp. 141-54.

⁵⁷ Weatherall, *In Search of a Cure*, pp. 149-50.

Interestingly, this happened after a visit by the Glaxo's then director of research, Harry Jephcott, to America, where he learnt of important developments in nutritional science, and subsequently made arrangements to buy the rights to the processes that had been developed there⁵⁸.

There were also a number of important milestones in the field of hormones during this period. These included the isolation of the active principle of the thyroid gland by E.C. Kendall at the Mayo Clinic in Rochester, Minnesota, in 1919; the extraction of the pancreatic hormone insulin, by F. Banting, J.J.R. Macleod, C. Best and J.B. Collip in 1921-1922 at the University of Toronto; and the characterisation of steroid hormones by various researchers in the 1920s and 1930s. The latter stimulated a race between rival scientific groups in Britain and Germany, and the decisive evidence, which resolved the controversy on the structure of the steroid nucleus, was provided by the British crystallographer J.D. Bernal⁵⁹. However, the development of insulin was perhaps the most significant from the point of view of the history of drug discovery⁶⁰. The University of Toronto had ceded the rights to manufacture and distribute the drug in North America to the American company Eli Lilly. In 1922, the MRC accepted Toronto's offer of the patent rights for insulin in Europe. As Christiane Sinding has shown, this transformed what until then had essentially been a North-American network into a triangular trans-national one, including Canada, the US and the UK⁶¹. Visits to Toronto and Indianapolis (where the Eli Lilly plant was located) were therefore arranged by Dale and another MRC researcher, W.H. Dudley, who studied their manufacturing processes and collected data on production costs. Discussions were also held between the MRC and a group of British companies, including Allen & Hanbury, British Drug Houses, and May & Baker as well as BW, with a view to granting licences for the right to produce the pancreatic extract, but also with the provision that the MRC would be responsible for testing their products⁶². Thanks to their efforts, and the protection against foreign competitors offered by the MRC and the Ministry of Health's Insulin Committee, by 1924 the production of British insulin was under way, and its cost had dropped below that of Eli Lilly. The companies selected for the production of insulin became the MRC's network of 'trusted companies' throughout the 1930s, and formed the nucleus of the Therapeutic Research Corporation (TRC), which was set up with encouragement of the MRC in 1941, and by 1942 was engaged in the manufacture of penicillin in Britain⁶³. In addition, the experience of developing insulin paved the way for the 'culture of quantification' that came to dominate clinical practice in Britain, and inspired the establishment of the TSA⁶⁴ in 1925.

B. The Second World War

In the history of Anglo-American relations, 1940 was a crucial year, the start of 'the Anglo-American special relationship'. This relationship was the result of a convergence of views on international relations, of common cultural, political and legal inheritance, but also of

⁵⁸ R. Davenport-Hines R. and J. Slinn, *Glaxo: A History to 1962*, Cambridge, Cambridge University Press, 1992, ch. 4.

⁵⁹ D.M.C. Hodgkin, 'John Desmond Bernal, 1901-1971', *Bio.Mem.FRS*, 22, 1980, pp. 17-84; H. Kamminga, 'Vitamins and the dynamics of molecularization: biochemistry, policy and industry in Britain, 1914-1939', in De Chadarevian and Kamminga (eds.), *Molecularizing Biology and Medicine*, pp. 83-105.

⁶⁰ M. Bliss, *The Discovery of Insulin*, Toronto, McClelland & Stewart, 1982.

⁶¹ C. Sinding, 'Making the unit of insulin: standards, clinical work, and industry, 1920-1925', *Bulletin of the History of Medicine*, 76, 2002, pp. 231-270 (242).

⁶² Liebenau, 'The MRC and the pharmaceutical industry', pp. 170-171.

⁶³ Quirke, 'Experiments in collaboration', chs. 2 and 3.

⁶⁴ Sinding, 'Making the unit of insulin', pp. 269-270.

Britain's dependence on American aid to fight the war, let alone win it⁶⁵! Soon after Dunkirk, Anglo-American discussions started with a view to setting up Lend-Lease agreements, by which the US would provide Britain with material support. As a result of these discussions, co-operative research programmes were begun in order to pool British and American scientific knowledge and technical expertise. The best known of these are the radar and atom bomb projects, but there were also collaborative schemes to develop pharmaceutical products. These schemes would constitute four of the main axes for pharmaceutical R&D after WW2: synthetic compounds, hormones, anti-cancer agents, and antibiotics.

a) Synthetic anti-malarials

At the start of the WW2, the production of sulpha-drugs was well underway outside Germany. Nevertheless, as in the Great War, supplies of other German synthetic drugs, including *Plasmaquin* and *Atebrin*, were once again interrupted. When the conflict extended from Europe to the Far East, exposing the troops to malaria and cutting off the main source of quinine from Java, this created potential difficulties for the Allied war effort. However, projects to synthesize novel anti-malarials had begun before the Japanese attack on Pearl Harbour in December 1941. These culminated in the development of *Paludrine* by ICI in 1945, and *Chloroquine* by Winthrop in 1946, which until resistance rendered them less active remained among the most widely used anti-malarials.⁶⁶

b. Cortisone

Because of a rumour that adrenal cortical extracts were being administered to German aircraft pilots to improve their ability to fly at high altitudes, compound E (later known as cortisone) had been synthesized from bile acids by Merck during the war using a method devised earlier by Kendall at the Mayo Clinic⁶⁷. However, although British scientists appear to have helped with the research, to my knowledge the cortisone project did not involve British pharmaceutical companies. This helps to explain why they found themselves relatively unprepared when Kendall's colleague, Philip Hench, demonstrated the spectacular effects of cortisone against rheumatoid arthritis at the 7th International Congress of Rheumatology in New York in 1949, an event that led to a veritable 'outpouring of steroidal investigations'⁶⁸.

3. Anti-cancer agents

Renewed fears about chemical gas attacks led researchers at Yale University, under contract with the Office for Scientific Research and Development (OSRD), to study nitrogen mustards. These displayed anti-tumour properties, which were observed on both sides of the Atlantic after the American workers had communicated their results to their British colleagues. The outcome of this research was the use of nitrogen mustards as the first anti-cancer chemotherapeutic agents. A search for other compounds exhibiting a similar alkylating action (i.e. combining chemically with cellular constituents) began, and ICI were one of the British companies working on this project⁶⁹.

⁶⁵ Dobson, *The Politics of the Anglo-American Economic Special Relationship*, pp. 18-19.

⁶⁶ Weatherall, *In Search of a Cure*, ch. 10.

⁶⁷ N. Rasmussen, 'Steroids in Arms: Science, government, industry and the hormones of the adrenal cortex in the United States, 1930-1950', 46, *Medical History*, 2002, pp. 299-324.

⁶⁸ Quirke, 'Making British cortisone'.

⁶⁹ Sneader, *Drug Discovery*, pp. 336-339.

d. Penicillin

By 1942, the programme to produce penicillin in large quantities for the treatment of war wounds, and to find a synthetic route to its manufacture, dominated the Allies' co-operative ventures in pharmaceuticals. Such was its importance, that after the war it would become a reference-point for many biomedical research projects, not only in Britain and America, but in other countries also⁷⁰. Moreover, institutions that had played a part in its development, such as the OSRD, became models for similar institutions elsewhere (in Britain leading to the creation of the NRDC). Although the story of penicillin deserves to be told in greater detail than it is possible here, I shall outline its two main aspects: the programme to mass-produce penicillin; the programme to unravel its structure and develop and a synthetic route to its manufacture.

- **The programme to mass produce penicillin**

A few days after the Lend-Lease agreements had been signed between Churchill's and Roosevelt's governments, Howard Florey flew to the US with Norman Heatley, the member of his team in Oxford who had developed a method for the surface culture and extraction of penicillin, in order to get the manufacture of the drug started there. The outcome of the combined British and American efforts was the mass production of the drug using deep-fermentation methods, which were developed by the North Regional Research Laboratory at Peoria, Illinois, and perfected by different American companies under the aegis of the OSRD⁷¹. These methods were later licensed to companies abroad, including British firms such as Glaxo, which bought the right to use Merck's process. The rumour that British companies might have to pay their American counterparts royalties on their patents became a '*cause célèbre*' of the post-war era, leading to resentment and tensions between the two nations⁷².

- **The programme to determine penicillin's structure**

Determining the chemical structure of penicillin was a prerequisite to its synthesis, considered during the war to be a possible, if not inevitable alternative to fermentation. Once again, a British X-ray crystallographer, and former student of Bernal, Dorothy Hodgkin, played a crucial role in its determination, providing the evidence needed to decide between two competing alternatives. Having obtained samples of pure crystalline penicillin from Henry Dale, who was on the MRC's Penicillin Committee, she was able to confirm the beta-lactam ring structure, which was later shown by biochemical studies to play a crucial role in the anti-bacterial activity of the molecule. Although the synthetic route, achieved many years later by John Sheehan at MIT, never fully replaced manufacture by deep fermentation of the drug, it paved the way for the semi-synthetic penicillins. The first of these was developed by the British company Beechams, which benefited from the expertise of Ernest Chain, a former member of the Oxford team who had become their consultant. Ironically, it was given the name *Penbritin* (i.e. 'Penicillin made in Britain!'), and launched⁷³ in 1959. After initial attempts at collaboration, Beechams and Sheehan later challenged each other's patents, and the litigation that followed was to go on for 20 years!⁷⁴ With antibiotics, the geographical centre of technological innovation and competitive advantage in pharmaceuticals had shifted from Germany to America. The trans-national space of which the British pharmaceutical

⁷⁰ Quirke, 'Experiments in collaboration', ch. 6; Gaudillère, *Inventer la biomedicine*, ch. 1.

⁷¹ G. Hobby, *Penicillin: meeting the challenge*, Yale, Yale University Press, 1985.

⁷² R. Bud, 'Penicillin and the new Elizabethans', *BJHS*, 31, 1998, pp. 305-333.

⁷³ H.G. Lazell, *From Pills to Penicillin: the Beechams story*, London, Heinemann, 1975.

⁷⁴ J.C. Sheehan, *The Enchanted Ring: the untold story of penicillin*, Cambridge, Mass., 1982.

industry had been a part still existed, but it was now dominated by transatlantic, rather than cross-Channel interactions.

3. Post-World War II: the ‘special relationship’, or collaboration and competition in pharmaceuticals

The period following WW2 saw a huge rise in the numbers of new drugs being developed and marketed. Some of them had their origins in the wartime programmes described earlier. However, many others were the product of increased investments in pharmaceutical and biomedical research in the aftermath of war, and of the mass-market for drugs created by the new national health services. In a period that saw dollar shortages and the Suez crisis, the Anglo-American ‘special relationship’ in pharmaceuticals created opportunities for conflict as well as co-operation. However, as the examples above have shown, until the 1960s, competition tended to be fiercest in the scientific arena, whereas in the industrial field British pharmaceutical companies were forced into (sometimes uneasy) partnerships with American firms. A story that illustrates this well is the development of cortisone and other corticosteroids by Glaxo in the 1950s.

A. A ‘typical’ case study? Glaxo and the development of corticosteroid drugs

After Hench, a renowned Anglophile, had presented his results on the efficacy of cortisone against rheumatoid arthritis in 1949, he invited a group of friends, many of whom were British, to visit him at the Mayo Clinic so that they could observe for themselves the effects of cortisone on rheumatic patients. An outcome of this visit was the creation of the Clinical Research Unit for Rheumatoid Arthritis in London.⁷⁵ At about the same time, Merck offered 1 kg of cortisone for the purpose of trials in Britain to the MRC, which had appointed an advisory committee on rheumatism. One of the motives behind Merck’s policy of encouraging enthusiasm for cortisone among British clinicians was the influence of British clinicians on international medical opinion. In the words of a Merck official (quoted by David Cantor): “The major achievement which Merck & Co., Inc., wants in Great Britain is not so much the sale of cortisone there, as it is the enthusiastic acceptance of it by the best of their medical men. The reason for this is the powerful influence which good British clinicians and clinical investigators exert in establishing the climate of medical opinion, both throughout Europe and in America. We can say what we like about American superiority, but a thoughtful article in the *Lancet* or the *Quarterly Journal of Medicine* will in its influence often outweigh a dozen or two of American publications.”⁷⁶

However, as with penicillin, cortisone would soon reveal the junior status Britain was acquiring in its post-war partnership with America. After it was found that cortisone could be used in a variety of diseases, and not only in rheumatoid arthritis, the MRC extended its research programme to other areas – rheumatic fever, ophthalmology, dermatology, and pulmonary disease. Unfortunately, this coincided with rising concerns about the drugs bill, and against a background of dollar shortages and growing national debt. Consequently, in 1950 the Ministry of Health (MoH) urged British companies to start making cortisone. Glaxo’s expertise in vitamins, their academic consultants – many of whom were organic chemists with a knowledge of steroids – and what they considered to be their ‘special

⁷⁵ J. Glyn, ‘The discovery and early use of cortisone’, *Jal Roy. Soc. Med.*, 91, 1998, pp. 513-517; *idem*, ‘The discovery of cortisone: a personal memory’, *BMJ*, 317, 1998, pp. 822-823.

⁷⁶ Quoted in D. Cantor, ‘Cortisone and the politics of drama, 1949-1955’, in J.V. Pickstone (ed.), *Medical Innovations in Historical Perspective*, Basingstoke, Macmillan, 1993, pp. 165-184 (179).

relationship with Merck',⁷⁷ gave them a head start compared with other British firms. Although in 1951-2 there was some hesitation about the usefulness of cortisone because of the discovery of its side-effects, the example of American companies, which showed commitment to the new field, were searching for less toxic analogues and cheaper methods of production, encouraged Glaxo to maintain their efforts, and sign an agreement with Merck to manufacture the drug using their process⁷⁸. Therefore, in September 1953, the representatives of Glaxo were shown 'the works' by Merck, and this included plant diagrams as well as bench and production operations. Hector Walker, Glaxo's medical director and a Scotsman, was among the representatives who went to the US. It was observed by his colleagues back in the UK that he had been accepted right away by the Americans, but at the same time, with a note of relief, that 'his Scottish instincts' were unlikely to lead him to making indiscreet revelations about Glaxo's work⁷⁹.

At about the same time, Glaxo agreed to work with the MRC's researchers at the NIMR, who had discovered an alternative route to cortisone from a sterling area material, a by-product of the East-African sisal industry, hecogenin. Any patents resulting from this collaborative effort were to be held by the newly-formed NRDC. Thanks to their dual collaborative strategy (with Merck, and with the NIMR), and to their strategy of vertical integration, which led them to take control of the sisal plants in East-Africa, by 1956 Glaxo eventually gained their independence from Merck.⁸⁰ By then, in any case, Merck were beginning to behave in a rather 'un-gentlemanly' manner – according to a Glaxo official 'seeking business' aggressively⁸¹ – and Glaxo wished the freedom of action to enter into agreements with companies other than Merck. By developing a process from hecogenin as a starting material, Glaxo had become attractive partners in their own right. Their most significant partnership was a joint agreement with Schering (like Merck, another American offshoot of a German company). It gave Glaxo access to Schering's new corticosteroid (betamethasone). In exchange, Schering gained access to the services of Glaxo's consultant, Derek Barton, who in 1969 won the Nobel Prize for his method of assessing the 3-D structure of steroids, developed while he was a visiting lecturer at Harvard in 1949. They also gained access to Glaxo's process from hecogenin to make betamethasone⁸². Out of this agreement, signed in 1957, Glaxo went on to develop their first truly novel medicine, the topical steroid Betnovate. It involved the help of Dr A.W. Mackenzie, a consultant dermatologist at St John's Hospital for Diseases of the Skin, who while on an exchange fellowship at the Western Reserve University at Cleveland, Ohio, had devised a new way of testing topical preparations. Back in England, he made regular visits to Glaxo's research centre at Greenford to show the researchers how to use and interpret his test, and he carried out a small scale trial with patients suffering from eczema⁸³.

Within a few years, clever marketing by the company, which associated the drug with national interest and a romantic view of the British Empire (from which the starting material for *Betnovate* – hecogenin – originated), had led *Betnovate* to overtake its competitors, despite the low prices imposed on Glaxo by the Department of Health. By 1966-1967 it represented

⁷⁷ Davenport-Hines and Slinn, *Glaxo*, pp. 141-149.

⁷⁸ GSK GGA 295: 'Cortisone 1953': J.M. Craig to Bide, 3 July 1953. Details of the Merck agreement implied that 2/3 profits would go to Merck, while only 1/3 to Glaxo, which was expected to lead to losses for Glaxo.

⁷⁹ *Ibidem*, Manning to Palmer, 8 Sept. 1953.

⁸⁰ *Ibidem*, 'Cortisone and Prednisolone, 1956': Back to Palmer, 7 Aug. 1956.

⁸¹ *Ibidem*, 'Cortisone, 1957': Back to Palmer, 27 Feb. 1957.

⁸² Quirke, 'Making British cortisone'.

⁸³ Jones, *The Business of Medicine*, ch. 13.

36 per cent of the group's pharmaceutical turnover and 20% of its exports, by 1969 its sales had overtaken those of Glaxo's antibiotics, and it remains a best-seller to this day⁸⁴.

B. A 'special' case study? ICI and the development of the beta-blockers

Created in 1926 and inspired by the German chemical giant IG Farben⁸⁵, in the interwar period ICI developed a close and at times strained relationship with the American group Du Pont de Nemours, under a Patents and Process Agreement signed in 1929, and which lasted⁸⁶ until 1949. This agreement, which had the purpose of dividing the world markets between the two groups and making it easier for them to compete with IG Farben, led to extensive sharing of scientific and technical information that was to benefit both companies. However, in the pharmaceutical field, which ICI entered earlier and more wholeheartedly than their American partners in 1936 with the creation of a Medicinal Section within their Dyestuffs Division, this led to restrictions on ICI's freedom of action to sign agreements with other firms, including Squibb which in WW2 had developed deep-fermentation methods to manufacture penicillin⁸⁷. Therefore, partly because of prior agreements with Du Pont, and partly also because of a different research culture, in contrast with Glaxo, ICI's Pharmaceutical Division were to develop most of their drugs on their own. The beta-blockers for the treatment of cardiovascular diseases are an example of this. However, relations with America and the American model still played a part in this discovery, as it had done in the development of *Betnovate*.

a. Forged by war: ICI's Pharmaceutical Divisiona.

During WW2, ICI became the British government's largest industrial agent, playing a crucial role in the projects to develop the atom bomb, radar, and also synthetic anti-malarials, penicillin and as we saw earlier, anti-cancer agents.⁸⁸ However, to my knowledge, there did not take part in the cortisone project, even though, like Glaxo, they had access to the top steroid chemists in the country. By 1944, the profits made from sulphonamide and anti-malarial drugs had led to the creation of a Pharmaceutical Division. By 1953, plans were being made for a new pharmaceutical research centre at Alderley Edge in Cheshire, defined as a 'centre for speculative chemotherapeutic research'.

b. The American 'model' and the building of Alderley Park

Its estimated cost was £1,250,000. Although there were no clear instructions at the time as to the proper amount to be spent on research, so far research expenditure at IC Pharmaceuticals had represented roughly ten per cent of its turnover, a figure similar, it was remarked, to that 'applied to IG Farben (pre war) and USA pharmaceutical firms [postwar]'. Expected turnover in 1957-60 was expected to reach £5,000,000 p.a., therefore it seemed likely that £500,000 p.a. would be spent on research⁸⁹. American firms, therefore, provided a working model for IC Pharmaceuticals.⁹⁰ The creation in 1949 of ICI's central research laboratory in the grounds

⁸⁴ *Ibidem*, pp. 316-319.

⁸⁵ Reader, *Imperial hemcial Industries*, vol. 1, pp. 326-7.

⁸⁶ D.A. Hounshell and J.K. Smith, *Science and Corporate Strategy: Du Pont R&D, 1902-1980*, Cambridge, CUP, 1988, ch. 10.

⁸⁷ *Ibidem*, pp. 448-449.

⁸⁸ See V. Quirke, 'War and change in the pharmaceutical industry: a comparative study of Britain and France in the twentieth century', *Enterprises et Histoire*, 36, 2004, pp.0 64-83.

⁸⁹ AZ\CPR3, special meeting, 16 March 1953.

⁹⁰ *Ibidem*, minutes of meeting, 18 Dec. 1951; also memo by D.G. Davey on his visit to the USA, 5-23 Apr. 1954.

of the Frythe, near Welwyn, reflected the growing importance of the American model in R&D. The Frythe laboratory realized the wish, expressed even before WW2, that ICI should possess laboratories where scientists might engage in fundamental research ‘freed from the urgencies and distractions of applied research’,⁹¹ and was inspired by Du Pont’s Experimental Station at Wilmington⁹². This wish would also – to some extent - be fulfilled with Alderley Park, where, from the very beginning, cardiovascular function was to be a major focus of research, as part of a wider programme to study chronic diseases. This programme was largely based on quantitative evidence prepared by one of ICI’s chemists, Alfred Spinks, who had been sent to Oxford to perfect his training in the biological sciences in order to design and lead ICI’s new pharmacology section. This evidence was drawn from epidemiological data, and also from the activities of firms and research centres in America, which suggested to ICI promising new fields for pharmaceutical R&D.⁹³

c. A departure from the American ‘model’? The beta-blockers

Therefore, when James Black arrived at Alderley Park in 1958 to work on coronary artery disease, a cardiovascular programme was already in place. However, Black brought with him something new, that was to provide ICI with an edge over their competitors in Britain and abroad: Raymond Ahlquist’s (of the University of Georgia at Atlanta) theory of alpha- and beta- receptors, which suggested to Black that it might be possible to treat angina-pectoris, from which his father had suffered and eventually died, by blocking the beta-receptors responsible for increased heart rate.⁹⁴ Black, a physiologist with medical training, had first come across this theory in 1954 in a pharmacology textbook, *Drill’s Pharmacology*, while working at the Veterinary School of the University of Glasgow, where he had set up a ‘state of the art’ physiological laboratory. There he was able to attract the academic surgeon George Smith, who had spent time in the US and become acquainted with American methods in cardiac surgery, to work with him. In 1958, Black was offered a post at Alderley Edge to work on his beta-blocker project, which he accepted.

Within a few months of his arrival, he had read in the most recent issues of the *Journal of Pharmacology and Experimental Therapeutics* about the American firm Eli Lilly’s new compound, dichloroisoproterenol (DCI), which had the kind of properties he was looking for. Eli Lilly, who had developed DCI as a bronchodilator, but found it to have unwanted cardiac side-effects, failed to see the compound’s potential in cardiovascular medicine. However, ICI, under Black’s direction, did, and promptly developed a derivative of DCI, pronethalol, the first clinically-useful beta-blocker. It underwent small-scale trials in 1961, and was launched in 1963 under the name Alderlin (after Alderley Park). In 1962, Black’s team was joined by R.G. Shanks, a physiologist who had spent a year with Ahlquist at the University of Georgia. Synthesis of analogues continued, in order to provide Alderlin with wide patent coverage and protect its market against possible competitors. In the process, a compound with greater activity than Alderlin had been discovered. It was propranolol, which was to replace Alderlin after it had been found to cause tumours in mice. Clinical trials began in 1964, and propranolol was launched in 1965 under the name *Inderal*. By then, interest in the beta-blockers among

⁹¹ Reader, *Imperial Chemical Industries*, p. 448. He quotes from M.T. Sampson and R.M. Winter, ‘The Butterwick Research Laboratories’, 12 Apr. 1949, ICIBR (Research Director).

⁹² Reader, *Imperial Chemical Industries*, p. 92. ICI had a long-standing agreement with DuPont. In *ibid.*, pp. 38-9.

⁹³ For more on this, see Quirke, ‘From evidence to market’.

⁹⁴ Quirke, ‘Black’, *Encyclopedia of Life Sciences*; *idem*, ‘Putting theory into practice: James Black, receptor theory, and the development of the beta-blockers at ICI, ca 1958-1978’, *Med. His.*, 2006, 50, pp. 69-92.

British clinicians, with whom ICI had developed good contacts, had risen sharply. The number of clinical centres investigating ICI's drugs therefore went up from 4 in 1961 to 45 in 1965. By then also, the new advisory board, the CSD (later re-named CSM) had been created, and ICI's Medical Department, who had begun targeting the American market, decided to prepare a submission. This exercise would later stand them in good stead when preparing FDA submissions. In 1969, ICI obtained clearance from the CSM to market *Inderal* in hypertension, followed in 1973 by the FDA's approval of the drug as an anti-hypertensive agent. These events helped to establish the use of beta-blockers in the treatment of hypertension, and paved the way for atenolol (*Tenormin*), ICI's best-selling hearty-drug, which within ten years of launch in 1976 generated sales worldwide of about £500 million, nearly 40% of which were made in the US⁹⁵.

d. A twist in the tale? H₂-antagonists at SK&F

Meanwhile, Black had become interested in another application of Ahlquist's dual-receptor theory: the development of H₂-antagonists for the treatment of peptic ulcers. However, he was unable to interest ICI in this new project, and therefore in 1964 moved to SK&F's new research centre at Welwyn Garden City where his former colleague at ICI, the pharmacologist Edward Paget, had just become research director. Paget and Black were soon followed by another former ICI colleague, also with experience of working on the beta-blockers, the biochemist Bill Duncan. In this way, elements of the pharmacological and biochemical expertise which ICI had built up around the beta-blockers were transferred to SK&F, where ten years later Black developed the first H₂-antagonist, cimetidine (*Tagamet*)⁹⁶. However, as SK&F's historian, Louis Finucane, wrote in 1989, 'there is a twist in Tagamet's tale': Tagamet inspired David Jack (a former SK&F scientist, who left to become research director at Allen & Hanbury's – later acquired by Glaxo) to develop Zantac, which soon overtook SK&F's drug, became one of Glaxo's top-selling medicines and made their fortune in the 1980s⁹⁷.

The post-war period saw an explosion of new drugs, of which *Betnovate*, *Inderal* and *Tagamet* are just a few. The histories of these other drugs also deserve to be written.⁹⁸ They were developed in a shared historical and national context, but by different companies, such as Glaxo and ICI, representing different research cultures, and different axes for pharmaceutical R&D (fermentation technology vs synthetic organic chemistry). As well as drugs, therefore, firms provide historians with useful units of analysis for studying the impact of the American model in pharmaceuticals. They suggest that industrial processes and business strategy should also be included in discussions of this impact.

Second Conclusion

Ever since the 19th century, the British pharmaceutical industry has operated within a trans-national space. Until WW2, this space was largely dominated by German chemical-pharmaceutical manufacturers. However, by the end of the conflict, the geographical centre of

⁹⁵ K. Holland, 'IC Pharmaceuticals', *Pharmaceutical Journal*, 12. Sept. 1987, pp. 286-288.

⁹⁶ M. Ennis and W. Lorenz, 'Histamine receptor antagonists', in Parnham and Bruinvels (eds), *Discoveries in Pharmacology* vol. 2, Amsterdam, Elsevier, 1984, pp. 623-645.

⁹⁷ L. Finucane, *SK&F: from Camberwell to Welwyn Garden City, 1956-1989*, Welwyn, SK&F, 1989, p. 53.

⁹⁸ For another example, see V. Quirke, 'From local knowledge to global market? Burroughs Wellcome's Zovirax as an example of transatlantic collaboration in pharmaceuticals', ABH conference, Cambridge, 30-31 May 2003 (unpublished conference paper).

innovation and competitive advantage had shifted from Germany to America. Hence, thereafter, the ‘model’ to follow was American. This paper has shown that in pharmaceuticals, this model consisted in scientific knowledge, technical know-how, and research tools and practices. However, it has also highlighted the importance of industrial processes and business strategy.

Like others who have studied this question, I have suggested that ‘following the American model’ was a two-way process, which in different instances and at different times benefited America as well as its European partners⁹⁹. Although they owed much to American knowledge, know-how, tools and practices, British partners brought local instrumental traditions, local knowledge and practices, and local networks of expertise to the Anglo-American collaborations that underpinned many of the drugs mentioned above and the growth of the companies involved in their development. These local traditions helped to transform the American model in pharmaceuticals into what was the ‘British pharmaceutical industry’, before national boundaries and interests became blurred in the 1980s and 1990s.

Efforts at building a science-base and developing academic-industrial networks in the interwar years, coupled with mobilization in wartime, came to fruition in the post-World War II period. Together, they made it possible for British scientists and companies to integrate and build upon, relatively rapidly, what they had learnt from their contacts with their American colleagues and brought back to the UK from their transatlantic visits. The history of Glaxo’s corticosteroids and ICI’s beta-blockers suggests that the 1960s were a turning point, after which the British pharmaceutical industry started to compete more successfully with its American counterpart. However, before long, with the biotechnological revolution of the 1970s, the US would become clear leaders again, and offer others once more an example to follow. Interestingly, the 1980 report on biotechnology, which helped to launch Britain’s biotech industry, had been prepared by Alfred Spinks, the chemist whose 1953 survey of new fields for pharmacological research had helped to launch ICI’s programme of research into chronic diseases. But that is another story!

General Conclusion

Our study has shown that in France, there was a great variety of American influences, and the different ways in which American firms entered the French market help to explain this diversity. In Britain, where links with American firms were far older, the drugs themselves, with penicillin playing a pivotal role, became an important vehicle for the exchange of knowledge and practices, and the history of British and American industry is to a large extent a shared history. Our two developments therefore highlight the contrast between the French and British experiences in pharmaceuticals. On the whole, our evidence supports the view that there was an American model, and that the success of American firms, which made the transfer of this model possible via their subsidiaries, was mainly related to the organisation of their R&D. However, until the 1980s, such an organisation failed to take root in France, where collaboration between academic scientists and industry remained a relatively rare phenomenon, except in the case of large firms such as Rhône-Poulenc and Roussel-UCLAF. This observation leads us to the question of why British companies succeeded in adopting American R&D practices and organisation when French firms did not. An obvious reason is the common language and cultural inheritance of Britain and the US. Another important reason seems to be the greater openness and liberal nature of the British economic and

⁹⁹ See V. Quirke, ‘French biomedicine in the mirror of America’, and Essay Review of *Inventer la biomédecine*, in *SHPBBS* (2004), 35, 765-76.

political system, in contrast with France, where State intervention had a deleterious impact on the indigenous pharmaceutical industry. However, the advent of the new biotechnology and the increased globalisation of the industry in the 1980's, after which Britain and France began to show greater resemblance with each other, challenge this distinction.

Our study also suggests a number of caveats concerning the notions of the American model and Americanization of the pharmaceutical industry, which are worth noting here:

- 'Following the American model' was a two-way process, which in different instances and at different times benefited America as well as its European partners¹⁰⁰. The British case has shown that, although they owed much to American knowledge, know-how, tools and practices, partners could also bring local instrumental traditions, local knowledge and practices, and local networks of expertise to transatlantic partnerships. These local traditions helped to transform the American model in pharmaceuticals in the different national contexts in which it was applied, before national boundaries and interests became blurred in the 1980s and 1990s.
- Both the French and English cases suggest that different countries could borrow different elements from the same model. The French and British pharmaceutical industries were not influenced in the same way by the 'American Model': these different national contexts set limits on the American model and its influence, and show the strength of national models (which put together can create other regional models, like the European one).
- We may also wish to be careful when we consider 'models' or influences: on the whole, the pharmaceutical industry has developed in the same way in different countries as the business relies on scientific discovery and innovations that do not remain national ones for long times. In this respect, the 1980s can be seen as a turning point in the diffusion of scientific knowledge and technical know-how, in the standardisation of business strategies as well as in the globalisation of the industry.

¹⁰⁰ See V. Quirke, 'French biomedicine in the mirror of America', and Essay Review of *Inventer la biomédecine*, in *SHPBBS*, 2004, 35, pp. 765-776.