PERSPECTIVES ON TWENTIETH-CENTURY PHARMACEUTICALS

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Perspectives on Twentieth-Century Pharmaceuticals: an introduction

One of the most striking features of the twentieth century has been the rapid growth of the pharmaceutical industry and the large increases in the use and consumption of its products, particularly in North America, Europe and Japan. By the end of the century, worldwide sales by drug companies were valued at approximately $350bn, and were expected to rise to a figure of $500bn within five years.[1] This trend began in the first half of the century, but accelerated most sharply after the Second World War, when the creation of national systems of healthcare created mass markets for drugs. The industry then assumed a major economic, social and political significance, and became one of the most highly regulated sectors of the economy.

These changes attracted the attention of industry analysts and academics, and have been reflected in the research and writing of the last few decades. As well as an expanding literature on the subjects of regulation and industrial policy,[2] there have been studies of the structure

1 IMS health 2000.

2 L. Hancher, *Regulating for Competition: government, law and the pharmaceutical industry in the United Kingdom and France* (Oxford: Clarendon Press, 1990); L.G. Thomas, 'Implicit industrial policy: the triumph of Britain and the failure of France in global pharmaceuticals', *Industrial and Corporate Change*, 3 (1994): 451–489; J. Abraham and H. Lawton Smith (eds), *Regulation of the Pharmaceutical Industry* (Basingstoke: Palgrave Macmillan, 2003); A.A. Daemmrich, *Pharmacopolitics: drug regulation in the United States and Germany* (Chapel Hill/London: the University of North Carolina Press, 2004); M.N.G. Duke, *The Law and Ethics of the Pharmaceutical Industry* (Amsterdam and Oxford: Elsevier, 2005); J. Slinn, 'Price Controls or Control through Prices? Regulating the cost and consumption of prescription pharmaceuticals in the UK 1948–1967', *Business History*, 47 (2005): 352–366.

of the industry and its importance to the economy;[3] histories of individual companies and of national drug industries;[4] accounts of drug dis-

3 C.J. Thomas, 'The pharmaceutical industry', in D. Burn (ed.), *The Structure of British Industry* (Cambridge: Cambridge University Press, 1958) vol. 2, pp. 331–375; K. Blunden, *Etude sur l'évolution de la concentration dans l'industrie pharmaceutique en France* (Luxembourg: Office des Publications Officielles des Communautés Européennes, 1975); W.D. Reekie, *The Economics of the Pharmaceutical Industry* (London: Macmillan, 1975); idem, 'Pharmaceuticals', in P.S. Johnson (ed.), *The Structure of British Industry* (London: Granada, 1980), pp. 106–130; G. Owen, *From Empire to Europe* (London: HarperCollins, 1999), chapter 13, pp. 360–387.

4 For example: H.G. Lazell, *From Pills to Penicillin: the Beechams story* (London: Heinemann, 1975); J. Slinn, *May & Baker, 1834–1984* (Cambridge: Hobsons Ltd, 1984); G. Tweedale, *At the Sign of the Plough: 275 years of Allen & Hanburys' and the British pharmaceutical industry, 1715–1990* (London: Murray, 1990); A. Blondeau, *Histoire des laboratoires pharmaceutiques en France: et de leurs médicaments* (Paris: Le Cherche Midi, 1992) vols. 1 and 2; R.P.T. Davenport-Hines and J. Slinn, *Glaxo: a history to 1962* (Cambridge: Cambridge University Press, 1992); E. Jones, *The Business of Medicine* (London, Profile Books: 2001) R.P. Amdam and K. Sogner, *Wealth of Contrasts: Nyegaard & Co. – a Norwegian pharmaceutical company, 1874–1985* (Oslo: Ad Notam Gyldendal, 1994); L. Galambos with J. Eliot Sewell, *Networks of Innovations: vaccine development at Merck, Sharpe & Dohme, and Mulford, 1895–1995* (Cambridge, Mass.: Cambridge University Press, 1995); M. Ruffat, *175 Ans d'industrie pharmaceutique française: histoire de Synhélabo* (Paris: La Découverte, 1996); C. Kobrak, *National Cultures and International Competition: the experience of Schering AG, 1851–1950* (Cambridge, Cambridge University Press, 2002); W. Abelshauser, W. von Hippel, J. Allen and R.G. Stokes, *German Industry and Global Enterprise BASF: the history of a company* (Cambridge: Cambridge University Press, 2004); R. Church and E.M. Tansey, *Knowledge, Trust, Profit: a history of Burroughs Wellcome & Co. and the transformation of the British Pharmaceutical Industry* (Lancaster: Crucible Publishing, 2007). There has also been a growing number of histories of national pharmaceutical industries: P. Starr, *The Social Transformation of American Medicine: the rise of a sovereign profession and the making of a vast industry* (New York: Basic Books, 1982); J. Liebenau, *Medical Science and Medical Industry: the formation of the American pharmaceutical industry* (Baltimore: Johns Hopkins University Press, 1987); idem, 'The twentieth-century British pharmaceutical industry in international context', 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. 123–133; M. Robson, 'The French pharmaceutical industry, 1919–39', in ibid., pp. 107–122; C. Davis, *The Pharmaceutical Industry and the Market in the USSR and its Successor States: from reform to fragmentation to transition* (Richmond: PjP Books, 1993); D.A. Rajimwale, *The Indian Pharmaceutical Industry* (New Delhi: the People's Pub. House, 1996); S. Chauveau, *L'Invention pharmaceutique: la pharmacie entre l'Etat et la société* (Paris: Institut d'Edition Sanofi-Synthélabo, 1999); T.A.B. Corley, 'The British pharmaceutical industry since 1851', in L. Richmond, J. Stevenson and A. Turton (eds), *The*

covery,[5] academic-industrial relations,[6] and pharmaceutical R&D and innovation.[7] Recent work has also explored the growth of the biotechnology

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Pharmaceutical Industry: a guide to historical records (Aldershot: Ashgate, 2003), pp. 14–32; A.D. Chandler, *Shaping the Industrial Century: the remarkable story of the evolution of the modern chemical and pharmaceutical industries* (Cambridge, MA: MIT Press, 2005).

5 M. Weatherall, *In Search of a Cure: a history of pharmaceutical discovery* (Oxford: Oxford University Press, 1990); R. Vos, *Drugs Looking for Diseases: innovative drug research and the development of the beta-blockers and the calcium antagonists* (Dordrecht: Kluwer Academic, 1991); W. Sneader, *Drug Discovery: the invention of modern medicine* (Chichester: John Wiley & Sons, 1996); V. Quirke, 'Making British cortisone: Glaxo and the development of corticosteroid drugs in Britain in the 1950s and 1960s', *Studies in History and Philosophy of Biology and Biomedical Sciences*, 36 (2005): 645–674; idem, 'From alkaloids to gene therapy: a brief history of drug discovery in the twentieth century', in S. Anderson (ed.), *A Brief History of Pharmacy* (London: the Pharmaceutical Society 2005), pp. 177–201; idem, 'Putting theory into practice: James Black, receptor theory, and the development of the beta-blockers at ICI, 1958–1978', *Medical History*, 50 (2006): 69–92; idem, 'The material culture of British pharmaceutical laboratories in the Golden Age of Drug Discovery, ca. 1935–1975', *International Journal for the History of Engineering and Technology*, 79 (2009): 280–299.

6 J.P. Swann, *Academic Scientists and the Pharmaceutical Industry: cooperative research in twentieth-century America* (Baltimore: Johns Hopkins University Press, 1988); J. Liebenau, 'The MRC and the pharmaceutical industry: the model of insulin', in J. Austoker and L. Bryder (eds), *Historical Perspectives on the Role of the MRC* (Oxford: Oxford University Press, 1989), pp. 163–180; J. Liebenau and M. Robson, 'L'Institut Pasteur et l'industrie pharmaceutique', in M. Morange (ed.), *L'Institut Pasteur: contributions à son histoire* (Paris: Presses Universitaires de France, 1991), pp. 52–61; T. Jones, 'The value of academia/industry links in R&D', in S.R. Walker (ed.), *Creating the Right Environment for Drug Discovery* (Lancaster: Quay Publishing, 1991), pp. 77–84; N. Oudshorn, 'United we stand: the pharmaceutical industry, laboratory and clinic in the development of sex hormones into scientific drugs, 1920–1940', *Science, Technology and Human Values*, 18 (1993): 5–24; J. Goodman, 'Can it ever be pure science? Pharmaceuticals, the pharmaceutical industry and biomedical research in the twentieth-century', in J.-P. Gaudillière and I. Löwy (eds), *The Invisible Industrialist: manufactures and the production of scientific knowledge* (Basingstoke: Macmillan, 1998), pp. 143–165, and other contributions in this volume; N. Rasmussen, 'The moral economy of the drug company-medical scientist collaboration in interwar America', *Social Studies of Science*, 34 (2004): 161–185; V. Quirke, *Collaboration in the Pharmaceutical Industry: changing relationships in Britain and France* (Abingdon/New York: Routledge, 2008); D. Tobbell, 'Allied against reform: pharmaceutical industry-academic physician relations in the United States, 1945–1970', *Bulletin of the History of Medicine*, 82 (2008): 878–912.

7 D. Schwartzman, *Innovation in the Pharmaceutical Industry* (Baltimore: Johns Hopkins University Press, 1976); J. Howells and I. Neary, *Intervention and Technological Innovation*

industry,[8] the globalization of the economy, and the challenges these have posed to the traditional pharmaceutical sector.[9]

At the same time, the growing dependence of the medical profession and the public on pharmaceutical products, and the resulting profits made by drug companies, which have been linked to the increasing role of marketing in firms' activities, have led to mounting criticism and controversies.[10] Many of these have been concerned with the advertising, prescription and

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(Basingstoke: Macmillan, 1988); A. Gambardella, *Science and Innovation: the US Pharmaceutical industry during the 1980s* (Cambridge: Cambridge University Press, 1995); J. Slinn, 'Research and development in the UK pharmaceutical industry from the nineteenth century to the 1960s', in R. Porter and M. Teich (eds), *Drugs and Narcotics in History* (Cambridge: Cambridge University Press, 1996), pp. 168–186, and other chapters in this volume; J. Slinn, 'Innovation at Glaxo and May & Baker, 1945–165', *History and Technology*, 13 (1996): 133–147; R. Landau, B. Achilladelis and A. Scriabine (eds), *Pharmaceutical Innovation* (Philadelphia: Chemical Heritage Press: 1999); V. Quirke, 'Standardizing pharmaceutical R&D in the second half of the twentieth century: ICI's Nolvadex Development Programme in historical and comparative perspective', in C. Bonah et al. (eds), *Harmonizing Drugs: standards in 20th Century Pharmaceutical History,* (Paris: Glyphe, 2009), pp. 123–50.

8 M. McKelvey, *Evolutionary Innovations: the business of biotechnology* (Oxford: Oxford University Press, 1996); R. Henderson, L. Orsenigi and G. Pisano, 'The pharmaceutical industry and the revolution in molecular biology: interactions among scientific, institutional and organizational change', in D.C. Mowery and R.R. Nelson (eds), *Sources of Industrial Leadership* (Cambridge: Cambridge University Press, 1999). See also various contributions to M. Mazzucato and G. Dosi (eds), *Knowledge Accumulation and Industry Evolution: the case of pharma biotech* (Cambridge: Cambridge University Press, 2006).

9 R. Ballance, J. Pogany and H. Forstner, *The World's Pharmaceutical Industries* (Aldershot: Edward Elgar, 1992); J.M. Taggart, *The World Pharmaceutical Industry* (London: Routledge, 1993); P. Ramirez, 'The globalisation of research in the pharmaceutical industry: a case of uneven development', *Technology Analysis and Strategic Development*, 18 (2006): 143–167.

10 For example: J.-P. Dupuy and S. Karsenty, *L'Invasion Pharmaceutique* (Paris: Le Seuil, 1974); H. Redwood, *The Price of Health: the link between research in the pharmaceutical industry and health care systems in the developed world* (London: Adam Smith Institute, 1989); J. Abraham, *Science, Politics, and the Pharmaceutical Industry: controversy and bias in drug regulation* (New York: St Martin's Press, 1995); P. Pignarre, *Le Grand secret de l'industrie pharmaceutique* (Paris: La Découverte, 2003); M. Urfalino, *Le Grand méchant loup pharmaceutique: angoisse ou vigilance?* (Paris; Textuel, 2004).

uses of psychiatric drugs.[11] Given the difficulties in accessing corporate archives and information about the industry and its activities, impartial judgement of these issues has become problematic, leading to both factual and fictional publications directed against 'Big Pharma'. This has been particularly so in the USA, the only significant market to permit direct-to-consumer advertising, where public interest and concern has helped to make popular books on the subject into bestsellers.[12]

However, in parallel, considerable scholarly research has been carried out on the development of drugs as medicines in national and international markets, on their regulation in different contexts and at different times, on their role in medical practice, as well as on their representation and use in society more widely.[13] Unsurprisingly for an industry that discovers, develops, manufactures and sells products that have come to occupy such an important place in human and animal health and well-being, the

11 A. Ehrenberg, *La Fatigue d'être Soi: dépression et société* (Paris: Odile Jacob, 1998); D. Healy, *Let them Eat Prozac: the unhealthy relationship between the pharmaceutical industry and depression* (New York and London: New York University Press, 2004); A. Tone, *The Age of Anxiety: a history of America's turbulent affair with tranquillizers* (New York: Basic Books, 2008).

12 For an early example see T. Mahy, *The Merchants of Life: an account of the American pharmaceutical industry* (New York: Harper, 1959). For more recent examples: J. Crawford, *Kill or Cure? The role of the pharmaceutical industry in society* (London: Arc Print, 1988); L. Marsa, *Prescription for Profit: how the pharmaceutical industry bankrolled the unlikely marriage between science and business* (New York: Scribner, 1997); J. Law, *Big Pharma: exposing the healthcare agenda* (Robinson Publishing, 2006); idem, *Big Pharma: how the world's biggest drug companies control illness* (London: Constable, 2006); J. Moran and C. Guerra, *Pill Pushers: a Big Pharma battle for market share* (Booksurge plc, 2007). See also the recent spate of novels portraying the dark world of the corporate drug industry, including E. Jacobs, *The Pawn of Pharma* (Outskirts Press, 2005); J. Prieve, *Big Pharma: a novel* (PublishAmerica, 2006).

13 J. Goodman and V. Walsh, *The Story of Taxol: nature and politics in the pursuit of an anti-cancer drug* (Cambridge/New York: Cambridge University Press, 2001); T. Pieters, *Interferon: the science and selling of a miracle drug* (London: Routledge, 2005); R. Bud, *Penicillin: triumph and tragedy* (Oxford/New York: Oxford University Press, 2007); J.A. Greene, *Prescribing by Numbers: drugs and the definition of disease* (Baltimore, Johns Hopkins University Press, 2007); N. Rasmussen, *On Speed: the many lives of amphetamine* (New York/London: New York University Press, 2008).

drugs themselves have therefore attracted researchers from many different disciplines – from health economics, to medical anthropology, and social studies of science, as well as history.[14] All of this has helped to provide a rich and somewhat better rounded picture.

This volume brings together a collection of papers exploring and reflecting upon some of the significant strands in the current studies of pharmaceuticals in the twentieth century. It is organized in five parts, each containing three chapters by three different contributors, structured thematically and thereby representing the variety and complexity of perspectives on the pharmaceutical industry and its products. To introduce this collection, we begin by giving a brief chronological overview of the development of twentieth century pharmaceuticals, placing each chapter in its historical context. We then set out the themes of each of the five parts of the book, with short summaries of each chapter.

Historical Overview of Twentieth-Century Pharmaceuticals and the Pharmaceutical Industry

In the twentieth century, drugs came to occupy a central place in medical practice, especially in wealthier countries, where they helped to transform the health and life expectancies of individuals. Most of these drugs were developed in corporate laboratories, using scientific knowledge and technical know-how from a number of disciplines, with chemistry playing

14 For example, M. Gilswijt-Hofstra, G.M. Van Heteren and E.M. Tansey (eds), *Biographies of Remedies: drugs, medicines and contraceptives in Dutch and Anglo-American healing cultures* (Amsterdam/New York: Rodopi, 2002); C. Bonah and A. Rasmussen (eds), *Histoire et médicament aux 19e et 20e siècles* (Paris: Editions Glyphe, 2005); J. Collin, M. Otero and L. Monnais (eds), *Le Médicament au coeur de la socialité contemporaine: regards croisés sur un objet multiple* (Sainte-Foy, Quebec: Presses Universitaires du Québec, 2006); A. Tone and E. Siegel Watkins (eds), *Medicating Modern America: prescription drugs in history* (New York: New York University Press, 2007).

a major role for much of the century. The costs of research and development were high, increasing exponentially over time, and the pharmaceutical industry, which came to be dominated by large corporations, sought economies of scale and international markets for its products. Towards the end of the century a number of new trends were emerging, which shaped the markets for medicines and challenged the industry, and are discussed in several papers in this selection. They include: the growth of biotechnology; the changing nature and extent of regulatory systems; the respective roles of research and marketing in drug development; the validity of clinical trials and their reporting; the appearance of patient-activist movements, and the part played by doctor–patient relationships in drug consumption.

Public and private institutions, and the scientific traditions and corporate cultures associated with them, underpin the evolution of drugs and the pharmaceutical industry in the twentieth century, providing it with significant sources of continuity. However, geopolitical events, in particular the two World Wars;[15] regulatory changes, especially in the USA; and last but not least key developments and discoveries, such as the discovery of diphtheria antiserum, antibiotics and, more recently, the development of biotechnology, have created major discontinuities. These help to structure our chronological overview, which is therefore in four parts: 1880s-World War One; the inter-war years; post-World War Two; since the 1970s.

The end of the nineteenth century until World War One

Medicinal plants have always played an important part in the treatment of disease. However, it was only at the beginning of the nineteenth century that the first therapeutically active principle was extracted from a plant. This was the narcotic principle of opium, which was later named 'morphine'.

15 See J. Goodman, 'Pharmaceutical industry', in R. Cooter and J.V. Pickstone (eds), *Medicine in the Twentieth Century* (Amsterdam: Harwood Academic, 2000), pp. 141–154; more particularly on the impact of war on the pharmaceutical industry 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), 64–83.

The isolation and identification of other plant alkaloids, many of them from tropical areas of the expanding European empires, soon followed. These included emetine from ipecacuanha root for dysentery, and quinine from cinchona bark for malaria. The pharmaceutical businesses that manufactured these drugs often also developed the chemical expertise required for selecting and extracting suitable material. Demand for quinine was especially high, but supplies difficult to obtain. Attempts were therefore made to synthesize it from material that was more readily available, such as coal tar. It was one such attempt, by a young British chemist named William Perkin, which led to the first artificial dye, mauveine, and hence to the synthetic dyestuffs industry.[16] Because of favourable economic and political conditions, the industry grew most rapidly in Germany,[17] and it was in the laboratories of the German chemical companies that many of the first synthetic drugs, including aspirin, were developed.[18]

Towards the end of the nineteenth century, the use of machinery for the manufacture of tablets became common in the industry, enabling the mass-production and facilitating the consumption of drugs such as aspirin. At around the same time, a new approach to the treatment and prevention of disease appeared. Also requiring an 'industrial' style of production, it was based on the use of vaccines and sera, and the first major application of this approach was in the mid-1890s, against diphtheria. In Chapter 1, Simon and Hüntelmann contrast the development of diphtheria antitoxin in France and Germany, highlighting the different organization of research and legal contexts for the production and sale of such medicines in the two countries. Also in the same period, the medical marketplace was re-structured, leading to a sharp distinction being made between 'ethical'

16 A. Travis, *The Rainbow Makers: the origins of the synthetic dyestuffs industry in Western Europe* (Bethlehem: Lehigh University Press, 1993).

17 J.J. Beer, 'The emergence of the German Dye Industry', *Illinois Studies in the Social Sciences*, 44 (1959): Ch. 7; G. Meyer-Thurow, 'The industrialization of invention: a case study from the German chemical industry', *ISIS*, 73 (1982): 363–381; E. Homburg, 'The emergence of research laboratories in the dyestuffs industry', *British Journal for the History of Science*, 25 (1992): 91–111.

18 For aspirin see D. Jeffreys, *Aspirin: the remarkable story of a wonder drug* (London:Bloomsbury, 2004).

and 'proprietary' medicines and their manufacturers.[19] This had important implications for the long-term evolution of the drug industry, helping to establish the connection between business and science that has lasted to this day. This is discussed by Huisman in his study of Dutch pharmaceutical firms in Chapter 2, and by Sismondo in his analysis of the relationship between marketing and research in Chapter 8.

Following the discovery of diphtheria antitoxin many drug companies, in France, Germany, and elsewhere, became involved in the manufacture of biological remedies. However, chemotherapy, rather than biotherapy, became the dominant approach to therapy in the twentieth century, and was used to target a wide range of illnesses, from infectious diseases, to chronic disorders, and cancer. The inventor of chemotherapy – the use of chemical substances for the prevention and treatment of disease – was the German bacteriologist and immunologist Paul Ehrlich, working at the Institute for Infectious Diseases in Berlin. As well as elaborating a theory of drug action (receptor theory, described by Prüll in Chapter 5), in 1910 Ehrlich developed the first chemotherapeutic remedy, Salvarsan, a 'magic bullet' targeting the micro-organisms responsible for syphilis without harming their human hosts.[20] However, in the period that followed the discovery of Salvarsan, other than some successes against tropical diseases caused by protozoa, chemotherapy appeared to have failed its early promise. It was not until the discovery of the sulphonamides in the 1930s that chemotherapy can be said to have come into its own.

19 See J. Liebenau, 'Ethical business: the formation of the pharmaceutical industry in Britain, Germany and the US before 1914', in R.P.T. Davenport-Hines and G. Jones (eds), *The End of Insularity: essays in comparative business history* (London: Cass, 1988), pp. 117–129.

20 J. Parascandola 'The Theoretical Basis of Paul Ehrlich's Chemotherapy', *Journal of the History of Medicine and Allied Sciences*, 36 (1981): 19–43; J. Liebenau, 'Paul Ehrlich as commercial scientist and research administrator', *Medical History*, 34 (1990): 65–78.

The inter-war period

Soon after the discovery of Salvarsan, the First World War interrupted European and American supplies of German imported drugs, leading to the abrogation of German patent rights, and stimulating the production of synthetic drugs in countries at war with Germany. Nevertheless, the innovatory advantage in drug discovery remained principally in Germany, where the close relationship that existed between academia and industry was an important contributory factor. This is well illustrated by the life and career of the malariologist Werner Schulemann, which spanned both the academic and industrial worlds, as well as the time periods before and after the Second World War, and is explored by Hulverscheidt in Chapter 4. Schulemann was involved in the development of the first synthetic antimalarial, Plasmochin (also known by its generic name, pamaquin), at the Bayer laboratories (IG Farben) in Wuppertal-Elberfeld, before moving in 1938 to the Institute for Pharmacology at Bonn University, where he continued to attract industrial funding for his research. It was in these same Bayer laboratories that, in the mid-1930s, Gerhard Domagk discovered the antibacterial properties of the red dye Prontosil Rubrum, the first broad-spectrum antibacterial sulphonamide drug, and a milestone in the history of drug discovery and the pharmaceutical industry.[21]

Between the wars there were also important achievements in 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, where a physiological approach to drug development provided an alternative to the chemical approach favoured by most German laboratories.[22] Insulin was discovered by researchers at the University of Toronto, in Canada, and knowledge about the hormone and know-how

21 See D. Bovet, *Une Chimie qui guérit: histoire de la découverte des sulfamides* (Paris: Payot, 1988); J.E. Lesch, 'Chemistry and biomedicine in an industrial setting: the invention of the sulfa-drugs', in S. Mauskopf (ed.), *Chemical Sciences in the Modern World* (Philadelphia: University of Philadelphia Press, 1993), pp. 158–215; idem, *The First Miracle Drugs* (Oxford: Oxford University Press, 2007).

22 See Weatherall, *In Search of a Cure*.

concerning the production method were transferred rapidly across the world through the firms chosen to be licensees.[23] As well as the sex and other hormones, in this period several vitamins were identified,[24] and various processes for their manufacture were devised and patented, thereby creating a precedent for the patenting of life-science innovations in the second half of the twentieth century.[25] Thus, in Chapter 13, Bächi recounts how, in an attempt to synthesize vitamin C, the Swiss drug company Hoffman-la Roche (now Roche), working in collaboration with the chemist Tadeus Reichstein, developed a new process that included a biotechnological step. A forerunner of the hybrid processes that became the hallmark of the biotechnological era, it gave much higher yields than either the extraction of the natural vitamin or a purely chemical synthesis, but was controversial at the time.[26]

These early successes and achievements of the biomedical sciences and the pharmaceutical industry led to increasing demand for drugs to treat an ever-growing variety of complaints. Despite the economic recession, in the 1930s there was a rising tide of concern about body weight and image, in particular in the USA. This coincided with the emergence – in an as yet largely unregulated market – of an effective but dangerous medicine, dinitrophenol. As Swann demonstrates in Chapter 10, dinitrophenol enabled weight loss, but its serious side effects created a potentially major

23 M. Bliss, *The Discovery of Insulin* (London: Faber and Faber, 1988). See also C. Sinding, 'Making the unit of insulin: standards, clinical work, and industry, 1920–1925', *Bulletin of the History of Medicine*, 76 (2002): 231–270.

24 See various contributions in S. de Chadarevian and H. Kamminga (eds), *Molecularizing Biology and Medicine: new practices and alliances, 1910s-1970s* (Amsterdam: Harwood Academic, 1998).

25 This would lead to debate and controversy in the post-war period, especially in connection with the patenting of penicillin. See R. Bud, 'Upheaval in the moral economy of science? Patenting, teamwork, and the World War II experience of penicillin', *History and Technology*, 24 (2008): 173–190, and other articles in this special issue. See also G. Dutfield, *Intellectual Property Rights and the Life Science Industries: past, present and future* (World Scientific Publishing, 2nd Edition, 2009).

26 A. Kornberg, 'The Two Cultures: chemistry and biology', *Biochemistry*, 26 (1987): 6888–6891; idem, *The Golden Helix: inside the biotech ventures* (Sausalito, California: University Science Books, 1995).

public health disaster. Although use of the drug persists to this day, the combined efforts of the American Medical Association, the Food and Drug Administration (FDA), and the journalists who publicized its dangers, contributed to a 'tectonic shift' in American drug safety legislation. This occurred in 1938, bringing the distribution of dinitrophenol under control of the FDA, and conferring upon the agency considerable influence. Because of the growing size and importance of the American market for medicines after the Second World War, this influence would be exerted not only in, but also outside the USA.[27]

Post-World War Two

The Second World War resulted in major discontinuities for science and industry, while at the same time providing a significant stimulus for growth during, as well as immediately after the hostilities, especially in the burgeoning field of antibiotics, and in the USA. The development of penicillin during the war is widely recognized as a watershed.[28] Celebrated as the first veritable cure for infectious diseases, demand for the drug was high in the post-war years, as Santesmases shows in the case of Spain, discussed in Chapter 3. Although penicillin itself could not be patented, the deep fermentation process developed in the USA during the war was protected by patents.[29] Therefore European companies wishing to use it – among them Spanish firms – had to pay royalties in return for the technical know-how and a licence to manufacture the antibiotic.

Hard on the heels of penicillin came streptomycin, giving new hope to tuberculosis sufferers, and that was followed by more new antibiotics developed and launched in the 1950s. The war and penicillin had brought

27 For more on the FDA see D. Carpenter, *Reputation and Power: organizational image and pharmaceutical regulation at the FDA* (Princeton: Princeton University Press, forthcoming in 2010).

28 See J. Le Fanu, *The Rise and Fall of Modern Medicine* (London: Abacus, 2000).

29 For patents and their uses see various papers in J-P Gaudillière (ed.), *History and Technology*, Special Issue 24.2. (June 2008).

new companies into the industry, perhaps most notably the American firm Pfizer, which built on its contribution to the deep fermentation process for penicillin and developed the novel antibiotic tetracycline. Like other American companies in the 1950s, Pfizer established manufacturing facilities abroad, at first mainly for the purpose of making and selling antibiotics, and this expansion helped to fuel the growth of the American pharmaceutical industry in the post-war period. Later, in order to capitalize on high-quality education systems, particularly in Europe, American firms also established R&D facilities abroad, for instance Pfizer's research centre at Sandwich in Britain.[30]

War created a special need for anaesthetics, antibiotics, anti-malarials, and other medicinal products. In Britain, and elsewhere, as well as mobilizing traditional drug companies for the war effort, it had helped to establish new firms in the pharmaceutical sector, such as the then largest British chemical group, Imperial Chemical Industries (ICI).[31] In the 1950s, ICI built a new R&D facility at Alderley Edge, South of Manchester, where in the 1960s and 1970s drugs such as tamoxifen and the beta-blockers were developed, the former for the treatment of breast cancer, the latter for the treatment of cardiovascular diseases. Underpinning the discovery of the beta-blockers and the other receptor antagonists or stimulants that followed them, was the concept of receptors. However, for the concept to become well established, particularly among the somewhat sceptical community of pharmacologists, it needed first to be successfully applied. In Chapter 5 Prüll examines the uneasy diffusion of Raymond Ahlquist's theory of alpha- and beta-receptors. Although it would play a key role in the development of remedies such as the anti-ulcer drugs Tagamet and

30 On the role of Anglo-American relations in the post-war growth of the UK pharmaceutical industry, see for example V. Quirke, 'Anglo-American relations and the co-production of American "hegemony" in pharmaceuticals', in H. Bonin and F. de Goey (eds), *American Firms in Europe* (Geneva: Droz, 2009), pp. 363–384. See also Tony Corley's contribution to this volume in Chapter 7. On the globalisation of the pharmaceutical industry more generally, see Ramirez, 'The globalisation of research in the pharmaceutical industry'.

31 W.J. Reader, *Imperial Chemical Industries: a history* (London: Oxford University Press, 1975), vol II; C. Kennedy, *ICI: the company that changed our lives* (London: Hutchinson, 1986).

Zantac, it was accepted mainly after it had been used to develop the first beta-blockers, which were found to be effective in the treatment of hypertension and other cardiovascular diseases.[32]

There were many other new drugs developed and launched in the 1950s and 1960s. These included not only antibiotics and receptor antagonists or stimulants, but also anaesthetics, psychiatric drugs, cortisone and other corticosteroid hormones, non-steroidal anti-inflammatory drugs (NSAIDs), and the contraceptive pill.[33] All contributed to meeting and reinforcing the expectations of the new national health services', of medicine's, and of industry's abilities to discover cures for dreaded diseases, as well as treat minor complaints and effect lifestyle changes. The latter is evidenced in Chapter 9, in Niquette and Buxton's discussion of popular pharmaceuticals, such as antacids, laxatives, and later the 'famous blue pill' (Viagra), as well as in Chapter 12 in Prescott's account of the morning-after pill and other contraceptive measures.

To what extent these expectations were lowered in the early 1960s in the wake of the thalidomide disaster, which contributed to public anxieties about the end of the 'Age of Optimism' and to undermining faith in science and medicine, has not yet been fully explored.[34] But thalidomide did usher in a period of tightening drug safety regulation across the world.[35] At the

32 For more on this, see Quirke, 'Putting theory into practice'.

33 J. Swazey, *Chlorpromazine in Psychiatry: a study of therapeutic innovation* (Cambridge, Mass: MIT Press, 1974); C. Djerassi, 'Steroid research at Syntex: "The pill" and cortisone', *Steroids*, 57 (1992): 631–641; E.M. Tansey, '"They used to call it psychiatry": aspects of the development and impact of psychopharmacology', in M. Gijswijt-Hofstra and R. Porter (eds), *Cultures of Psychiatry and Mental Health Care in Postwar Britain and the Netherland* (Amsterdam: Rodopi, 1998), pp. 79–101; L. Marks, *Sexual Chemistry: a history of the contraceptive pill* (New Haven/London: Yale University Press, 2001); D. Healy, *The Creation of Psychopharmacology* (Cambridge, Mass.: Harvard University Press, 2004).

34 Le Fanu, *The Rise of Modern Medicine*, Part 2; Bud, *Penicillin.*

35 On the impact of thalidomide on British drug safety legislation, see for example E.M. Tansey and L.A. Reynolds (eds), 'The Committee on Safety of Drugs', *Wellcome Witnesses to Twentieth Century Medicine* (London: Wellcome Trust, 2007), vol. 1, pp. 103–132. More specifically on ICI, see J. Abraham and C. Davis, 'Testing times: the emergence of the practolol disaster and its challenge to British drug regulation in the modern period',

same time, growing concerns about the costs, prices and profits made by the industry were voiced, especially in the USA and in the UK. This led to the Kefauver Committee hearings in the former, and the investigations of the Sainsbury Committee in the latter.[36]

Since the 1970s

In the last quarter of the century, it was becoming clear that the number of new drugs launched in the market was decreasing, the rate of innovation was beginning to slow down, and the period of the so-called 'Therapeutic Revolution' (roughly from the 1930s to the 1970s) was drawing to a close. Stricter regulatory procedures and more extensive clinical trials meant that it took much longer for new medicines to be approved, thereby eating into the patent period and reducing profitability. For some firms, increased financial risks, combined with greater scepticism, and sometimes outright opposition from the medical profession and the public towards the products' intended purpose or use, had the effect of discouraging innovative R&D. Prescott argues in Chapter 12 that this was the case with contraceptive drugs and devices in the USA, while Tobbell shows in Chapter 11 that, combined with other factors such as continuing disparities in regulatory practices and the uneven development of disease-based organizations, this could result in very different national therapeutic regimes, as illustrated by the treatment of thalassemia patients in Britain and the USA.

Partly because of increased social, political and economic pressures, in the 1980s and 1990s the industry underwent significant consolidation and restructuring, and despite persisting national differences, much of it was transnational in character. Thus, in Chapter 7, Corley examines the

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Social History of Medicine, 19 (2006): 127–147; also V. Quirke, 'The impact of thalidomide on the British pharmaceutical industry: the case of Imperial Chemical Industries', in J.-P. Gaudillière and V. Hess (eds) 'Ways of Regulating: therapeutic agents between plants, shops and consulting rooms', (Max Planck Institut für Wissenschaftgeschichte, Preprint 363, Berlin, 2009), pp. 125–141.

36 For more on the latter see Slinn, 'Price controls or control through prices?'.

effects of one of the larger consolidations: the merger of the British-based Beecham Group with the American firm SmithKline, Beckman, which in 1985 produced SmithKline Beecham (SB). By seeking assistance from across the Atlantic in order to overcome deficiencies at home, the merger helped to transform the British company's previously inward-looking ethos into one which made effective use of innovation and marketing to overtake its rivals. This raised Beecham to somewhere near the top of the world's pharmaceutical league, and prepared it for its next big merger with the British industry leader, Glaxo Wellcome, to form GlaxoSmithKline (GSK), in 2000.

Increasingly, large corporations such as SB, and later GSK, were urging their R&D on to search for 'blockbuster' drugs, i.e. those which would find large markets across the world. In the 1970s and 1980s, they included anti-ulcer drugs, such as Glaxo's Zantac, and in the 1990s, Pfizer's Viagra. Viagra was one of the first of what are now called 'lifestyle' drugs, and as such has attracted considerable interest. However, as Niquette and Buxton argue in Chapter 9, the success of Viagra cannot simply be attributed to the industry's promotional campaigns. Indeed, they show that the popularity of drugs like *Viagra* is rooted in the everyday relationships people have with medication, as well as with others through medication. These have shaped the social representation of pharmaceuticals at the same time as reflecting the relational requirements of life in modern, post-industrial societies.

As to prescription medicines, they have reached the consumer through a series of transactions that has become increasingly complex, partly because of the requirement for informed consent that was introduced in many countries after the Second World War.[37] In Chapter 6 Richard and Lussier focus on one specific transaction, that between doctors and patients. The exchange that takes place during medical consultations remains the primary way of informing the patient, to enable him to give his informed consent and take his medication correctly. Knowing that patient participation is associated with better health outcomes, Richard and Lussier examine the

37 On the history of informed consent, see P.J. Weindling, 'The origins of informed consent: the International Commission for the Investigation of Medical War Crimes and the Nuremberg Code', *Bulletin of the History of Medicine*, 75 (2001): 37–71; idem, *Nazi Medicine and the Nuremberg Trials: from medical war crimes to informed consent* (Basingstoke: Palgrave-Macmillan, 2004).

content, attitudes and emotions in audio-recorded primary care encounters, and devise a model to help not only improve the quality of doctor–patient exchanges, but also increase patient participation.

The complexity of transactions through which prescription medicines reach the consumer has, since the beginning of the twentieth century, required a considerable marketing effort directed at the prescribers. However, it would seem that it is only in recent decades that the marketing function in pharmaceutical corporations has become more directly involved in creating a market and, potentially, in playing a decision-making role in R&D. This trend is dissected by Sismondo in Chapter 8. Drawing on books by marketers and cases that have recently come to light, he argues that, in the rational world centred on health which the industry and its various customers have helped to create, there is no intrinsic divide between research and marketing.

It is unclear as yet how far the growth of the marketing function in traditional pharmaceutical firms has been related to the shift that has been taking place in innovation from Big Pharma to biotechnology start-ups. Indeed, since the 1990s, many of the most innovative drugs have not come from the large R&D laboratories of the pharmaceutical industry, but from the much smaller biotech companies. These developed in clusters, first in the USA, then mainly in Europe, and most recently in some countries of the Far East. In Chapter 15, Saives, Mehran, Desmarteau and Garnier discuss the Quebec biotechnology cluster, the largest in Canada, where it has benefited from a number of positive factors, such as geographical proximity to the American market, government policies stimulating innovation in the biopharmaceutical sector, and the presence of Montreal as a world-class research centre in life and health sciences, and analyse the evolution of 100 biotech firms located within it.

What is now regarded as first-generation biotechnology, i.e. brewing and baking, as well as the cross-breeding of plants and animals, has a long history.[38] The second generation evolved in the first half of the twentieth

38 For histories of biotechnology, see R. Bud, 'Biotechnology in the Twentieth Century', *Social Studies of Science*, 21 (1991): 415–457; idem, *The Uses of Life: a history of biotechnology* (Cambridge: Cambridge University Press, 1993); Kornberg, *The Golden Helix*.

century with the development of biological products such as vaccines, vitamins, hormones, and antibiotics. This is studied by Bächi in Chapter 13 through the example of the Swiss company, Hoffman-la Roche, which in the 1930s succeeded in adding a biotechnological step to enhance its yields of synthetic vitamin C. The third generation of biotechnology has developed since the 1970s, based on two fundamental discoveries from the new discipline of molecular biology: Cohen and Boyer's discovery of recombinant DNA in 1973, and the development of hybridoma and monoclonal antibodies by Milstein and Kohler in 1975.[39] However, while the traditional pharmaceutical sector watched these developments with interest, only a few firms entered the biotechnology business themselves.[40] Perhaps in part because of its early experience with vitamin C, one of the first of these firms was Hoffman-la Roche, whose establishment of a molecular biology laboratory in Nutley, New Jersey, contributed to its transition from a chemistry-based company to a life-science enterprise, and is examined by Bürgi and Strasser in Chapter 14.

Many of the developments discussed in this brief chronological overview occurred in the West, which for much of the twentieth century remained the hub of drug discovery and the heart of the world's pharmaceutical sector. At the beginning of the twenty-first century, inevitably the direction the industry and drug development will take is unclear. The

39 L.E. Kay, *The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the rise of the new biology* (New York: Oxford University Press, 1993); P.G. Abir-Am, 'The Molecular Transformation of Twentieth-Century Biology', in J. Krige and D. Pestre (eds), *Science in the Twentieth Century* (Amsterdam: Harwood, 1997), pp. 495–524; R. Bud, 'Molecular biology and the long-term history of biotechnology', in Arnold Thackray (ed.), *Private Science: biotechnology and the rise of the molecular sciences* (Philadelphia: University of Pennsylvania Press, 1998), pp. 3–19; M. Morange, *A History of Molecular Biology* (Cambridge, MA: Harvard University Press, 1998); S. de Chadarevian and Bruno Strasser (eds), 'Molecular Biology in Postwar Europe', Special issue of *Studies in the History and Philosophy of Biological and Biomedical Sciences*, 33C (2002); P.G. Abir-Am, 'Molecular Biology and its Recent Historiography: a transnational quest for the "Big Picture"', *History of Science*, 44 (2006): 95–118.

40 See L. Galambos and J. Sturchio, 'Pharmaceutical firms and the transition to biotechnology: a study in strategic innovation', *Business History Review*, 72 (1998): 250–278.

effects of the creation and dissemination of new scientific knowledge, as well as the expanding generics industry and rising affluence in the world's two fastest growing economies, India and China, have yet to be seen. Nevertheless, that biotechnology has transformed therapeutic innovation at the end of the twentieth century cannot be doubted. It has encouraged Big Pharma into strategic alliances with start-ups and academia, leading to the growth of what is known as the 'Bioscience industry'. Although the extent to which it has fulfilled its early promise in the field of human healthcare has been questioned, there have been some significant achievements; these include human insulin, human growth hormone, and recombinant human interferon. And at the beginning of the twenty-first century, bioscience continues to promise us new and better therapies, such as therapeutic cloning and gene therapy, and medicines targeting the individual patient rather than the disease.

Themes and Structure in Twentieth-Century Pharmaceuticals

Part 1: Different countries, times and perspectives

The launch of new drugs has varied from one country to another, as also has the use and mode of delivery of a drug. National differences of this type, identifiable in the late nineteenth and early twentieth century, have been persistent in ways not always anticipated, and indeed continue today. In Part 1 these continuities and variations are explored in several European countries over different time periods. In Chapter 1, Simon and Hüntelmann contrast the French and German experience of diphtheria serum. In the late nineteenth century, serum therapy was developed as a new method for the treatment and prevention of disease. The first successful application of this principle was against diphtheria, starting in the mid 1890s. By the beginning of the twentieth century, the serum was being mass-produced around Europe and in the USA. This chapter explores the different models

for serum production in France and in Germany, models that were related not only to the contrasting institutional organization of research and development, but also to very different legal contexts for the production and sale of such medicines in the two countries.

In France, the research into potential treatments (principally vaccination) for diphtheria was conducted at the newly founded Pasteur Institute by Roux and Yersin, who in 1888 famously isolated the toxin produced by the diphtheria bacteria. In Berlin, Behring pursued his own line of research that resulted in the discovery that the serum of the blood from animals immunized against diphtheria could confer immunity on ones that had never been exposed to the disease. This discovery formed the basis for the development of a treatment for humans using the serum of blood extracted from animals inoculated with the diphtheria toxin. In France, production was for the most part controlled by the Pasteur Institute, which, with the help of generous contributions from the French public, set up its own dedicated stable/factory for the production of the diphtheria 'antitoxin'. In Germany, the responsibility for mass production was assumed by private pharmaceutical laboratories such as Hoechst, which worked in partnership with government-employed research scientists. The chapter explores the effects that these different configurations of public/private collaboration had on the forms of production, distribution and consumption of the diphtheria antitoxin. The production of the serum therapy was also the subject of different legislation in the two countries. In Germany, the state required that all sera be checked by a national laboratory before they could be sold. Thus the government founded the Institut für Serumprüfung und Serumforschung, which in 1899 became the Königlichen Institut für experimentelle Therapie, under the direction of the illustrious Paul Ehrlich, and which was responsible for providing official approval of the medicine. In France, on the other hand, the issue of quality control was left to the producers of the therapies although they had to apply for approval from a special commission. The chapter concludes with a consideration of the effect that these different legal situations had on the relationship between the manufacturers of these therapies, the government, and the public at the beginning of the twentieth century.

Chapter 2 takes us to the Netherlands, where Huisman explores the development and transformation of the national pharmaceutical industry in the first half of the twentieth century. It is often assumed that the pharmaceutical industry 'took off' only after the Second World War. While the industry certainly enjoyed enormous growth in that period (due to the introduction of new medicines), its expansion was facilitated by structures that had come into existence much earlier, between 1880 and 1940. By using the perspective of the medical market, Huisman argues, it is possible to do justice to the many dimensions of this early transformation of pharmaceutical production. Thus, the market perspective may enrich the historiography on pharmaceuticals, because it does not restrict itself to only either 'scientific' or 'successful' companies. It could even be argued that a similar one-dimensional view on the healthcare system (focusing on theory or success) has impoverished the historiography, because it excludes discussions about the dynamics of its evolution.

Traditionally, pharmacists had been the most important professional producers of medicines. In the course of the nineteenth century, the pharmaceutical industry developed, representing an enormous threat to them. The market was flooded by standardized, cheap, industrial products that were produced on a large scale, meeting a growing demand. In its advertising campaigns the new industry addressed itself directly to the public, disregarding the profession. Pharmacists felt threatened in their economic position as well as in their professional self-esteem. United with physicians and lawyers in the Association against Quackery they tried to do battle with the new industry by drawing a sharp line between ethical and unethical medicines and producers, 'scientificity' being the criterion of demarcation. 'Scientific' stood for ethical, humanitarian, and public; its opposite for unethical, commercial and secret. The construction of this distinction, the chapter suggests, was an important part of the professional strategy of pharmacists and – later on – of the pharmaceutical industry in an attempt to gain legitimacy and obtain a greater share of the market.

Initially the industry defended itself by calling upon the liberal principle of the freedom of trade. Gradually, however, some pharmaceutical entrepreneurs realized that a 'scientific' profile need not stand in the way of commercial success. Furthermore, it could facilitate the cooperation

of physicians and pharmacists. As it turned out, pharmacists were more than willing to associate themselves with the 'ethical' part of the industry, appreciating its complementary – and growing – pharmacological expertise. New alliances were shaped, and a new pharmacological landscape developed. However, the success of 'ethical' pharmaceutical companies did not mean that their 'unethical' counterparts disappeared. It would seem that the success of a remedy and its producer is less dependent on its pharmacodynamic 'effects' or its legal status than on its cultural image. Whereas some consumers were attracted to 'neat' products with appealing brand names and fancy packaging, others preferred 'ethical', scientific remedies. While sections of the new industry were transformed from threat into allies, acquiring an unchallenged position, quackery and self-medication never vanished. The added value of the medical market perspective, Huisman concludes, is that it does not selectively focus on medical progress or growing professionalization. Using the market model makes it possible to show how some groups decide to join forces, and exclude others. In the process, the traditional image of a linear development of medicine is replaced by a new, multidimensional, vision of the structuring of the health market.

In Chapter 3 we move to a different time period – the 1950s – and to a different country, Spain, where Santesmases discusses the arrival, the manufacture, and the impact of antibiotics. The discovery of penicillin enjoyed world-wide publicity which led, initially, to demand far outstripping the availability of the drug in Spain, as elsewhere. The first antibiotics made in Spain did not reach the Spanish market until 1955, although Spanish physicians had started to report on the uses of penicillin and streptomycin, and academic researchers had received information about the drug from the Professor of Biology at the University of Madrid, Florencio Bustinza, well before that. The drugs themselves were available before that date, but mainly through the black market, as only small amounts of imported drugs were released by the Spanish government. Strong demand already existed, and fictional accounts (famous novels on the post-war period) placed these very limited supplies – or, when available, the huge prices – of early antibiotics in Spain after the Second World War at the core of public imagination and culture. It was in this context that Franco's government launched a public competition to approve two factories for penicillin production in

Spain. The manufacture of antibiotics in Spain was dependent on foreign patents, and agreements were signed between Spanish pharmaceutical firms and American firms to give them access to American technical processes and expertise. This created a strong dependency on foreign innovations concerning the manufacture of penicillin and on any further innovation concerning production of other antibiotics developed outside Spain.

Thus, the production of antibiotics in Spain lagged behind not only the demand for them generated by physicians and scientists, but also their production abroad. While Fleming and Waksman were becoming public heroes, the production of antibiotics in Spain began and provided the firms involved with long-lasting success in the pharmaceutical field.

Part 2: Different actors: scientists, doctors and patients

The processes by which drugs are discovered, brought to the market, prescribed for patients and eventually consumed by them, involve many actors. The three chapters in this section focus on the scientists working on the research that leads (sometimes) to drug development and, at the other end of the complex series of transactions involved, on doctor–patient relationships.

In Chapter 4, Hulverscheidt explores the life and work of the German malariologist, Werner Schulemann (1888–1975), and offers a perspective on how pharmaceutical research was funded in Germany between 1920 and 1970. Schulemann was, by any standard, an extremely successful researcher over a long period of time. He worked at the Bayer Laboratories (IG Farben) in Wuppertal-Elberfeld until 1936, became a Professor and the Director of the institute for pharmacology at Bonn university in 1938, and was involved in the development of the first synthetic anti-malarial, Plasmochin. For his research he received the Mary-Kingsley-Medal from the Liverpool School of Tropical Medicine. He had a great talent for obtaining money for his work; being able to attract funding from the pharmaceutical industry, as well as from the University, from the state and from the DFG (a foundation which funded scientific research). His applications show how, at different times, different rationales were needed. He was not involved in

anti-malarials in the 1950s, since due to the effectiveness of DDT at that time there was little demand for such drugs. But in the early 1960s, when the first cases of resistance against DDT were documented, Schulemann returned to his earlier work using his old recipes to develop anti-malarials. He was then more than 70 years old, and was still being funded by the DFG. The example of Schulemann shows how a scientist can spend his entire lifetime on a single line of research. Funding depends not only on the quality of ideas and outcomes, but also on the contacts and abilities of the individual researcher. The chapter discusses whether, and in what ways, funding regulations influence the direction and progress of research.

In Chapter 5, Prüll presents a very different perspective on the development of influential scientific ideas, more particularly, the receptor concept. In 1948, Raymond P. Ahlquist (1914–1983), then head of the Pharmacological Department of the Medical College of Georgia/Augusta, published a theory on drug binding which has had a decisive influence on the development of scientific pharmacology and drug discovery in the second half of the century. 'Receptors' are proteins on the surface of the cell, which enable the latter to attach to foreign or bodily substances. Ahlquist differentiated between two receptors of the adrenergic system, which is responsible for heart rate and blood pressure. With this research he paved the way for pharmacological research on an ever-growing number of receptors, and for the development of drugs to treat an increasing variety of diseases, from heart, lung, to gastric disorders and cancer. However, the contribution of Ahlquist's theory remained unacknowledged until the 1960s, and he waited in vain for the award of the Nobel Prize.

Based on the thesis that scientific knowledge is socially constructed, Prüll's chapter analyses the fate of Ahlquist's concept. Using printed and unprinted sources as well as interviews with Ahlquist's former friends and colleagues in Augusta, Prüll delivers the first detailed examination of the subject. Several factors caused problems for Ahlquist: misunderstandings about his theory, the ambiguities of the theory itself, Ahlquist's personality and his own attitude towards his 'dual adrenoceptor concept'. Prüll concentrates on difficulties related to the orientation of Ahlquist's research work within pharmacology, and to the fact that Eli Lilly and Co. sponsored much basic research on the adrenergic system in the 1940s and 1950s. Ahlquist

and other research groups depended on that sponsorship and were part of a competitive network that tried to unravel the fundamental mechanisms of the adrenergic system.

Although Ahlquist had the practical application of his concept in mind, initially the concept remained in the realm of theoretical pharmacological research. Prüll argues that Ahlquist's research environment was largely responsible for the late recognition of his work. Because of the narrow scope of his research, a vision of how to apply his approach to medicine only began with the work of Sir James Black on the beta blockers in 1957.

With Chapter 6, the focus shifts to examine the roles of very different actors in the transaction outlined above. Richard and Lussier put a microscopic lens on the nature and intensity of discussions between patients and physicians on the subject of medications, and present us with their results. The purpose of their study is to examine the content, attitudes and emotions in audio-recorded primary care encounters. They measure the extent of the dialogue which takes place between patient and physician, and relate it to the content in terms of whether the encounter concerns new prescriptions, repeat prescriptions, or ongoing medication. Their analysis, set out in this chapter, identifies three clusters of themes from their observations. This enables them to suggest a model to be used in further explorations of the patient-physician relationship, in order to improve communication between doctor and patient and in the hope of improving health outcomes for the patient.

Part 3: Developing, selling and representing drugs

As the industry grew rapidly in the second half of the twentieth century, the ways in which drugs were marketed and sold were transformed. In Chapter 7, Corley explores the changes as they were reflected in one corporation, the Beecham Group, in the last two decades of the century. By 1985 the British-owned Beecham Group, lately evolved from a pills and proprietaries manufacturer into the innovator of semi-synthetic penicillins, had clearly lost its sense of direction. It lacked an overall corporate strategy, so that its

pharmaceutical and consumer product sub-groups scarcely spoke to each other, and it had diversified into such non-core products as cosmetics and DIY requisites. It had few contacts with the institutions – which held 80 per cent of its shares – or the City analysts. In principle it avoided using management consultants. Instead, it relied on a strong 'Beecham' ethos, nourished by the pre-1968 innovation- and marketing-driven Leslie Lazell. Following some dismal half-year results, the Beecham chairman was sacked in a boardroom coup.

The new chairman, an American, deliberately and relentlessly set out to eradicate that inward-looking ethos. He replaced most of the incumbent directors with executives brought in from more progressive companies, such as Cadburys and BOC, to head the key finance, corporate communications and personnel functions and to act as enforcers of his new strategy, based on Harvard Business School principles. He hired a firm of American consultants, which recommended a 'merger of equals' with a company of similar size, to raise Beecham from 23rd in the world pharmaceutical league to somewhere near the top.

The American corporation SmithKline Beckman was chosen as partner on account of its advanced R&D facilities in Philadelphia and its well-trained sales force. After the merger in 1989, the new SmithKline Beecham (SB) pursued a thorough programme of integrating every level of management across the Atlantic, advised by McKinsey & Co. as consultants. Within a few years SB markedly improved its performance. It licensed some of its drugs and information to other companies, enhanced its corporate image and shifted emphasis from mere curative medicines to the broader health care concept.

SB was soon faced with external pressures such as an accelerating merger movement throughout the industry, the introduction of managed health care and stricter drug regulations, but also the onset of the biotechnology revolution, manifested in the very costly gene sequencing process. In 1998 it therefore sought to merge, again on an equal footing, with the British industry leader, Glaxo Wellcome, a bid which succeeded in 2000. As its head office was in London but the operational headquarters were in Philadelphia, it had become truly outward-looking.

The pharmaceutical industry's marketing function has become in recent years a focus for research and debate. This is reflected in Chapter 8, in Sismondo's examination of the links between R&D and marketing. He starts with the view of the management guru, Peter Drucker, that the overarching goal of a business is 'to create a satisfied customer'. From this formula, it not difficult to see that both the customer and their satisfaction need to be created. In any case, marketing is the prime force behind the creation at least of customers, and perhaps also their satisfaction.

Yet pharmaceutical companies have to portray themselves as research and development organizations involved only by necessity in marketing and sales. Most of their various customers – for prescription drugs these are traditionally physicians, though increasingly drug companies pay attention also to patients, potential patients, pharmacists, health maintenance organizations, hospitals, government agencies, nursing homes, and clinics – want their drugs to be part of a rational world centred on health. Any visible aspect of drug research, development, or promotion that is not part of a logic of health is immediately suspect. Thus ghost-writing of research is hidden, recognition of the pleasure drugs can produce is carefully managed, and marketing often takes an educational form.

Sismondo goes on to describe in very general terms the integration of clinical research and marketing, drawing on books by marketers and recent cases that have come to the public eye. The tools that have been used to accomplish this integration over the past half-century are various, but they all stem from a realization that in a rational world centred on health there need be no intrinsic divide between research and marketing. Most obviously, marketing drugs to physicians, who are professionals acting within their own spheres, depends crucially on research. Physicians respond, and need to see themselves as responding, to facts, figures, and studies. The well-chosen images and vehicles for marketing campaigns must be subordinated to research. Yet at the same time research is a means of increasing sales.

Pharmaceutical companies are, of course, among the most successful of businesses. They have become so by resolving, or at least appearing to resolve, the conflicts between the logic of business and the logic of health. Big Pharma and its representatives easily and often argue that their actions are innocuous: just as research and marketing (and education) are

necessarily connected, if the drugs are seen as efficacious then improved sales means improved patient outcomes. Thus, the chapter concludes, we need to look carefully both at conflicts and their management to understand why we should care about pharmaceutical marketing.

Aspects of marketing are also explored in Chapter 9, in which Niquette and Buxton discuss the role that the development of advertising has played in the growth of the pharmaceutical industry in the twentieth century. They begin by noting that advertising itself has been greatly influenced by the promotion of patent medicines, body-care products and pharmaceutical drugs. Drawing on the example of medications that have become part of global popular culture over the last century – such as pain killers, cough syrups, anti-itching ointments, analgesic balms – they offer us a theoretical model through which the representations of pharmaceuticals can be studied in relation to social practices. They begin by describing the modern characteristics that make pharmaceuticals an object radically different from others; secondly, they show how these characteristics have contributed to the transformation of everyday life; and thirdly, how the changes in the role that pharmaceuticals play in society are reflected in the social representations that circulate in the public sphere.

It is commonly thought that the day-to-day uses of pharmaceuticals are closely related to the discourses that are promulgated by the drug industry and disseminated by the medical establishment. However, few studies have addressed the fact that social practices surrounding the use of medications are the product not only of professional and promotional discourses, but also of the very process by which popular images of pharmaceuticals are constituted. In other words, the social representations of pharmaceuticals are rooted in the everyday relationship people have with medication, and with others *through* medication. For instance, the popularity of the Sildenafil Citrate (Viagra), as compared to other pharmaceuticals used for the treatment of symptoms associated with the andropause, cannot simply be attributed to the success of promotional campaigns. The representations used to promote the famous blue pill are inspired by the various ways in which this medication was already involved in society, beyond the quest for more satisfying intercourse. These representations include themes such as social status in a highly competitive environment, male timidity in the

doctor's surgery, the desire to experience a constant good mood, the sense of obligation to make one's partner happy, and the ideals of autonomy and spontaneity in sex. All these themes are typical of the relational requirements of modern life in post-industrial societies. Therefore, studying the changes in the relational themes through which the uses of medication have been depicted from the beginning of the twentieth century up to the present allows us to understand the process by which pharmaceuticals, beyond their therapeutic functions, have become reflexive tools by which we relate to one another.

Part 4: Drug regulation and its limits in the USA

Over the course of the twentieth century, the pharmaceutical industry became one of the most highly regulated industries, a contentious issue in Europe and North America especially. The three chapters in this part of the book each illustrate certain aspects of regulation. In Chapter 10 Swann examines the case of the weight-reducing drug, dinitrophenol, in the USA in the 1930s. At that time, he argues, the conjunction of a rising tide of concern for body image and weight consciousness with the emergence of an effective but hazardous medicine to lose weight laid the foundation of a potentially major public health disaster. The public was being told increasingly in advertising, motion pictures, and other venues of the desirability of a lithe, trim, and athletic figure in both women and men. It was in this social context that dinitrophenol, a toxic component used in the munitions industry of the First World War, came to be understood by pharmacologists as capable of raising the metabolic rate to such an extent as to readily dissipate body fat. Its narrow margin of safety, however, prompted many to advise against its indiscriminate use by the public. Two leading researchers who studied dinitrophenol argued that it should be restricted only to those professionals who could monitor a patient's basal metabolic rate. But at this time in the USA there was no mechanism to compel such a limit on distribution of a medicine of this kind. Consequently, dozens of dinitrophenol-containing products were launched on the market for self-medication, often without the active ingredient even being labelled on

the package. The American Medical Association and journalists tried to publicize the dangers associated with the use dinitrophenol, which could result in serious injuries such as cataracts, as well as fatalities. The Food and Drug Administration (FDA) joined in this effort, using creative means to alert the public. But there was little else the FDA could do under the then current food and drug law. A tectonic shift in the drug law in 1938 had a swift impact on the distribution of dinitrophenol in the USA, although use of the drug has persisted, even up to the present.

In Chapter 11, Tobbell explores the concept of nationally distinctive pharmaceutical 'cultures', created in part by different national systems of regulation. Arthur Daemmrich has argued that different systems of drug regulation, clinical trials, and post-marketing surveillance of pharmaceutical drugs developed in Germany and the USA because of differences in the 'therapeutic cultures' of the two countries; that is, the relationships among the state, the pharmaceutical industry, the medical profession, and disease-based organizations.[41] Tobbell describes the development of iron chelation therapy for the treatment of thalassemia in Britain and the USA in the second half of the twentieth century as a case study for examining the importance of 'therapeutic cultures' in pharmaceutical development. While British physicians readily incorporated iron chelators such as Desferal (marketed by Ciba-Geigy, now Novartis) into medical practice in the 1960s, physicians in the USA were more reluctant to do so. Despite the publication of several reports from Britain in the early 1970s demonstrating the long-term efficacy of Desferal, American physicians continued to question the clinical value of iron chelation therapy, and Desferal remained on the margins of American therapeutic practice. The reasons for this difference in medical practice include, in particular, the different ways in which thalassemia patients and their families, physicians and researchers, pharmaceutical companies, and the state influenced the development of iron chelation therapy in Britain and the USA in the second half of the twentieth century.

41 Daemmrich, *Pharmacopolitics.*

National regulatory differences in the approach to contraception are the subject of Chapter 12, focussing on the USA. In the late 1980s, Prescott writes, officials from various American and international family planning organizations reported an alarming trend: due to an increasingly hostile legal and regulatory environment precipitated by lawsuits against the contraceptive pill, the Dalkon shield, and other potentially harmful reproductive technologies, women in the USA had fewer birth control options than they did in the previous decade. Indeed, family planners in the 1980s observed that women in Third World countries, which continued to use birth control methods that had been banned or were no longer in use in the USA, actually had more options than did their American counterparts. Drawing on records from the U.S. Food and Drug Administration, Planned Parenthood Federation of America, and the National Institutes of Health, as well as interviews with contraceptive researchers, this chapter explores how the political, legal, and regulatory environment of the 1970s and 1980s hindered contraceptive research and development in the USA. It also shows how recent work by non-government organizations has made new reproductive technologies available by going beyond the venture capital model used by most pharmaceutical companies in the USA.

Part 5: From Pharma to Biotech

The development of the biotechnology industry in the last three decades of the twentieth century has had a significant impact on the pharmaceutical industry and its products. Often seen as a 'new' industry in the last three decades of the century, evidence of an earlier biotechnological process is brought to the fore by Bächi in Chapter 13. In 1933, in a laboratory at the Swiss Federal Institute of Technology (Zurich), the synthesis of l-ascorbic acid (vitamin C) was achieved by Tadeus Reichstein and his collaborators. When the patents concerning the Reichstein procedure, owned by the small Swiss foodstuff company Haco, were offered to the Swiss pharmaceutical company F. Hoffmann-la Roche, Basle, in May 1933, Roche was not really interested in them. That is, not until Reichstein had improved the synthesis by introducing a *biotechnological* step which allowed the use of glucose as

a basic raw material. By using bacteria to transform sorbitol into sorbose (an idea already floated in the nineteenth century), he had found that the synthesis of vitamin C brought higher yields compared with the extraction of natural vitamin C. Therefore, Roche bought the patent, a decision that led to Roche's first (traditional) biotechnological production step.

However, there remained much corporate and academic research to be done in order to translate Reichstein's laboratory synthesis into industrial manufacture. Above all, the use of bacteria caused unforeseen troubles, and a number of resistances had to be overcome. First of all, Roche's industrial chemists, who simply had no experience of handling bacteria and would have preferred a purely chemical synthesis, disapproved of the bacteriological technique. Introducing biotechnology into the chemical company therefore required intense cooperation between academia and industry. Moreover, the scaling up of this microbiological step caused new kinds of problems different from the ones experienced in a scientific laboratory. Last but not least, during the economic crisis of the 1930s, Roche's general director hesitated in making such an investment into new, expensive equipment indispensable for this biotechnological step.

In the process of introducing biotechnology into the pharmaceutical industry, corporate traditions, path-dependency, and academic-industry relations have played an important role, but so have different social and national contexts. Thus, while the fear of bacteria helped to sell synthetic vitamin C to consumers, the same fear hampered the diffusion of the Reichstein procedure. In Nazi Germany, I.G. Farben favoured the purely chemical Helferich synthesis for the vitamin, refusing to have bacteria present in their production plants, because, as they told Roche's management, they feared 'poisoning and degeneration'.

In Chapter 14 Bürgi and Strasser examine Roche's approach to drug development over two critical decades, the 1960s and 1970s, more particularly its move into research in molecular biology. Early in 1967, Sidney Udenfriend and Herbert Weissbach, both collaborators of the National Institutes of Health, and John J. Burns, director of research at Hoffmann-la Roche in Nutley (New Jersey, USA), discussed the establishment of a research institute guided by academic scientists and financed entirely by the company. Two months later, the company's top management in Basel

approved the project and soon the construction of the Roche Institute of Molecular Biology (RIMB) in Nutley began. In 1972, the new building opened its doors to 128 scientists.

The establishment of the institute meant two major changes to the research policy of Hoffman-la Roche: first, the company embarked on its own 'academic' line of research; second, the emphasis on biological research challenged the position of organic chemistry as the main supplier of scientific knowledge inside the company. The decision to build a corporate research institute devoted to fundamental biological research was reached within a very short time. However, the conditions that made it possible for the company to change its research policy so quickly had been developing since the late 1950s. An analysis of the minutes of the Roche Research Management Group (RRMG), founded in 1956, and the reports composed for its annual meetings, make it possible to identify five determining factors: business success, new conceptions of research management, changes in regard to the legal environment, the growing influence of the company's American subsidiary, and difficulties in recruiting qualified staff.

Soon after it had been founded, the RIMB was recognized as an academic research institution. Its members were integrated into university networks and benefited from the exchange of ideas and materials. In 1970, the RRMG for the first time discussed the opportunities offered by 'genetic bioengineering'. In 1977, together with the industrial research department in Nutley and with Genentech, the RIMB embarked upon developing recombinant human interferon, which has been sold by Hoffmann-la Roche since 1986. In the 1990s, the company closed the RIMB and contracted a large number of start-up companies and university institutions. The RIMB was, in essence, just a phase within Hoffman-la Roche, but what it did was to contribute to the company's transition from a chemistry-based enterprise to a bioscience company.

Across the world the biotechnology industry is generally to be found in clusters, and Canada is no exception to this rule. In Chapter 15, Saives, Mehran, Desmarteau and Garnier present and discuss the results of their exploratory study of the Quebec biotechnology cluster, the largest in Canada. As the literature on innovation management has shown, with the advent of a new scientific paradigm, new players within the biopharmaceutical

industry have emerged, i.e. firms dedicated to biotechnology, often regarded as essential partners to traditional pharmaceutical companies. These enterprises focus on the management of innovation with the aim of entering a growth cycle based on R&D projects, on the choice of intellectual property to be protected and traded, and with the aim of managing financial options. The purpose of the study is to obtain a deeper understanding of the technological and organizational development cycle of these firms. It relies on a series of data extracted from semi-structured interviews taken from over 110 biotech firms located within the bio-industrial cluster of Quebec. Close to 30 qualitative variables describing the stages of classical evolution within growing firms are examined using a multi-factorial analysis. This exploratory field study leads to the observation of a number of discrepancies between the organization of knowledge creation and the type of financial governance within biotechnology firms. It concludes that three modes of development are present: that is pre-entrepreneurial, entrepreneurial and managerial, and that the passage from one to the other is marked, in the first instance, by a teleological gap, and in the second by a creativity gap.

Concluding remarks

The papers in this collection illustrate the wealth and variety of perspectives on pharmaceuticals and their development over the course of the twentieth century. They touch upon many of the issues that are matters of concern and debate today, including the pharmaceutical industry, biotechnology, innovation, academic-industrial relations, the interaction between doctors and patients in the Age of Information, as well as the drugs themselves and their uses and representation in society. We hope that this cross-national and multidisciplinary approach will stimulate further debate on the subject.