EUROPEAN SCIENCE FOUNDATION

SETTING SCIENCE AGENDAS FOR EUROPE

**RESEARCH NETWORKING PROGRAMME**

# STANDARD DRUGS AND DRUG STANDARDS – A COMPARATIVE HISTORICAL STUDY OF PHARMACEUTICALS IN THE 20TH CENTURY (DRUGS)

Standing Committee for the Humanities (SCH)

# Introduction

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History and sociology of modern medicine have traditionally focused on three elements: physicians, scientific discoveries and medical institutions such as hospitals or public health systems. From this perspective, drugs themselves play a relatively minor role except as molecules discovered by researchers, prescribed by a doctor, paid for by the state or, in more anthropologically oriented studies, consumed by the patient. Today, there is an increasing interest in pharmaceuticals – and the industry that produces them – as objects of research in their own right. This interest is shared not only by historians, sociologists and anthropologists studying medicine, but also by business historians working on innovation and legal scholars interested in property rights. From an interdisciplinary point of view, physicians and pharmacists reflecting on their knowledge and practices are equally receptive to the role played and the difficulties raised by drugs regarding their effectiveness and side-effects, their testing and quality control and their use, abuse and wider socio-economic implications. Nevertheless, although growing, the study of pharmaceuticals is a relatively new field, and one of the principal aims of this project is to identify and bring together researchers in a variety of disciplines whose work concerns this topic.

While the present networking programme holds considerable interest for sociologists, economists, and medical administrators, it remains primarily an historical project. Its main contributions will be to the history of the biomedical sciences. Following an investigation of the history of pharmaceutical research and development, many lessons can be drawn concerning the origins and nature of today's industry, but such conclusions are of additional value to the contributions we aim to make to the conceptualisation and practise of the history of 20th century medicine.

The running period of the ESF DRUGS Research Networking Programme is five years from March 2008 to February 2013.

# Aims and Objectives

The programme is directed at the analysis of standardisation in the development, regulation, marketing and use of modern pharmaceuticals. Rather than taking 20th century developments in the production and evaluation of drugs as 'natural' responses to a series of practical problems, the project examines the evolution of industrial standards and drug trials, along with prescription and clinical practices, from an historical perspective. The DRUGS programme mobilises interdisciplinary analytical tools and at the same time addresses overreaching characteristics of modern techno-scientific systems.

Standardisation – as a practice on the one side and as an analytical tool on the other – is the key concept around which the proposed networking programme is organised.

## 1. Standardisation as a practice refers to three different domains:

**Standardising the objects of production**
The history of pharmaceuticals as objects of production takes into account the standardised procedures that provide a very high degree of conformity between individual units manufactured in large quantities and standardised procedures that ensure precise control over purity, concentration and activity of the ingredients. Thus standardisation of the therapeutic agents themselves and the standardisation of the production process, from laboratory to marketing, and conditions of use need to be considered.

**Standardising state administration**
The monitoring and regulation of drugs are rooted in the development of state health administrations and took place in the course of 19th century. This development has increasingly enforced a form of quality control and, consequently, it has centralised evaluation procedures. In all European countries this entailed the establishment of new administrative bodies with new administrative responsibilities and accordingly bureaucratic standardisation.

**Standardising bedside practices**
The introduction of new medicaments is accompanied by changes in therapeutic practices at the bedside such as diagnostic strategies and categories, indications, dosages etc., established through the development of therapeutic protocols considered as 'gold-standards' for drug evaluation and leading to 'guidelines' or 'treatment of choice' consensus. Today, this process is further reflected in the concept of quality certification or in the idea of 'evidence-based medicine'.

## 2. Standardisation as an analytical tool

Standardisation, understood as the collection of techniques that result in selection and homogenisation, offers a common heuristic framework for the diverse approaches to the objects of study within the different domains of economy, health policy and medicine. A second meaning of standardisation refers to the essential feature of industrial production and product quality control as well as administrative and bureaucratic procedures, and can be identified in the moves to standardise clinical treatment by means of prescription guidelines and consensus conferences. It offers a view on the mechanism shaping local standards of experimental practices, national styles of regulation regimes, as well as localised markets, regional demands and habits of usage. More generally, standardisation has enabled communication, interaction, negotiation, and – not the least important – trading between partners separated by geography or even time. It is a key technology of trust and serves as one of the founding principles of modern society. Accordingly this Research Networking Programme approaches the history of 20th century pharmacy from the perspective of standardisation, taking into account the areas of research and development, production, local and international marketing, quality control, pre-clinical and clinical testing, and the practices of prescription and consumption of pharmaceutical products.

Heuristically, in order to delimit such a wide-ranging field of research, the programme adopts the pragmatic attitude of pursuing historical investigations starting from four major drugs families:

**Antibiotics (Team 1)**
Communicable diseases continue to play an immense role as leading causes of death in today's world, and antibiotics remain the therapeutic agents of choice against such diverse diseases as tuberculosis, stomach ulcers caused by *Helicobacter pylori* or Staphylococcal infections. A report by the business information service Report Buyer estimates that the global market for antibiotics will reach 25 billion US dollars by 2010. Six specific antibiotics have achieved annual sales valued at more than 1 billion US dollars each, and increased problems with drug-resistant disease agents drive the research and development of new antibiotics as existing medications lose their efficacy. This cycle of innovation, rapid clinical application and the development of resistance is a characteristic of antibiotics that has started to attract the attention of historians. Members of our team have investigated changes in the hospital environment as well as international comparative perspectives on resistance and policy responses.

# Aims and Objectives

With the emergence of MRSA and a wide spectrum of hospital-based, so called 'nosocomial' infections, the relationship between antibiotics, the hospital environment and medical intervention has become somewhat problematic, and further research on this is required.

Part of the market success of antibiotics lies in their importance for out-patient primary care. Recent research published in *The Lancet* suggests that in France, 32.5 defined daily doses of antibiotics per 1000 population were prescribed in out-patient general practice, as opposed to 10.0 such doses prescribed in the Netherlands between 1997 and 2002. This points in part to cultural differences within Europe regarding acceptable levels of drug prescription, but it also reflects the commodification of antibiotics and their framing as 'magic bullets' within localised contexts. Antibiotics certainly led the way when it came to popular as well as clinical reputation and can in many ways be seen as the proverbial magic bullet. This has strong implications for the history of disease management and general practice and will require careful further analysis.

The history of antibiotics and the development of randomised clinical control trials are strongly intertwined. The first such trial, to assess the effectiveness of Streptomycin against tuberculosis, achieved two separate aims: it irreversibly established a new standard regime for assessing drug safety and efficacy whilst at the same time proving that one of the major killers of the 20th century could be successfully controlled with antibiotics. The repercussions have been immense, and the history of clinical trial regimes as well as the new-found emphasis on evidence-based medicine are yet to be fully investigated by historians.

**Cardiacs (Team 2)**

Cardiovascular disease today is a leading cause of death, and cardiovascular drugs are big business. A report by the business information service Espicom estimates the global market for medicines used in the management of blood pressure and cholesterol levels at around 38.5 and 34 billion US dollars respectively. A significant proportion of this money is spent on a small number of blockbuster drugs. In most cases these medicines are taken by patients whose high blood pressure or cholesterol levels do not cause them any direct suffering. They are not 'magic bullets', but are taken over long periods of time to reduce the long-term risk of strokes or heart attacks. These drugs have become part of normal everyday life for many in the developed world. But medicines that treat risk must not in themselves pose a risk. Since pharmaceuticals never come without side-effects, and because of their high sales, which make even the rarest side-effects visible, the development of these drugs can be risky for pharmaceutical companies, as the example of Bayer's anti-cholesterol drug Lipobay has shown. Members of Team 2 have worked on the history of the transformation of cardiovascular drugs into blockbuster medicines, which took place in Western pharmaceutical research, development and marketing after the Second World War. The team will pursue this work, examining how taking such powerful (and often expensive) drugs regularly and over long stretches of time has become considered as 'normal'.

Cardiovascular drugs have become some of the most therapeutically effective and commercially successful drugs of the 20th century, and many of them have rich histories. Plant extracts, the best known of which is digitalis, have long been used to treat 'heart weakness'. They serve as examples for the classic story of drug invention, from the observation of the effects of a plant, via the purification of its active substances in the laboratory and the analysis of their structure and function, to the synthesis of this active principle. As for other biologicals, in order to use these plant substances as medicines, standardising their effects is essential, and the principles and processes of '*Wertbestimmung*', as proposed by Paul Ehrlich, are central to this enterprise. The team will also study the commercial exploitation of such plant extracts, active principles and synthetic products. Other natural compounds such as the arrow poison curare were long used by physiologists as research tools. For decades they had no clinical use until the epidemiological transition of the mid-20th century in Europe and North America made the development of drugs for cardiovascular disorders an increasingly high priority. Curare was thought to be useful in anaesthesia, but the identification of its active principle also led to the observation that synthetic analogues lowered the blood pressure of laboratory animals. The team will study the ways in which natural and synthetic drugs travelled from the physiological laboratory into the clinic. Standardisation in this context involved not only laboratory techniques, but also the development of new clinical approaches, the education of doctors, nurses and patients, the gathering of large sample populations in order to collect statistical data and test compounds, the use of new monitoring technology, and in some cases the creation of new disease entities.

**Biological drugs (Team 3)**
Biotechnology today is often portrayed as a radically new era of innovation, playing a central role in the transformation of industrial and medical practices. However, biological drugs have a long history illustrative of the changing relations between biological laboratories, clinical services, industrial settings and regulatory bodies. Recent discussions about the widespread use of oestrogen replacement therapy in post-menopausal women, the balance of their effects (reducing the risk of osteoporosis on the one hand, increasing the risk of breast cancer on the other hand) illustrate the potency as well as the dangers of these drugs, their massive consumption, as well as the various – and occasionally conflicting – interests involved in their production, circulation and evaluation. There is a rich history of such configurations.

While many pharmaceuticals of the 19th century were preparations made out of plant and animal bodies, the industrialisation of drug making in the 20th century has resulted in the appearance of new classes of biological drugs ranging from vaccine and sera to vitamins and hormones. These new active substances posed specific scientific, industrial, medical and legal problems that make them especially interesting for understanding the therapeutic revolution and its relations to standardisation. The new biologicals were seen as the best examples of what bacteriological or biochemical research could contribute to medicine. Characterised as pure and natural substances, they were taken as extremely potent physiological modulators acting in a specific way and in very small quantities. However, the diversity of their effects and side-effects challenged the clear-cut definition of dosage and indications essential to the aims of pharmacological and clinical standardisation. Biological drugs were also extracted, produced and commercialised long before one could characterise them at the molecular level. As a consequence of both the variability of the biological raw material and of the uncertainties regarding the composition of extracts, standardisation was equated with the conduct of biological assays. Up to the present these assays have been major targets of industrial as well as administrative forms of regulation and standardisation. One final issue for which the trajectory of hormones and biological drugs is highly revealing is the question of appropriation and market construction. It is often forgotten that in most European countries therapeutic agents were not patentable. As they were not included in the traditional pharmacopoeia, biological drugs were the pharmaceutical 'terrain' upon which several forms of patenting and intellectual property protection that became dominant in the late 20th century were experimented.

Biological drugs will therefore serve as key examples in the history of standardisation in production, in state administration and patent offices, as well as the bedside.

**Psychochemicals (Team 4)**
The ways of experimental development, production, search for indications, clinical trials, implementation, regulation of drugs and their various effects on clinical-scientific as well as socio-cultural contexts are currently the focus of intense historical research in countries such as Belgium, Denmark, Germany, Netherlands and Switzerland. Under the auspices of the ESF RNP on DRUGS, researchers have been allied in a European-wide working group on psychochemicals.

Over the last fifty years, health care systems in European countries have become increasingly dependent on industrially produced psychopharmaceuticals, whose implementation has led to a deep transformation in psychiatry and the mental health sector in general. The introduction of the first neuroleptics and tranquilisers had a deep impact on therapeutic practices as well as on daily life in mental health facilities. This not only led to the elimination of straitjackets and the old somatic treatments, but also gave way to a diversification of psychiatric institutions and to more ambulant and flexible treatment for mental health problems. In response to the effects of psychochemicals, diagnostic categories and the perception and conception of 'madness' changed and were scientifically standardised.

# Aims and Objectives

Among the many drugs that are present in modern medicine and in our daily life, psychochemicals have a special status. Similar to other substances, patients and psychiatric practitioners see in them the power to relieve suffering and to cure, or at least manage, disease. But psychochemicals are an even more potent category, since they seem to be aiming at the 'psyche' or 'mind' and have the ability to moderate our mood and our conduct. They are therefore strongly entangled with hopes, but also with fears: A widespread unease towards modern medicine and the strategies of pharmaceutical companies as well as exorbitant expectations for enhancement and self-modulation are often associated with psychoactive drugs.

Psychochemicals stand at the centre of complex networks that bind together various actors and social fields, such as the pharmaceutical companies who produce them, the psychiatrists or doctors who prescribe them, as well as the patients who consume them. Members of Team 4 will study different 'drug trajectories' through these networks and their historical contingencies. Therefore, an interdisciplinary and comparative approach that seeks a more thorough exchange between the history of science and technology, the (social) history of medicine, social-cultural history, and the history of economy is key to the psychochemical group.

## Postgraduate/Postdoctoral Programme

In 2008 DRUGS offers four travel grants in the field of modern drugs history, notably oriented to the four major drug classes which constitute the main themes of the teams. The aim of the Postgraduate/Postdoctoral Programme is to encourage young researchers to engage in comparative international or transnational research projects on the development of 20th century medicine with a European perspective. This will enable PhD and posdoctoral students to spend a term (a total of 24 weeks split into two or four exchange visits with local groups) at participating institutions of the network. More details about these grants can be found on the DRUGS website: **http://drughistory.eu/**

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For the latest information on this Research Networking Programme consult the DRUGS websites:
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and **www.esf.org/drugs**

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