

Clinical Pharmacology in Denmark in 2016 – 40 Years with the Danish Society of Clinical Pharmacology and 20 Years as a Medical Speciality

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Abstract: The Danish Society of Clinical Pharmacology was founded in 1976, and mainly thanks to the persistent efforts of the society, clinical pharmacology became an independent medical speciality in Denmark in 1996. Since then, clinical pharmacology has gone from strength to strength. In the Danish healthcare system, clinical pharmacology has established itself as an indispensable part of the efforts to promote the rational, safe and economic use of drugs. Clinical pharmacologists are active in drug committees both in hospitals and in the primary sector. All clinical pharmacology centres offer a local medicines information service. Some centres have established an adverse drug effect manager function. Only one centre offers a therapeutic drug monitoring service. Clinical pharmacologists are responsible for the toxicological advice at the Danish Poison Information Centre at Bispebjerg University Hospital in the Capital Region. The Department of Clinical Pharmacology at Aarhus University Hospital works closely together with forensic toxicologists and pathologists, covering issues regarding illicit substances, forensic pharmacology, post-mortem toxicology, expert testimony and research. Therapeutic geriatric and psychiatric teach-inns for specialist and junior doctors are among the newest initiatives organized by clinical pharmacologists. Clinical pharmacologists work also in the Danish Medicines Agency and in the Danish pharmaceutical industry, and the latter has in particular a great growth potential for creating new jobs and career opportunities for clinical pharmacologists. As of July 2016, the Danish Society of Clinical Pharmacology has 175 members, and 70 of these are specialists in clinical pharmacology corresponding to approximately 2.5 specialists per 1000 doctors (Denmark has in total 28,000 doctors) or approximately 12 specialists per one million inhabitants.

Almost 50 years ago, some of the international pioneers of clinical pharmacology realized that clinical pharmacology must reach out to patients in order to develop and become an integrated part of health care. Thus, in 1970 [1] under the auspices of the World Health Organization, WHO, it was concluded that the roles of clinical pharmacology should be as follows:

- to improve patient care by promoting the safer and more effective use of drugs;
- to increase knowledge through research;
- to pass on knowledge through teaching; and
- to provide services, such as drug information, drug analysis, monitoring of drug abuse and advice on the experimental design of clinical drug studies.

In 1988, WHO defined clinical pharmacology as a medical discipline, which, on a scientific basis, combines pharmacological and clinical expertise with the ultimate goal of improving efficacy and safety in the clinical use of drugs [2]. Clinical pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and human beings [3,4], according to the International Union of Basic and Clinical Pharmacology, IUPHAR and WHO. A ‘clinical pharmacologist’ is normally used in a professional sense to refer to physicians who are specialists in clinical pharmacology and as such are directly and indirectly involved in the medical care of patients [3,4].

Although clinical pharmacology has existed as a teaching and scientific discipline for more than 50 years, there are still many countries in the world where it is not a medical speciality. Thus, among the 31 European countries that are represented in the European Association for Clinical Pharmacology and Therapeutics (EACPT), there are only 22,

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including Denmark, in which clinical pharmacology in fact is [5].

In 1976, a small group of farsighted Danish physicians with an interest in clinical pharmacology established the Danish Society of Clinical Pharmacology [6]. Chairs in clinical pharmacology were established a few years later at the universities in Copenhagen, Aarhus and Odense (fig. 1). Thanks to 20 years of persistent efforts by a handful of passionate members of the Danish Society of Clinical Pharmacology, clinical pharmacology became a medical speciality in June 1996. Ever since 1996, clinical pharmacology has gone from strength to strength in Denmark, and on the occasion of the combined 40-year anniversary of the Danish Society of Clinical Pharmacology and the 20-year anniversary of the medical speciality, we have written this progress report on the development and current status of the discipline in Denmark. It is our hope that the report will serve as a source of inspiration for clinical pharmacologists in other countries who are pursuing to develop the discipline.

How to Become a Specialist in Clinical Pharmacology in Denmark

All Danish physicians who want to become specialists in any medical speciality must first work as house officers for 12 months in two different specialities immediately after their graduation. The duration of the subsequent specialization in

clinical pharmacology is 5 years including a 12-month introductory programme as senior house officer in one of the three specialized clinical pharmacology departments in Copenhagen, Aarhus or Odense (fig. 1). The subsequent 48-month specialist registrar programme in clinical pharmacology is currently offered at the three regions for further education in Denmark, being The Capital Region of Denmark, The Region of Southern Denmark and The Central Denmark Region (fig. 1). The specialist registrar programme includes 24 months of work in clinical departments and 24 months of clinical pharmacology (table 1). The clinical training includes 12 months in a general internal medicine subspeciality department where the specialist registrars make the same kind of clinical work and work together with other physicians in their introductory year in general internal medicine

Table 1.

Training programme in Denmark.

A representative main training programme in clinical pharmacology in Denmark could look like this:

- Year 1: House officer in a clinical pharmacology department
- Year 2: General internal medicine
- Year 3: Clinical pharmacology at The Danish Medicines Agency/ Pharmaceutical Industry/ 'away' clinical pharmacology department
- Year 4: Two times 6 months at two of the following departments: haematology/geriatrics/nephrology/psychiatry/general practice
- Year 5: Clinical pharmacology ('home' reference department)

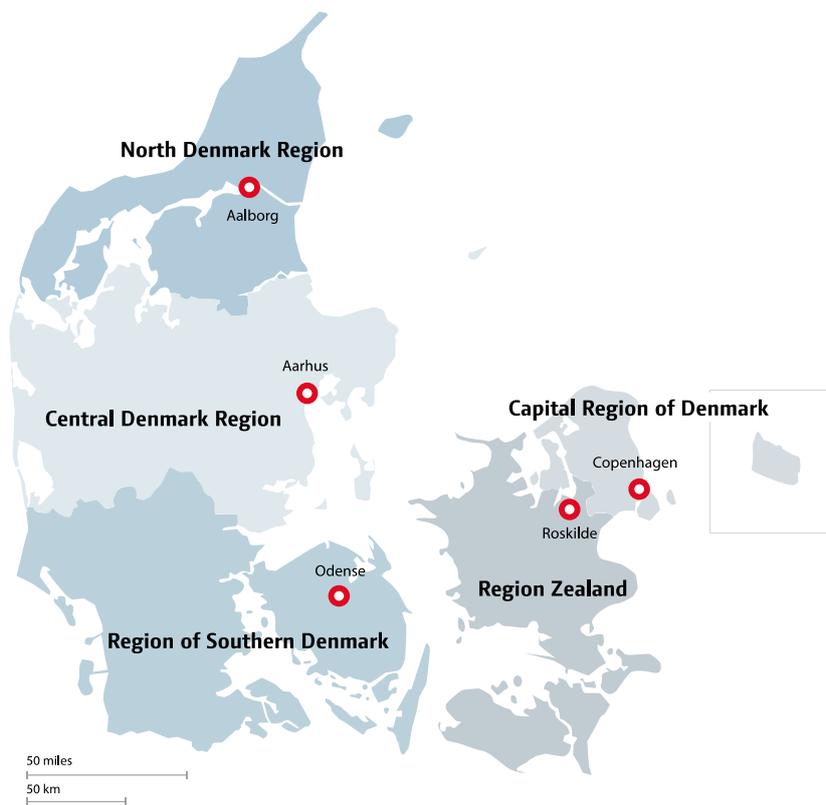


Fig. 1. The 5 Danish regions (number of inhabitants in brackets): The Capital Region of Denmark (1.8 m), Zealand Region (0.8 m), Region of Southern Denmark (1.2 m), Central Denmark Region (1.2 m) and North Denmark Region (0.6 m).

and acquire identical competences. During the last 12 months, the specialist registrars work the entire period or two times 6 months in one or two other internal medicine department(s) or in another specialized department including general practice, where pharmacological intervention must be the main treatment. Of the 24 months of specific training in clinical pharmacology, 12 months must take place at a department of clinical pharmacology, while the remaining 12 months can be in a hospital department with functions within clinical pharmacology, or at The Danish Medicines Agency or in the pharmaceutical industry with functions relevant to clinical pharmacology. There are about 10 yearly positions available as senior house officer in clinical pharmacology, and the ratio of these positions to specialist registrar positions is about 2:1. Objectives of the educational programme have been defined and are updated regularly. Further, educational programmes describing mandatory competences, which need to be achieved, teaching strategies, methods for evaluation of achieved competences, a 'log book' for documentation of the educational process, and individual plans for the education and future career have been produced. General courses and courses specific for the speciality are incorporated into the educational programme. There are nine specialized courses with a total duration of 28 days/196 hr: (i) pharmacokinetics and drug assay/therapeutic drug monitoring; (ii) pharmacogenetics/-genomics, metabolism and excretion of drugs; (iii) pharmacoconomics; (iv) pharmacodynamics; (v) pharmacoepidemiology; (vi) adverse drug reactions and poisoning; (vii) drug development and administrative pharmacology; (viii) evidence-based pharmacotherapy; and (ix) rational pharmacotherapy of patients at risk. An obligatory research training programme of at least 20 days is also included, and finally, three modules of a general course titled 'The Organization and Management of the Health Care System' are also obligatory. In each of the three clinical pharmacology departments in The Capital Region of Denmark, The Region of Southern Denmark and The Central Denmark Region, there is a chief physician who serves as the programme manager. The programme manager acts as the main supervisor, who is allocated for each senior registrar. Besides, each senior registrar has a local programme manager in each clinical or clinical pharmacology department, in the Danish Medicines Agency and in the pharmaceutical industry. The training is co-ordinated between the main supervisor and the local programme managers, while at the same time, all specialists in clinical pharmacology in the departments serve as day-to-day co-supervisors.

The 12-month senior house officer positions are filled after job interviews with applicants, whereas a national board evaluates and performs job interviews with applicants for the specialist registrar positions. Recruitment of young doctors for clinical pharmacology is an ongoing challenge as for other small 'paraclinical' or laboratory specialities. While the branding of clinical pharmacology as a medical speciality has improved significantly over the last 5–10 years, it is still not quite as recognized among physicians as more classical specialities, and role models or icons may be less obvious to

identify. At present, however, the number of applicants for the advertised positions is in a favourable balance.

Clinical Pharmacology in Numbers in Denmark

Denmark has approximately 5.6 m inhabitants, and the country is divided into five regions with populations that range from approximately 0.6 to 1.8 m inhabitants (fig. 1). The five regions manage the healthcare system with taxpayer money provided by the national government. For historical and other reasons, the units of clinical pharmacology are slightly differently organized in Denmark.

The Department of Clinical Pharmacology in the Capital Region is physically located at Bispebjerg University Hospital (fig. 1). The department also has a laboratory, which is placed at Rigshospitalet, the major referral and tertiary hospital in Denmark. It is the largest clinical pharmacology entity in Denmark because it provides clinical pharmacology services to hospitals and primary care responsible for approximately one-third of the Danish population. In Aarhus (fig. 1), which is Denmark's second largest city and the largest city in the Central Denmark Region, The Department of Clinical Pharmacology is also an independent department at Aarhus University Hospital. For historical reasons, clinical pharmacologists work closely together with basic pharmacologists at the Institute of Biomedicine at Aarhus University with regard to research and undergraduate teaching. Accordingly, the department is still physically located at the former Pharmacological Institute at Aarhus University. In Denmark's third largest city, Odense (fig. 1), which is the largest city in the Region of Southern Denmark, clinical pharmacology has a dual organization. The Research Unit of Clinical Pharmacology and Pharmacy at the Department of Public Health, University of Southern Denmark, is the frame for research and undergraduate teaching, and the Department of Clinical Biochemistry and Pharmacology at Odense University Hospital is the frame for specialist training and healthcare activities. Physically, however, the two legs of the organization are placed together at the Faculty of Health Sciences very close to Odense University Hospital. In Denmark's fourth largest city, Aalborg (fig. 1), which is the capital and largest city of the North Denmark Region, there is a unit of clinical pharmacology at Aalborg University Hospital, which works closely together with the department in Aarhus. Recently, the Region Zealand established Clinical Pharmacology Unit at the Zealand University Hospital, Roskilde (fig. 1).

When clinical pharmacology became a medical speciality in 1996, there were for obvious reasons no formal specialists and hence chief physician positions in the discipline. Thus, nine leading persons in clinical pharmacology, six in the Capital Region, two in the Region of Southern Denmark and one in the Central Denmark Region were appointed as chief physicians with the purpose to build up the speciality. Five to 7 years later, this number had doubled when the first generation of doctors had completed the formal training.

The 2016 number of specialists and doctors in training to become clinical pharmacologists in the five clinical

pharmacology departments are as follows: The Capital Region – nine specialists, six senior house officers and two specialist registrars; Central Denmark Region and North Denmark Region – eight specialists, four senior house officers and two specialist registrars; Region Zealand – three specialists; and the Region of Southern Denmark – five specialists, three senior house officers and three specialist registrars.

In the Danish Medicines Agency, there are five specialists and one specialist registrar. As detailed below, there are six specialists and one senior registrar in the Danish pharmaceutical industry. In addition, there are 34 specialists in clinical pharmacology who are either employed as clinicians within other clinical specialities or in university affiliations or who have retired.

In Denmark, there are approximately 28,000 doctors. Thus, there are approximately 2.5 specialists in clinical pharmacology per 1000 doctors or 12 per 1 m inhabitants. Most certainly, the number of specialists and the number of positions will continue to increase in future.

Clinical Pharmacology in the Danish Healthcare System

In 2011, the total healthcare costs in Denmark were approximately 171 billion DKK (23 billion €) including 21 billion DKK (2.8 billion €) for drugs out of which the patients would cover approximately 5.4 billion DKK (0.73 billion €). The main aim of clinical pharmacology in the healthcare system was to promote the rational, safe and economic use of drugs. Although Danish clinical pharmacologists are physicians and trained to practice medicine, there are in fact only a few who do so or are involved in direct patient care. Nevertheless, Danish clinical pharmacologists have an important role in supporting safe prescribing and providing specialist advice to clinicians both in hospitals and in primary care. Accordingly, all Danish centres of clinical pharmacology offer a local medicines information service that receives written or telephoned requests from healthcare staff for advice on drug-related problems in patients [7]. Questions regarding drug–drug interactions, choice of drug, adverse drug reactions, pregnancy and lactation are among the most frequent inquiries. Saved as reports in a national database that contains more than 11,000 entries, written replies are available for future requests.

For many years and even before the establishment of clinical pharmacology as a medical speciality, doctors interested in clinical pharmacology were involved in the drug committees. An important aspect of this work was the development of drug formularies, one of the first links between clinical pharmacology and patient care. After the establishment as a medical speciality, working in drug committees is still one of the most important obligations of a clinical pharmacologist. Ever-increasing drug expenditures and focus on patient safety have placed an ever-increasing emphasis upon this aspect of our task and are an important part of rational drug therapy.

To deal with the global problem of adverse drug event (ADE) under-reporting, the centres in the Capital Region and the Region Zealand (fig. 1) have established an ADE manager function. This is a telephone and email service operated by

young medical doctors or pharmacists assisting hospital physicians in the reporting suspected ADEs to the Danish Medicines Agency. Having access to necessary information in the electronic patient records, the ADE managers complete the majority of the ADE forms to the authorities and respond to requests for supplementary information with no further involvement of the clinicians. On request, the ADE manager offers advice on the nature and clinical implications of the ADE to the prescriber. This approach to ADE management has reduced some of the bureaucratic obstacles related to clinicians' spontaneous ADE reporting and led to a significant increase in the number of ADE reports [8].

At the Danish Poison Information Centre (DPIC) at Bispebjerg University Hospital in the Capital Region, clinical pharmacologists are responsible for the toxicological advice regarding enquiries involving drugs and drugs of abuse, while specialists in environmental medicine provide specialist advice in relation to enquiries involving exposure to, for example, chemicals at work or in the environment [9]. DPIC is a nationwide institution with specialist nurses comprising the front-line staff answering poison calls 24 hr a day, 7 days a week. The role of the clinical pharmacologists is to write and review protocols and action cards, to review all replies, to offer education and to provide physician-to-physician consultations when the care of a poisoned patient is beyond the scope of practice of the nurses.

The Department of Clinical Pharmacology at Aarhus University Hospital (fig. 1) works closely together with forensic toxicologists and pathologists, covering issues regarding illicit substances, forensic pharmacology, post-mortem toxicology, expert testimony and research.

Therapeutic geriatric and psychiatric teach-inns for specialist and junior doctors are among the newest initiatives organized by clinical pharmacologists to support safe prescribing. With a starting point in one or more complex patient cases, a senior clinical pharmacologist takes a leading role in a head-to-head discussion with the specialist in charge of the patient's care. In addition to the review of the medication history, the exchange of ideas and the dialogue on the therapeutic challenges, the conferences provide a unique opportunity for clinical pharmacologist-led problem-based learning to the clinicians. In preparation for the conferences, the clinical pharmacologists have access to the complete patient record and receive a written introduction to the therapeutic challenges that the clinicians have faced and wish to discuss.

For many years, paediatrics was not covered by the drug committee system, and drugs for children were not included in the drug formularies. At Bispebjerg University Hospital in the Capital Region (fig. 1), a 3-year project has led to the development of a drug formulary, which involves the rational use of drugs in paediatric and neonatology departments. The initiative is supported by teaching sessions in pharmacology with special focus on 'off label' treatment for the paediatricians.

A phase I trial centre with 10 fully equipped beds for phase I drug trials is part of the clinical pharmacology department at Bispebjerg University Hospital as a joint venture between clinical pharmacologists and private organizations.

Pharmacokinetic services in collaboration with the local chemical pathology services were foreseen as an important clinical pharmacology function in district hospitals. Advice on therapeutic drug monitoring (TDM), however, plays only a minor role in the tasks undertaken by Danish clinical pharmacologists. Thus, it is only at the Department of Clinical Biochemistry and Pharmacology at Odense University Hospital in the Region of Southern Denmark (fig. 1) that clinical pharmacologists review and comment TDM results from the drug laboratory and offer expert advice on the interpretation of the analyses.

As in other developed countries, polypharmacy is common among Danish patients [10]. Many prescribers may feel overwhelmed when encountering a patient whose drug therapy regimen is complex. Consequently, Danish clinical pharmacologists have become increasingly involved in the process of reviewing individual patients' complex drug regimens for inappropriate polypharmacy. Although the medication information services address a wide range of questions related to polypharmacy and complex medication, the involvement of Danish clinical pharmacologists in the direct care of patients with complex drug regimens is currently being reinforced. Hence, at Bispebjerg University Hospital, the clinical pharmacology department is about to establish a clinical pharmacist-led polypharmacy ambulatory service for referred patients. In the Zealand Region, the clinical pharmacologists collaborate with an interprofessional team of clinicians in a medical outpatient polypharmacy clinic.

As clinical pharmacologists in Denmark are trained as medical practitioners with special interest in proper use of drugs, their postgraduate teaching potential is big. Thus, all the Danish clinical pharmacology departments place great emphasis on the teaching of rational pharmacotherapy. This teaching is directed to medically qualified hospital practitioners from other disciplines, general practitioners as well as junior staff, nurses, pharmacists and other clinical staff. Pharmacists involved in drug analysis in primary care and education of general practitioners are also connected to the clinical pharmacology departments.

Regional and National Commitments

Besides their local commitments, clinical pharmacology in Denmark plays a key role in regional and national committees making decisions concerning the use of new drugs and drafting guidelines. Clinical pharmacologists are represented both in the steering and in the associated working groups. Below, some of the most important ones are briefly described.

The 'Council for Coordinating the usage of new drugs used in Hospitals' [Danish: KoordineringsRådet for Ibrugtagning af Sygehusmedicin' (KRIS)] was founded in 2012 and has the purpose to ensure an equal access to new hospital drugs and in particular cancer drugs across the five regions in Denmark. Members of KRIS are two representatives from each region, one from each of the Danish Health Authority, the Danish Medicines Agency and Danish Patients, which is an umbrella organization for 79 patient associations in Denmark. One of

the clinical departments supports the council with a description of the new drugs and literature review of available data.

'The Danish Regions', which is the professional organization for the five regions in Denmark established in 2010 the 'Council for the Use of Expensive Hospital Medicines' ['Rådet for Anvendelse af Dyr Sygehusmedicin' (RADS)]. The purpose of RADS is to ensure that all Danish patients have equal access to treatment with expensive hospital medicines on a unified professional nationwide basis. RADS is led by a steering committee consisting of representatives from the five regions in Denmark, the Danish Medicines Agency, the Danish Society of Clinical Pharmacology, Danish Patients, AMGROS, which is a pharmaceutical organization of the five Danish Regions, and 'The Danish Regions'. RADS elaborates common clinical treatment guidelines for the use of each medication. Adhering to these clinical treatment guidelines in all Danish hospitals is mandatory. Thus, RADS recommendations comprise drugs that are a major hospital expense, drugs characterized by a fast-growing rise in costs, new drugs with a high cost potential and areas in which consensus across regions is needed. AMGROS conducts a tender on the basis of the RADS guidelines. About 50 such guidelines have been approved and implemented. The Danish Society of Clinical Pharmacology is entitled to appoint one member in the steering committee, and in addition, two of the regions have also appointed a clinical pharmacist. One clinical pharmacist is appointed in each of the approximately 50 clinical committees who draft suggestions for the common clinical treatment guidelines in distinct disease entities.

As of January 2017, KRIS and RADS will be merged to form National Medicines Council (Medicinrådet), which will deal with both the evaluation of new drugs and making national treatment guidelines. Besides, a thorough evidence-based evaluation of new drugs, a health economic assessment will also be made. Along with the Reimbursement Committee (see below), this is the first attempt in Denmark to make a prioritization of drugs based on costs as well as evidence. It is planned that two clinical pharmacologists shall be members of this council along with one representative from each of the five regions, the Danish Medicines Agency, the Patient Organization, AMGROS, Danish Regions and possibly a member from the Danish Association of the Pharmaceutical Industry.

The Reimbursement Committee is powerful because it gives advice to the Danish Medicines Agency regarding reimbursement from the regions both with regard to general reimbursement of costs for one particular drug and reimbursement for individual patients treated with certain drugs. This committee has up to seven members of which two must be general practitioners. The members are appointed for 4 years, and together, they have a wide-ranging expertise. As of May 2016, two of the members including the chairman are double specialists in clinical pharmacology and general practice or psychiatry, respectively.

The Institute for Rational Pharmacotherapy (Institut for Rationel Farmakoterapi, IRF) was founded in 1999 by a distinguished Danish clinical pharmacist, Jens Peter Kampmann, and in the beginning, it was a partly independent

institute under the Danish Medicines Agency and later the Danish Health Authority. The aim of the institute is to promote the most rational use of current and future drugs with respect to both clinical and economical aspects. This aim is directed towards both primary and hospital care. The first two managers of the institute were distinguished clinical pharmacologists, and the institute continues to work closely together with the units of clinical pharmacology in the Danish health-care system. The institute is responsible for the National List of recommended drugs. The purpose of the list is to support physicians' prescriptions for drugs with regard to the choice of drug among the available drugs in a therapeutic class. Generally, the list does not contain treatment guidelines. Besides the National List, the main tasks of the institute are as follows: to publish a monthly medical journal (in Danish), arrange courses for general practitioners in relevant pharmacotherapeutic areas, prepare pharmacotherapeutic guidelines for selected areas in co-operation with the relevant scientific societies, arrange professional meetings on rational pharmacotherapy, support local region-based medicinal advisers of medicinal products, survey statistics on the consumption of medicinal products, arrange and actively participate in postgraduate education in the fields of rational pharmacotherapy, initiate projects and scientific investigations in areas of major pharmacotherapeutic and economical concern and prepare reviews that critically evaluate new, Danish medicinal products relevant to a large number of people.

The clinical pharmacologists in each of the three regions for further education in Denmark organize twice a year a 1-day course in rational pharmacotherapy, which is mandatory for all senior house officers in general internal medicine and subspecialties.

Clinical Pharmacology in Danish Drug Regulation

The Danish Medicines Agency (DMA) is an agency of the Danish Ministry of Health that regulates drugs in Denmark. The agency licenses medicines for the Danish market, authorizes clinical trials involving medicines, monitors the safety of medicines, for example maintains a database for pharmacokinetic drug interactions, and authorizes and inspects pharmaceutical companies. These activities are for most part undertaken in close collaboration with other medicines agencies in the EU as well as the European Medicines Agency (EMA) of the European Commission. In addition, the agency organizes the pharmacy structure in Denmark and supervises pharmacies and retailers selling medicines. Finally, the agency also monitors medical devices in Denmark. Clinical pharmacology has for the last 20 years – and continues to have – a prominent position at the agency. Both clinical pharmacologists and specialist registrars in clinical pharmacology have throughout these years worked full-time or part-time (10 hr per week) for the agency and have constituted a large proportion of the agency's medical workforce. As detailed above, a 1-year assignment with the agency may be a part of the formal specialist training programme for clinical pharmacology in Denmark.

The vast majority of clinical pharmacologists at the agency have been affiliated with the licensing division making assessments of documentation supporting marketing authorization applications and updates to the product information. The pharmacokinetic, pharmacodynamic and safety documentation is obviously a key area for a clinical pharmacology assessor, but the agency frequently also uses clinical pharmacologists to evaluate efficacy data, methodological and biostatistical problems, Good Clinical Practice (GCP) inspection findings and their impact on the benefit–risk balance, and much more. The licensing function also involves frequent scientific advice interactions with the pharmaceutical industry, both at a national level and at the level of the EMA through the Scientific Advice Working Party. Over time, clinical pharmacologists employed at the agency have held positions in various committees and working parties under the auspices of the EMA: Committee for Medicinal Products for Human Use (CHMP), Pharmacovigilance Risk Assessment Committee (PRAC), Scientific Advice Working Party (SAWP), Pharmacogenomics Working Party (PgWP) and CNS Working Party (CNSWP). Table 2 outlines activities at the DMA in which clinical pharmacologists or physicians in specialist training to become clinical pharmacologists are or have been involved.

Clinical Pharmacology in the Danish Pharmaceutical Industry

In 2015, Denmark's export of medicinal products was 11.8bn € making the pharmaceutical industry one of the most important export industries of the country. The rise of clinical pharmacology in Denmark began in 1995 when the Danish

Table 2.

The responsibilities of clinical pharmacologists in drug regulation at the Danish Medicines Agency.

Division	Activities
Medicines licensing and availability	Clinical assessments of marketing authorization applications and variations Scientific advice EMA committee and working party membership Governmental work (support to Ministry of Health, responses to minister and members of parliament) Assessment and approval of clinical trial protocols
Pharmacovigilance and medical devices	Pharmacovigilance assessments Pharmacoepidemiological research Scientific advice EMA committee membership Support to drug–drug interaction database GCP inspections
Medicines control and inspections Pharmacies and reimbursement	Assessments of applications for reimbursement of medicines The Danish Reimbursement Committee (chair and several members)

EMA, European Medicines Agency; GCP, Good Clinical Practice.

government granted 70 m DKK (9.41 m €) for the 5-year period of 1996–2000 on the grounds that clinical pharmacology was considered a framework condition for the pharmaceutical industry. Although it did not work out quite that way, specialists in clinical pharmacology are attractive candidates to the pharmaceutical industry because of their unique training including both practical clinical experience and clinical pharmacology as detailed above. In the industry, a specialist in clinical pharmacology can fulfil various roles in many areas, both involving early-phases of drug development (phase 1), proof-of-concept/dose-finding (phase 2), confirmatory phase 3 programmes, preparation for submission to health authorities or post-marketing activities including phase 4 trials or medical affairs/marketing. Other job opportunities include safety surveillance (pharmacovigilance), regulatory affairs (fulfilment of regulatory requirements/regulatory interactions) or health economics (market access activities including interaction with bodies of reimbursement/health technology assessment bodies). An international career is another possibility when joining the (bio) pharmaceutical industry. Finally, a career path within management is an additional opportunity, which can bring the clinical pharmacologist close to decision-making.

As mentioned above, five of the 70 specialists in clinical pharmacology with a Danish certification are currently employed in the pharmaceutical industry. The number of industry-employed specialists with a foreign certification is unknown.

Within the pharmaceutical industry, the knowledge of clinical pharmacology as a medical speciality is still limited. It is a common misunderstanding that specialists in clinical pharmacology mainly have interest in pharmacokinetics and pharmacodynamics why employment within a department of clinical pharmacology or in a phase I unit is often suggested per default. A better understanding of the competencies of specialists in clinical pharmacology and a clear distinction from pharmaceutical medicine is warranted. At the same time, the pharmaceutical industry has not succeeded in attracting or maintaining specialists in clinical pharmacology.

In the future, specialists in clinical pharmacology will likely work in the interface between academia, political institutions, regulatory authorities and the pharmaceutical industry. Successful drug development not only requires strong qualifications in research and knowledge of regulatory requirements but also an in-depth understanding of patient needs, the society and payers' perspectives. The specialist in clinical pharmacology has many of these competencies and has the potential to play a key role in research and development within the pharmaceutical industry. Specialists in clinical pharmacology already employed by the pharmaceutical industry need to be ambassadors for the speciality, and they have the task to reinforce the value of the clinical pharmacologist within the industry. Simultaneously, the pharmaceutical industry could further promote the job opportunities that exist – often in multidisciplinary teams in a dynamic, flexible and international environment with generally high job satisfaction and many opportunities for personal development. Besides advertising and personal referencing, this can be done by supporting and

taking responsibility in the education of future specialists in clinical pharmacology, for example by offering training positions in the industry. Finally, there should be more awareness of the high-quality research being performed by the pharmaceutical industry according to high regulatory and ethical standards. This could potentially also improve the image of the industry and attract more medical doctors.

Research in Clinical Pharmacology

The pioneers of clinical pharmacology in Denmark were also pioneers in the field of detecting and studying metabolic drug–drug interactions, and their discovery that sulphaphenazole effectively inhibits the oxidation of tolbutamide in 1963 [11] was made almost 30 years before the source enzyme, cytochrome P450C9 (CYP2C9), was identified. Danish clinical pharmacologists were also among the first to study drug metabolism in patients with liver failure [12]. Eigill F. Hvidberg, who was the first professor of clinical pharmacology in Denmark from 1973 to 1997, was one of the founding fathers of GCP [13]. Lars F. Gram, who was the first professor of clinical pharmacology at the University of Southern Denmark in Odense from 1978 to 2001, is one of the pioneers of clinical pharmacology in psychiatry [14] with a particular interest in the pharmacokinetics, drug–drug interactions and therapeutic drug monitoring of tricyclic antidepressants [15]. In 1980, he was a co-founder and chairman for the subsequent 25 years of the steering committee of a permanent multi-centre group, the Danish University Antidepressant Group (DUAG), which is still active [16]. Thus, a foundation was laid for the next generation of Danish clinical pharmacologists who have made extensive studies of pharmacogenetics of antidepressants and opioids in relation to CYP1A2, CYP2C19 and CYP2D6 [17]. Most recently, several Danish clinical pharmacology research groups have studied the impact of pharmacogenetic variation in drug transporters for the biodistribution of metformin [18,19]. Although the field of pharmacogenetics has existed since the 1950s, advances in sequencing technology now allow for large-scale clinical testing for constitutional pharmacogenetic variants implicated in interindividual drug response variability [20]. Danish clinical pharmacologists are involved in translating these discoveries into clinical use by exploring metabolism and mechanisms of action of drugs with special emphasis on the impact of genetic variations. These efforts are conducted in close collaboration with both clinical and paraclinical departments [21–23]. Oxidative stress in clinical pharmacology is another area of interest [24].

Denmark also has a strong research tradition within pharmacoepidemiology [25]. One of the main reasons is the abundance of population-based registers with full coverage of a stable population for up to several decades. Of particular importance is the Danish National Prescription Registry [26], which has provided full coverage of all redeemed prescriptions in primary care since 1995. The data are available for research in the settings of Statistics Denmark and the Danish Health Data Authority, and in both resources, it is possible to link the

prescription data to a plethora of other data [27]. Danish clinical pharmacologists have been in the forefront with certain methodological developments, for example with screening tools to capture aberrant prescribing patterns [28] or unsuspected adverse drug effects [29], and they have been instrumental in other strong pharmacoepidemiological research environments, such as the cardiology unit at Gentofte University Hospital [30].

Undergraduate Teaching in Clinical Pharmacology

Since 1994, Danish basic and clinical pharmacologists jointly have published a textbook 'Basic and Clinical Pharmacology' ('Basal og klinisk farmakologi') in Danish, which is used by most medical and other students within health care. Aarhus University provides a separate 10 ECTS (European Credit Transfer and Accumulation System) course in basic pharmacology for medical students during the bachelor programme and in extension hereof a separate five ECTS course in clinical pharmacology during the master programme. Clinical pharmacology is taught as part of an interdisciplinary course, with the overall objective to train doctors to act professionally in relation to patients, relatives, colleagues and collaborators. Thus, clinical pharmacology has on average 10 lessons per semester in each of the six semesters of the master programme. Lessons are divided into lectures and case-based tutorials. The students are evaluated by a separate written 2-hr examination.

At University of Southern Denmark in Odense, basic pharmacologists teach basic pharmacology with some help from clinical pharmacologists during the bachelor programme. The bachelor programme is organized in 12 organ or systems modules, and basic pharmacology is taught as a small part in each of these. During the master programme, there is at the present moment not a defined clinical pharmacology curriculum for medical students. The master curriculum has been structured according to organ systems and diseases with 13 such 'blocks' that are each finalized with a multiple choice question examination. The teaching of clinical pharmacology is spread across these blocks with varying intensity and volume. Altogether, students are taught clinical pharmacology for about 40 hr including both lectures and case-based tutorials. While the most important clinical pharmacology issues are covered, the nature of this structure allows for little systematic teaching. There is no separate examination in clinical pharmacology and, accordingly, the students do not prioritize clinical pharmacology. At the end of the master programme, there is an overall objective structured clinical examination (OSCE), which includes one written clinical pharmacology-oriented question. Currently, the master programme is being extensively overhauled. This includes a new separate 2-week clinical pharmacology course with a separate examination. This reform will be in effect from 2019 and will undoubtedly result in a substantial elevation of the graduate physician's clinical pharmacology competences. The Research Unit of Clinical Pharmacology and Pharmacy at University of Southern Denmark also is responsible for a master programme in clinical

pharmacy, and this among other things implies three separate 10 ECTS courses in clinical pharmacology and therapeutics for pharmacy students.

At University of Copenhagen, a separate course in clinical pharmacology and therapeutics has been established by first semester of 2016. The course is intended for about 300 medical students at 7th semester and consists of a total of 32 hr of confrontation including 20 lectures for all students and 12 classroom tutorials for 24 students, each during a period of 3 weeks in which no other subjects than clinical pharmacology are taught. The course is finalized by a written 2-hr examination counting 2.5 ECTS points. Furthermore, a station with prescription/patient information is included in the OSCE examination, and clinical pharmacology questions are embedded in the written, combined internal medicine/surgery examination.

Clinical Pharmacology in Denmark and International Relations

The International Union of Basic and Clinical Pharmacology, previously known as the International Union of Pharmacology (IUPHAR), was founded in 1965 [31], and ten years later a Section of Clinical Pharmacology which in 1996 became a Division of Clinical Pharmacology within IUPHAR was established. The Danish Society of Clinical Pharmacology has never been an independent member of IUPHAR, but Denmark is represented by the sister society, the Danish Society of Pharmacology, Toxicology and Medicinal Chemistry. The section or the division organized nine separate world congresses in clinical pharmacology and therapeutics between 1980 and 2008: London (1980), Washington (1983), Stockholm (1986), Heidelberg-Mannheim (1989), Yokohama (1992), Buenos Aires (1996), Florence (2000), Brisbane (2004) and Quebec City (2008). Then, it was decided to join forces between the two arms of pharmacology and to have only combined world congresses of basic and clinical pharmacology. The first of these was the 16th World Congress of Basic and Clinical Pharmacology or in short WorldPharma2010, which the Danish Society of Pharmacology, Toxicology and Medicinal Chemistry and the Danish Society of Clinical Pharmacology organized together for approximately 3000 participants in July 2010.

The Nordic journal '*Acta Pharmacologica et Toxicologica*' was founded in 1945, and Knud Ove Møller (1896–1973), professor in pharmacology at University of Copenhagen, became the first editor-in-chief. He was replaced in 1964 by his successor as professor of pharmacology, Jens Sølvér Schou (1929–), who in 1987 changed the name of the journal to '*Pharmacology & Toxicology*'. Kim Brøsen (1954–) replaced Jens Sølvér Schou in 2003, and in order to comply with IUPHAR, he changed the name of the journal to '*Basic & Clinical Pharmacology & Toxicology*' (BCPT) in 2004. In the July 2010 issue of BCPT, the journal published a position paper on clinical pharmacology and therapeutics drafted by a group of international renowned clinical pharmacologists under the auspices of IUPHAR [4]. This article was later

developed further by IUPHAR, WHO and the Council for International Organizations of Medical Sciences (CIOMS) into an official WHO technical report on clinical pharmacology [3] which was published in 2013.

The European Association of Clinical Pharmacology (EACPT) was founded in 1993 and the Danish Society of Clinical Pharmacology became a member shortly thereafter. One or two Danish clinical pharmacologists have been a regular or co-opted member of the executive committee between 1995 and 2015. In 1999, EACPT published a 'Guide to Training in Clinical Pharmacology in Europe' which was edited by Kim Brøsen from Denmark. [6]. Since 1995, EACPT has organized biannual congresses and the 5th EACPT Congress took place in Odense, Denmark, and the Centre of Clinical Pharmacology in Odense organized it for approximately 850 registered participants.

In 2015, the 'Union Européenne des Médecins Spécialistes' (European Union of Medical Specialists, UEMS) accepted pharmacology as a medical speciality, and Denmark is represented by two clinical pharmacologists in the management committee.

Conclusion

The official recognition of clinical pharmacology as an independent medical speciality in Denmark in 1996 has had an enormous positive influence on the development of the discipline in the country. The uniform training requirements of clinical pharmacologists mean that employers know exactly which professional skills and competences they acquire when employing a clinical pharmacologist. As expected, this has proven a big advantage for both the speciality and the employers, whether it is a clinical pharmacological centre/units, the Danish Medicines Agency or within the pharmaceutical industry. The main purpose of clinical pharmacology is to promote the rational, safe and economic use of drugs. Additionally, clinical pharmacologists play a key role in drug regulation in Europe, and it is foreseen that they also in future will play an even more important role in the pharmaceutical industry. They also play an important role in implementing and surveillance of adherence to new guidelines in the drug area. Rather than pursuing individual academic interests, it is widely accepted by prescribers, managers in the healthcare system and politicians that clinical pharmacology in Denmark has proven very useful in supporting prescribers in practising rational pharmacotherapy. The continued success of the discipline will very much depend on the continued effort of clinical pharmacologists to adapt to new challenges in a healthcare system and a drug scene that continuously changes. Rational pharmacotherapy is mainly about making the best choice of drugs among several possibilities, and prescribers generally are not trained to make such choices. Decisions on the implementation of new drugs and overall approach to a rational use of drugs are increasingly being centralized in Denmark. Hence, as described in detail above, clinical pharmacologists participate in most of the official committees and councils concerned with rational pharmacotherapy in Denmark. Clinical pharmacologists also play a

key role in implementing treatment guidelines in practice in the healthcare system in Denmark.

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