



CHDR
Centre for Human Drug Research

Annual Review 2013





- 4 **CHDR in 2013**

- 8 **SCIENCE**
- 10 Scientific Advisory Board
- 10 Bibliometric analysis
- 10 Publication output
- 12 Citation impact
- 13 Conclusions

- 14 **RESEARCH AREAS**
- 16 Psycho-neuropharmacology
- 16 Project revenues
- 16 Academic achievements
- 16 Clients and collaborations
- 17 Future developments
- 18 Vascular Medicine and Immunopharmacology
- 18 Turnover – business opportunities
- 18 Staff and training
- 18 Education and science
- 19 Food and Nutraceuticals
- 19 PK/PD

- 20 **OPERATIONS**
- 22 Volunteer subjects
- 22 Accommodation use
- 23 Quality assurance

- 24 **MANAGEMENT and SUPPORTING STAFF**
- 26 CHDR Board of Trustees and Management
- 26 Scientific Advisory Board 2013
- 27 Business Development
- 28 Human Resources
- 28 Management and staff changes
- 28 Sick leave
- 28 Employee Council
- 28 Terms of Employment
- 29 Social Policies
- 29 New-employee orientation
- 29 Education
- 29 Annual personnel evaluations

- 30 **PUBLICATIONS**

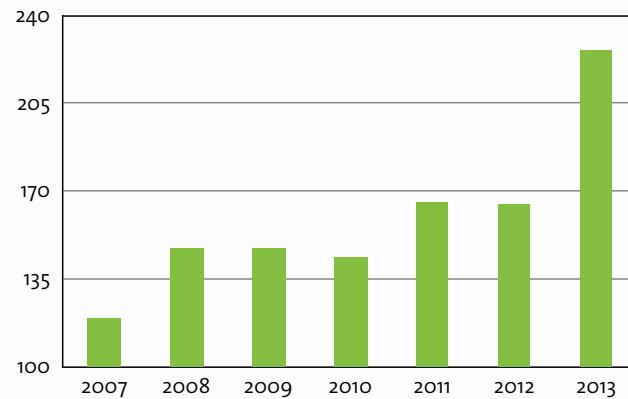
CHDR in 2013



CHDR in 2013

At the end of 2012, CHDR was ready to move into the new building. This move represented the final phase of a long planning trajectory that began in 2008, when the plot of land adjacent to the building at Zernikedreef 8 was secured. The construction phase was completed within budget and on schedule, and on Friday, February 1, CHDR moved with a tightly controlled operation led by chief administrator Helma Nederend. All systems were operational by the following Monday, and the total loss of productivity was less than one week. This smooth transition marked the end of a process that included construction that was completely uneventful, thanks to our architects at CEPEZED, the builders Du Prie Bouw & Ontwikkeling, and our building coordinator Thomas Lohse.

Figure 1. Contract revenue per year, relative to 2006.



The seasonality in turnover that we experienced continued in 2013, and this turnover was perhaps slightly more severe due to clients waiting for the new facility to become operational. However, any uncertainties that the building would be too large soon disappeared, as CHDR experienced our largest turnover growth in our history, reaching approximately 40% and yielding our highest annual contract revenue since 2006 (Figure 1). This was accomplished with our existing staff, supplemented by a flexible layer of technical and nursing staff, as well as the continuation of our consistently high client satisfaction ratings.

The new building exceeded our expectations both architecturally – the building won the 2013 prize for the most beautiful office building in Leiden – and operationally. The study subjects greatly appreciated the new facilities, and the increased possibility of accommodating much larger studies contributed to the return of many top 10 pharma clients.

The completion of one of the largest CNS pharmacodynamic studies ever performed – including the flawless use of ten neurocarts simultaneously – was a technical feat that would have been impossible in our old facility. The new building also quickly became a meeting place for many clinical pharmacology – related disciplines, hosting participants from Leiden, Rotterdam, and Amsterdam.

The opening ceremony for the new building was held on May 31st, with Mayor Henri Lenferink in attendance. Mayor Lenferink and 350 guests from as far as Japan attended the opening symposium and dinner, which included lectures by Laura Herman (the managing director at FSG), Andreas Wallnoefer (Global Head of Development at Roche), and Adam Cohen (CHDR's CEO). The 25 (+1) Jubilee was also commemorated in the book "Timelines and Working Spaces", which describes the organization's history beginning in 1987.

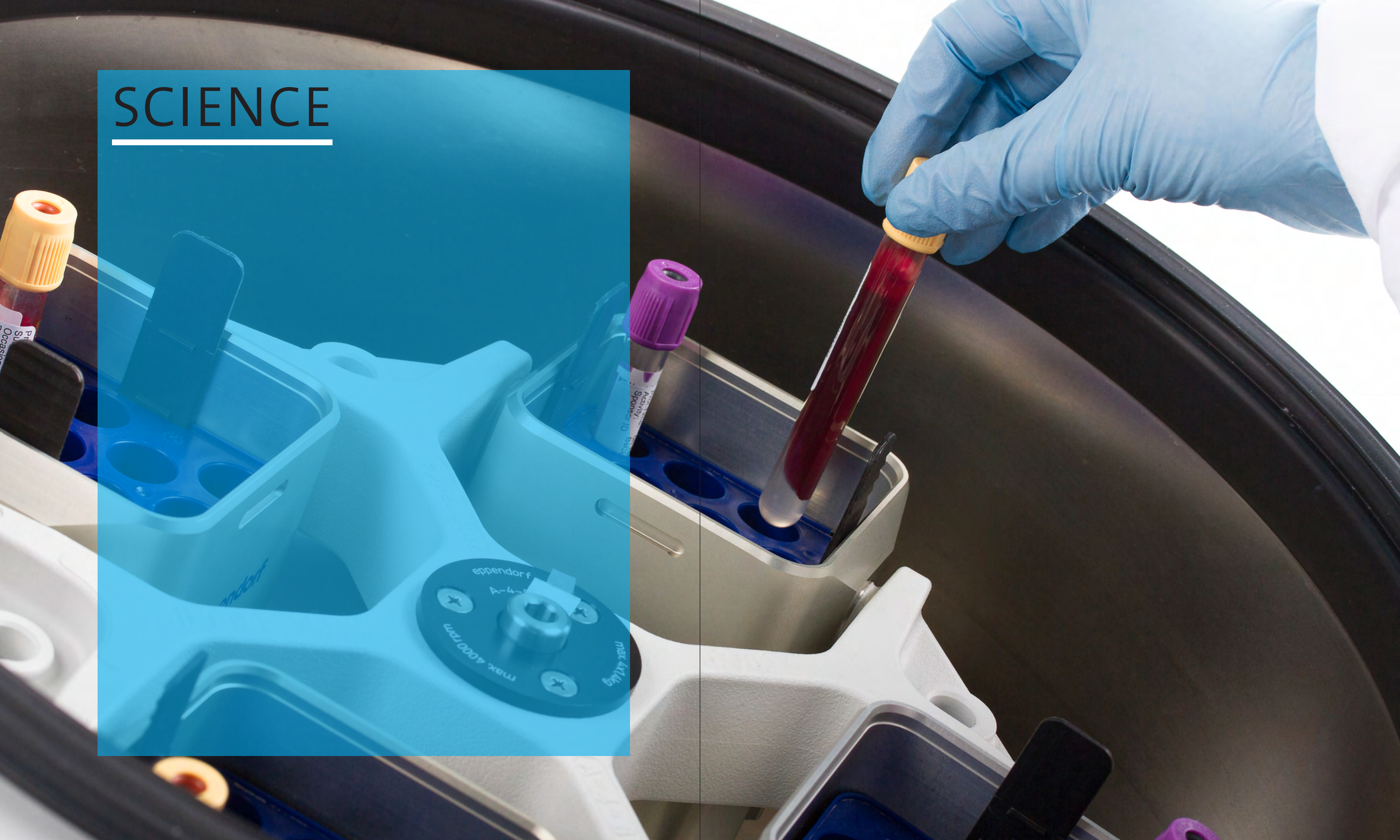
Koos Burggraaf, our research director of Vascular Medicine, saw his long tenure at CHDR recognized academically through his appointment as a Professor of Translational Pharmacology at Leiden University. Prof. dr. Burggraaf's inaugural lecture in October was another high point in this special year.

Sadly, 2013 was also marked by the unexpected death of Frank Stap, our Financial Director. Frank played an extremely important role during the critical phase of our transition to the new building. Frank will be missed as a friend and colleague, as a keen amateur musician, and – above all – as a valued member of the CHDR family.

This is also an appropriate place to mention the many extraordinary people at CHDR. The CHDR family achieved a transition that may have seemed daunting to many, and we did this while maintaining the high scientific quality that has made CHDR famous. We are truly grateful to each of our clients, collaborators, subjects, and employees for helping us reach our true potential.



SCIENCE



SCIENCE

Scientific Advisory Board

A Scientific Advisory Board (SAB) advises the management of CHDR regarding the scientific quality of the research performed. The SAB is composed of experienced scientists whose expertise encompasses the research activities at the CHDR. The SAB meets monthly to advise the executive management and to help educate the project leaders; these meetings are attended by all CHDR research staff. Each new project is first discussed among the project leaders, after which the SAB members provide coaching and advice as needed. In 2013, Prof. dr. M. Danhof resigned as the chairperson after serving for many years. Prof. dr. Danhof was a member of the SAB since it was founded, and he will continue to serve as an active SAB member. The new research director of the LACDR, Prof. dr. P. H. van der Graaf, is now the SAB chairperson.

Table 1. Benchmark institutes for bibliometric analysis

PRA	PRA International, Zuid-Laren, the Netherlands
Edinburgh	BHF Centre for Cardiovascular Science, Edinburgh (Pharmacology, Toxicology & Therapeutics)
Heidelberg	Clinical Pharmacology and Pharmacoepidemiology
LUMC	Leiden University Medical Center (Clinical Pharmacy and Toxicology)
Radboud	Nijmegen St. Radboud Medical Centre (Pharmacology and Toxicology)
UMCG	University Medical Center Groningen (Clinical Pharmacology)

Bibliometric analysis

In 2013, CHDR performed a bibliometric analysis in order to evaluate CHDR's publication performance. This analysis helps us evaluate the influence and/or performance of CHDR's research, and it provides a convenient tool for comparing CHDR's output with other institutions. The benchmarks used in this bibliometric analysis included national and international research institutes and clinical departments (Table 1).

Publication output

Although many research activities can be quantified, the number of journal publications is used commonly as an approximate measure of research output. Please note that the total number of publications in a given year can only be determined in the course of the following year; therefore, this annual review of 2013 shows the number of articles published through 2012.

The number of CHDR's publications increased steadily from 2004, then stabilized around 2010 (Figure 2). CHDR's publication output is similar to the output from the university benchmarks (with the exception of UMCG) and considerably higher than PRA's output (Figure 3). Although ranking institutions in terms of their publication number can be helpful for comparing CHDR's output against other institutions' output, the number of researchers at the institution should be taken into account in order to allow more direct comparison between institutions. Thus, because the number of researchers differs between the benchmarks, comparing the publications' impact may be more appropriate than comparing the absolute number of publications.

Figure 2. Number of CHDR publications in 3-year bins from 2001 through 2012.

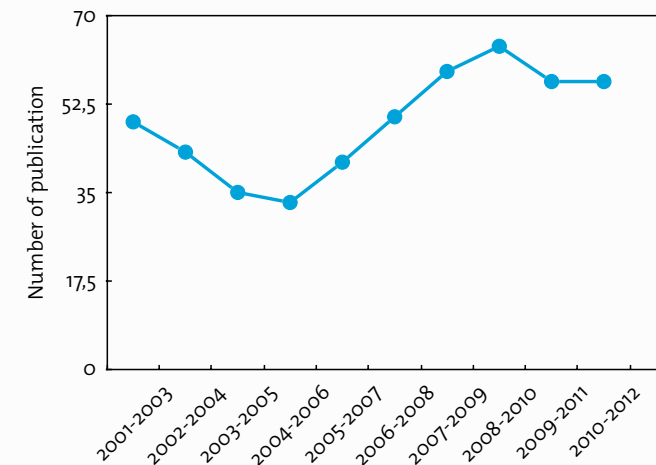
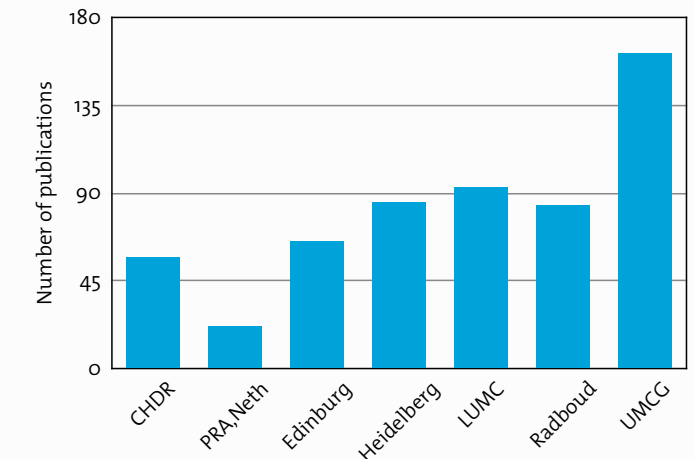


Figure 3. Number of CHDR publications in 2010-2012 versus the benchmark institutions.



SCIENCE

Citation impact

In publications, authors refer to (i.e., “cite”) previously published research. Publications that are cited more than others have more impact on the research field. Thus, tracking the number of times a publication has been cited can be used to quantify the impact and influence of that publication (and the research reported therein). We assessed CHDR’s research performance in terms of citation impact (Figure 4), and we compared the results with our benchmark institutions (Figure 5).

We used the Mean Normalized Citation Score (MNCS) to measure each institute’s citation impact (table 2). MNCS is the normalized impact with a citation window of four years, excluding self-citations. An MNCS of 1.0 reflects an equal number of citations between a given publication and the average for the field.

Counting the number of citations – and thus estimating the citation impact – requires measurements for at least one year after the publication date. Therefore, we can report the citation impact through 2011.

CHDR’s citation impact increased steadily from 2001 and was generally stable from 2009 onwards (Figure 4). CHDR’s citation impact during 2009-2011 was similar to the world average and was similar to the Radboud University and Heidelberg benchmarks (Figure 5).

Indicator	Dimension	Definition
MNCS	Impact	Average normalized number of citations of the publications
MNJS	Journal impact	Average normalized citation score of the journals in which a research unit has published

On the other hand, PRA, Edinburgh, and UMCG had higher impact scores in the same time period, for various reasons. For example, PRA’s high citation impact was due to a small number of highly cited publications regarding a new class of potent antiviral drugs. Moreover, these publications were the result of international collaborations and were published in high-impact journals; in contrast, CHDR’s publications are based primarily on national collaborations. Similarly, UMCG had a small number of publications that were cited many times (one publication was cited >3000 times). To account for this type of impact score bias, a bubble plot can be used to graphically depict the publications as a percentage of the entire oeuvre and the accompanying citation frequency. This analysis shows that CHDR’s citation impact pattern is similar to our university benchmarks (Figure 6).

A similar trend was observed with respect to journal impact (MNJS). CHDR’s journal impact was higher than the citation impact, indicating that CHDR generally publishes in journals that attract more citations than our own publications.

Conclusions

CHDR’s research output and publication impact are comparable to our benchmark university research centers and similar to the global average. Given that CHDR is a unique company that focuses on both research and data processing, finding suitable benchmarks is challenging. With the exception of PRA, the benchmarks that we used in our bibliometric analysis are university departments. Although PRA is a full research contract organization, it differs from CHDR in that PRA is part of a worldwide organization.

Based on our bibliometric analysis, we can conclude that CHDR’s output and impact increased through the years and stabilized in recent years. Moreover, CHDR publishes in high-impact journals, and this may help increase the visibility of CHDR’s research.

Figure 4. Average citation impact of CHDR publications in 3-year bins from 2001 through 2011.

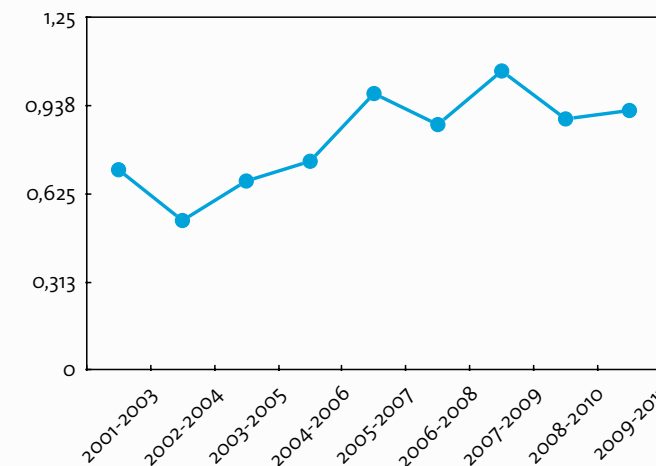


Figure 5. Average citation impact of CHDR publications in 2009-2011 versus the benchmark institutions

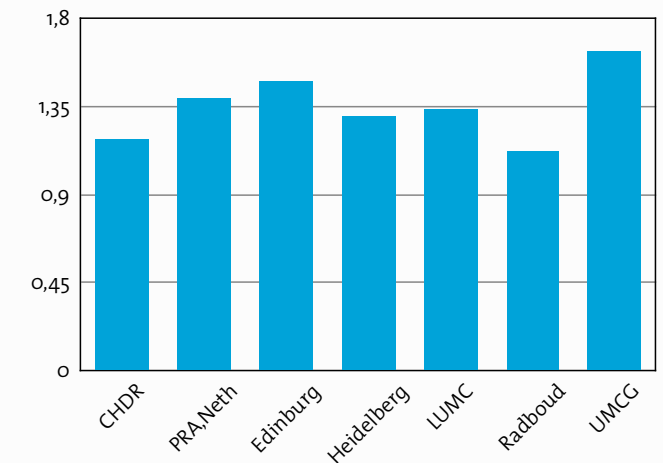
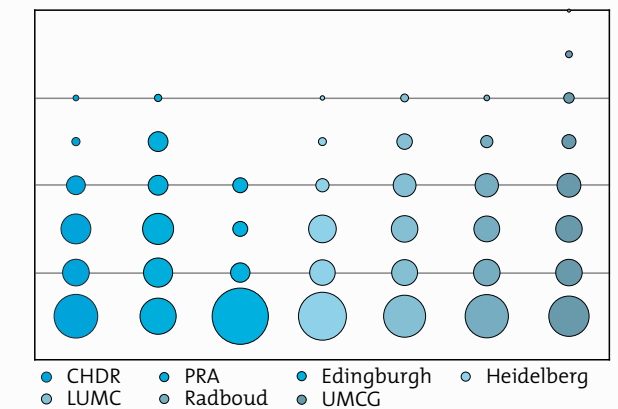


Figure 6. Bubble plot depicting the relative number of publications (as the relative size of each bubble) plotted against the number of times each publication has been cited.



RESEARCH AREAS



RESEARCH AREAS

Psycho-neuropharmacology

2013 was a particularly good year for the CNS group. Neurology and Pain activities and turnover continued to grow at approximately the same rate as 2012, and Psychopharmacology turnover doubled compared to 2012 (having already tripled in 2012 compared to 2011). While 2012 was a year of recovery for CNS, 2013 was a year of consolidation and growth. Half of this success can likely be attributed to steadily building upon our experience and existing contacts, together with active Business Development; the other half can be attributed to clients who approached CHDR directly based on our particular expertise and experience.

Project revenues

Activities in psychopharmacology increased by 60% compared to 2012, which is the largest sales result in CHDR's history. In total, 14 studies were performed in 2013; half of these studies were completed in 2013, and most of the other studies are still ongoing, ensuring a good start to 2014. Two of the studies were canceled on short notice, which seems to reflect the uncertainties related to working with small clients and/or innovative products. Neurology and Pain revenue also increased in 2013 (by 21% compared to 2012). Twelve studies were performed in 2013; two studies were completed, and seven new studies were initiated. The sponsors' evaluations of the completed studies were positive, with an average score of 4 out of 5. The increase in early psychopharmacology studies reflects the cautious re-entry of the pharmaceutical industry into this field following its sudden massive withdrawal in 2010-2012. However, the large increase in general CNS activities reflects the pharmaceutical industry's increasing interest in the innovative approaches to early drug research that CHDR developed in recent decades. This trend shows the likelihood of continued growth in the future. CNS revenues increased by 68% compared to 2012 and accounted for approximately 56% of CHDR's total revenues in 2013.

A particularly interesting new development in 2013 was the fact that funding was obtained for studies that were designed to develop new methodologies for measuring pharmacological effects. These studies – which would otherwise have been funded by CHDR – were altered slightly such that three different clients could help cover the studies' expenses. This model, in which methodologies, biomarker development, and validation studies are supported by future clients who will develop compounds that may benefit from the particular techniques, is exactly within CHDR's wheelhouse and will help position CHDR securely in the realm of high-tech contract research.

Academic achievements

Publications in psychiatry and neuroimaging continue to profit from long-term investments in scientific output and academic relations. The number of annual publications decreased slightly to 13; this is likely due to the emphasis placed on operational efforts, and it may also reflect the transient decrease in psychopharmacology research in recent years. On the other hand, three doctoral theses were completed in 2013 and will be defended in early 2014. With respect to Neurology and Pain, after five years of sowing and cultivating, harvesting can now begin. Although only two papers were published in 2013, five manuscripts are in preparation and two doctoral theses should be nearly completed by 2014. In addition, eight posters were presented at three scientific conferences, and one invited lecture was given.

Clients and collaborations

One key account generated nearly half of the Neurology and Pain revenue in 2013, and they continue to be one of our most important clients. At least three methodology studies and one new commercial study are planned for 2014, and discussions regarding funding a dedicated postdoctoral position are ongoing. Another CNS key account performed several methodology studies in 2013; these studies were aimed specifically at new compounds that we expect will be advanced to human trials in the near future. Others expressed interest in CHDR in terms of both sponsoring several methodology studies and performing a first-in-man study (such studies are routinely performed in one of their in-house units). These ongoing collaborations with major pharmaceutical companies will be the focus of CNS business development in coming years.

New collaborations were established with the Oogziekenhuis Rotterdam, the Neurovascular Group at vumc, and the Neuromuscular Diseases Group at UMC Utrecht in order to accommodate a study in which three new methodologies will be combined. Our ongoing collaboration with Tangent Data resulted in the start of study performance in Romania, and our collaborations with the vumc Alzheimer Center and the Alzheimer Research Center were expanded, yielding a joint strategy to collect healthy elderly patients with subjective memory complaints for future studies in preclinical Alzheimer's disease. Finally, our long-standing collaboration with the Neuroimaging Group at LUMC has begun to bear fruit, including one completed study and several upcoming pharmaco-MRI studies.

Future developments

We will attempt to improve the way in which we recruit specific patient populations, as early-phase clinical pharmacology studies in patients are currently regarded as an area with high growth potential and for which we have a competitive advantage. Studies using new neurological and psychiatric patient populations have been initiated, and more studies are expected in both methods development (ALS, schizophrenia) and clinical pharmacology (SMA, MAD). Demonstrating that CHDR can perform these studies as a solo center and on schedule will be extremely important. To meet this goal, we expanded our clinical networks, and two experienced clinicians joined the CNS team: Dr. Gabriel Jacobs is a psychiatrist at vumc who will establish collaborations with all major regional psychiatric institutions, and Ellen 't Hart is a neuropsychologist who manages the TRACK-HD network.

Pain activities will benefit greatly from a newly established collaboration with the Pain Group at vumc. In 2014, Geert Jan Groeneveld will join the new multidisciplinary pain team to be established at vumc. Pain research at CHDR will also benefit from this clinical experience in the field of pain, and the vumc's pain outpatient clinic can be a direct source of pain patients for inclusion in new studies. Joop van Gerven was appointed as the vice-chairman of the ccmO (the Central Committee on Human Research and Clinical Trial Competent Authority of the Netherlands) in 2013.

RESEARCH AREAS

Vascular Medicine and Immunopharmacology

Turnover – business opportunities

The turnover of the Vascular Medicine research area was consistent with our expectations. The turnover was dependent to a large extent on one particularly large project with several phases, and the remainder of the turnover was generated from smaller projects. Therefore, the group is actively securing a large client base, as this will likely generate the highest turnover. Client satisfaction has also remained high.

2013 was also the first year of a strategic partnership with an international pharmaceutical company. This partnership yielded three large projects that were awarded to CHDR and established CHDR as the preferred supplier. Our partnership also demonstrated that CHDR is a valued partner in drug development; nevertheless, the company decided to abandon its drug development division.

The recently established research line “clinical pharmacology of skin diseases” has developed into a mature revenue-generating activity and has led to the creation of a collaborative trial network for attracting potential clients.

Staff and training

The number of staff members did not change from 2012 (with 2-3 senior project leaders and 5 project leaders). The training of senior project leaders has also gone according to schedule: the candidates have completed most of the obligatory steps required to qualify for board certification as clinical pharmacologists.

Education and science

The group’s scientific output increased in 2013, with 15 peer-reviewed publications and 1 successful doctoral thesis. Additional education efforts included teaching students in BioPharmaceutical Sciences, our usual hosting of elective students, and the organization of the Clinical Pharmacology course for Biomedical Students as part of their Master’s program.



Food and Nutraceuticals

Our ongoing collaboration with TNO continued with the completion of three trials in early 2013. However, few trials were performed thereafter due to a reorganization within TNO that will result in TNO no longer working with external food companies; thus, the master contract between CHDR and TNO will not be extended. Despite the loss of the master contract, the use of micro-tracers in micro-dose studies will continue, and several new projects are under discussion. Common business development for this type of trial will be intensified.

Direct contacts with several major food and nutrition companies have been initiated and will lead to at least one signed contract in 2014.

The Food and Nutraceuticals group has remained embedded in the Vascular Medicine group, primarily because the two groups’ research questions focus on identical themes, thereby creating synergy between the groups. In this context, the Food and Nutraceuticals group provides medical and organizational support. On the other hand, cognition enhancement studies using caffeine and/or tea are performed by the CNS group.

PK/PD

The PK/PD group continued to improve its infrastructure for analyzing pharmacometric data using state-of-the-art multi-core hardware together with advanced software programs such as NONMEM and R. The workflow for pharmacometrics was also optimized, ensuring that both the transparency and reproducibility of our reported results meet industry standards.

Several non-compartmental analyses were performed to investigate pharmacokinetics, safety, tolerability, drug-drug interactions, and pharmacodynamics for novel biomarker research in the fields of congenital hemophilia, sepsis, dementia, and refractory epilepsy. Population PK/PD studies were also performed to support clinical studies at CHDR by analyzing and interpreting quantitative data regarding the Alzheimer’s disease, and congenital hemophilia. Models and simulations were used to improve the design of studies for multiple sclerosis and dementia. Consultancy services included projects in the field of cancer and two large projects to study the treatment of septic shock in the field of translational pharmacometrics. The pharmacometrics group also expanded their use of meta-analysis techniques to combine several in-house datasets in order to improve the analysis and interpretation of data regarding the scopolamine-, alcohol clamping-, and glucagon-challenge tests. In pediatric populations, PK/PD models and simulations were developed to study children with nephrotic syndrome and ADHD.

One three-day hands-on introductory course was organized in order to teach CHDR personnel, PhD students, and Master’s students how to apply population PK and PK/PD modeling using the non-linear mixed effects modeling software package NONMEM. In addition, three scientific papers were published. In the coming years, our group will focus on increasing capacity in order to ensure high scientific output and to support CHDR’s other services.

OPERATIONS



OPERATIONS

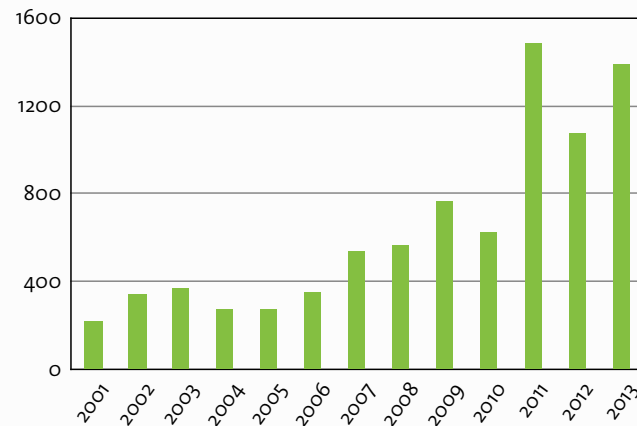
Volunteer subjects

The number of screened volunteers was 1,385 in 2013, an increase of 29% compared to 2012 (Figure 7). Of these 1,385 volunteers, 657 (47%) passed screening, and 627 (45%) were included in a study. This rate is similar to 2011, in which 46% of screened subjects were included in a study.

Table 3. Summary of accommodation use in 2012 and 2013

	Days	Evenings	Nights	Total
2012	2,346	1,765	1,472	5,583
2013	3,241	2,462	2,361	8,064
% Increase	38.2	39.5	60.4	44.4

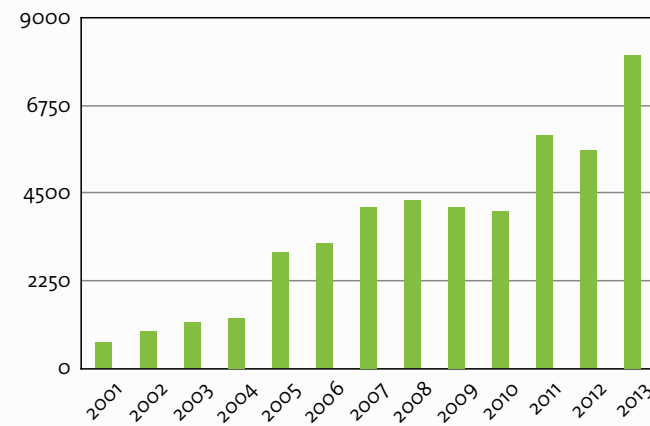
Figure 7. Total number of volunteers screened per year.



Accommodation use

In 2013, the total number of accommodation days was 8,064, an increase of 44% from 2012 (Table 3 and Figure 8).

Figure 8. Total number of accommodation days used from 2001 through 2013.



Quality assurance

In 2013, CHDR was audited by pharmaceutical companies ten times, compared to nine audits in 2012 (Table 4). Three audits were performed at the LUMC pharmacy, and seven audits were performed at CHDR. Two additional audits were scheduled for 2013, but they were either postponed or canceled by the sponsor.

The audits revealed no critical findings. Four of the seven audits performed at CHDR reported no major findings. However, the other three audits performed at CHDR reported major findings that led to several improvements in CHDR processes and quality, including:

- The development of several statistical procedures for writing and validating scripts, and
- An evaluation of the current SOP training procedure and the development of an action plan for improving this procedure.

The audits performed at the LUMC pharmacy also reported no critical findings. However, one audit reported a major finding (a follow-up audit was recommended). One audit provided no written feedback. In addition, six internal audits were performed (Table 5).

Two supplier audits were performed to examine new suppliers, and both suppliers were found to provide suitable services to CHDR. A third supplier audit was performed during a study's execution, and no significant findings were observed. Three system audits were performed to investigate the following areas:

- IT facilities and processes,
- General clinical laboratory facilities and general clinical procedures, and
- Archiving facilities and processes.

The findings reported by these audits either were resolved or are currently being addressed.

Table 4. Summary of audits

Audit type	Number of audits in 2012	Number of audits in 2013
Qualification / system audit	8 (including 2 GMP audits at the LUMC pharmacy)	9 (including 3 GMP audits at the LUMC pharmacy)
Study audit	1	1
Total number of audits	9	10

Table 5. Summary of internal audits performed in 2013

Audit type	Number of audits
Supplier audit	3
System/process audit	3
Total number of audits	6

MANAGEMENT and SUPPORTING STAFF



MANAGEMENT and SUPPORTING STAFF

CHDR Board of Trustees and Management

In 2013, Douwe Breimer and Klaus Rabe left the Board of Trustees. For Dr. Breimer, this marked the end of his second term on the Board; however, he will be available to the Board as a senior advisor. The members of the Board of Trustees are as follows:

- Dr. L.M. van der Mandele, Chair
- H.W. te Beest, Vice-chair
- Dr. B. Cohen
- J.H. Egberts

The management of CHDR is as follows:

- Prof. dr. A.F. Cohen, CEO
- Dr. P.A.M. Peeters, COO
- Prof. dr. J.M.A. van Gerven, Research Director of Psycho-neuropharmacology
- Prof. dr. J. Burggraaf, Research Director of Vascular Medicine
- Dr. G.J. Groeneveld, Research Director of Neurology and Pain



Scientific Advisory Board 2013

The following members served on CHDR's SAB in 2013 (listed in alphabetical order):

- Dr. A.G. de Boer, Leiden Academic Center for Drug Research (Pharmacology)
- Dr. B.N.M. van Berckel, vumc (Nuclear Medicine)
- Prof. dr. M. Danhof, Leiden Academic Center for Drug Research (Pharmacology)
- Prof. dr. P.H. van der Graaf (Chair), Leiden Academic Center for Drug Research (Pharmacology)
- Prof. dr. T. Hankemeier, Leiden Academic Center for Drug Research (Metabolomics)
- Prof. dr. T.W.J. Huizinga, Leiden University Medical Center (Rheumatology)
- Prof. dr. E.R. de Kloet, Leiden Academic Center for Drug Research (Pharmacology)
- Prof. dr. C. Kluft, Good Biomarker Sciences (Biomarker Science)
- Dr. K.E. Malone, Good Biomarker Sciences (Biomarker Science)
- Prof. dr. C.J.M. Melief, Leiden University Medical Center (Immunology)
- Dr. R.N. Sukhai, Leiden University Medical Center (Pediatrics)
- Dr. E.L. Swart, vumc (Clinical Pharmacology)
- Prof. dr. C.J.M. Taube, Leiden University Medical Center (Pulmonology)
- Prof. dr. F. Zitman, Leiden University Medical Center (Psychiatry)

Business Development

All budgeting and contracting is now performed under the supervision of the COO, who serves as the head of Business Development. A budget calculation and presentation template, including a tracking system for sending out budgets, has been developed and installed. Starting in Q3-2013, key sponsor accounts are assigned to the management members, with monthly review. The Business Development team leads CHDR's marketing and communication strategy (including website design and optimization, the development of marketing materials, LinkedIn, Google, and search engine optimization, social media, photography and videography, fact sheets, company folders, and newsletters).

MANAGEMENT and SUPPORTING STAFF

Human Resources

At the end of 2013, CHDR employed 216 individuals, including six elective students. The employees included 59 men and 157 women. One hundred and twenty employees were on-call employees, 56 were employed under a part-time contract, and 34 employees had a full-time contract. In addition to the abovementioned 216 employees, 17 guest employees participated in studies, including PhD students from the LUMC, as well as three nurses, one laboratory technician, and one financial officer who were placed at CHDR by a temp agency.

This workforce corresponded to 107 full-time equivalent (FTE) employees at the end of the year, with an average of 94 FTEs throughout the entire year of 2013 (for comparison, CHDR employees provided 92 FTEs at the end of 2012 and an average of 89 FTE throughout 2012). The distributions of FTEs by contract type and department are shown in [Figure 9](#) and [Figure 10](#), respectively.

Management and staff changes

Frank Stap, CHDR's Financial Director since 2008, died unexpectedly in March 2013. Edgar Nettle served as the interim Financial Director, and Bart Mooy was hired as Frank Stap's replacement in July 2013. Jan Freijer, the Research Director of Pharmacometrics, left CHDR after 2.5 years of service to launch a new career in the pharmaceutical industry.

Anna Chaudhuri and Abdelrahman Elsharkawy joined the Business Development department, adding two more nationalities to CHDR's diverse international staff. Jules Heuberger, Willem Birkhoff, Jasper van der Aart, and Charlotte Hoogstins joined CHDR's research staff, and Enrico Napoli was appointed as CHDR's Facility Officer.

Sick leave

Illness-related absences in 2013 were 1.71% (compared to 2.33% in 2012). One hundred and forty-eight reports of illness were received in 2013 (exactly the same number received in 2012), with 1,816 total sick days (compared to 2,612 sick days in 2012). Thus, the average number of days absent per employee was 12.27 days in 2013 (compared to 17.36 days in 2012). These figures improved considerably from 2012, and they were well below the national averages for our employment sector.

Employee Council

The following four members comprised the Employee Council at the end of 2013: Rob Zuiker (chair), Joanne Dannijis, Helene van Gorsel, and Lisette Mastebroek. The Employee Council met eight times, plus three additional times with the CEO. In addition, one general meeting was held for all employees.

Terms of Employment

The Terms of Employment were updated on October 1, 2013, including a salary increase of 1%.

Social Policies

New-employee orientation

Each new employee participates in a customized introduction program that includes a personal tutor. New employees also have compulsory introductory meetings with the QA Manager, the Data Manager, the Office Manager, the Nursing Staff Manager, and the CEO, who provides a general introduction to CHDR.

Education

CHDR prides itself in providing a rich educational experience, and 2013 was no exception. In 2013, two nurses graduated as Advanced Nursing Specialists for Clinical Research through a program that CHDR initiated together with the Hogeschool Leiden. In addition, 47 employees presented at 30 conferences (giving oral and/or poster presentations). Approximately 55k was also spent on educating and training CHDR staff. Eighteen students studied as interns, and three administrative interns received valuable experience in the Administration Department and the CRU Administration Department.

Each employee must attend a Good Clinical Practice (GCP) course every three years. The HR Manager keeps track of all employee courses and ensures compliance.

In 2013, the following three CHDR research staff members received their board certification as clinical pharmacologists: Matthijs Moerland, Geert Jan Groeneveld, and Eveline van Poelgeest.

Annual personnel evaluations

A new peer-review system based upon the "360-degree view" platform was developed specifically for CHDR by the HR department and the Chairman of the Employee Council. The system runs on the Intranet and provides customized assessments of employee competencies for various functions. A pilot test was performed with CHDR's senior clinical scientists. Peer review of all key personnel will begin in 2014 and will supplement the annual employee evaluations by the line manager.

Figure 9. Summary of full-time equivalents (FTEs) at the end of each quarter in 2013, by contract type.

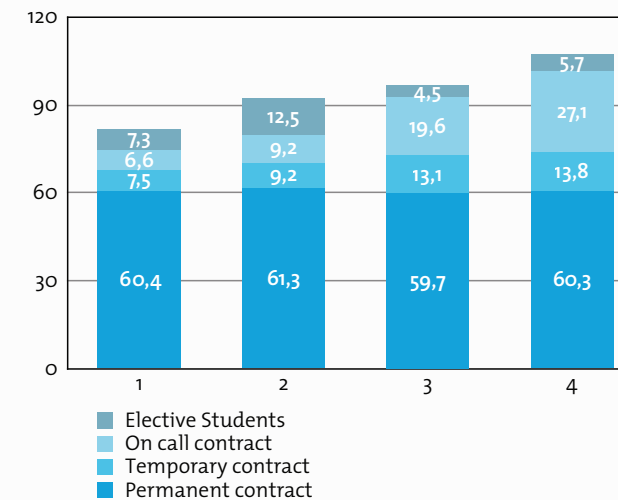
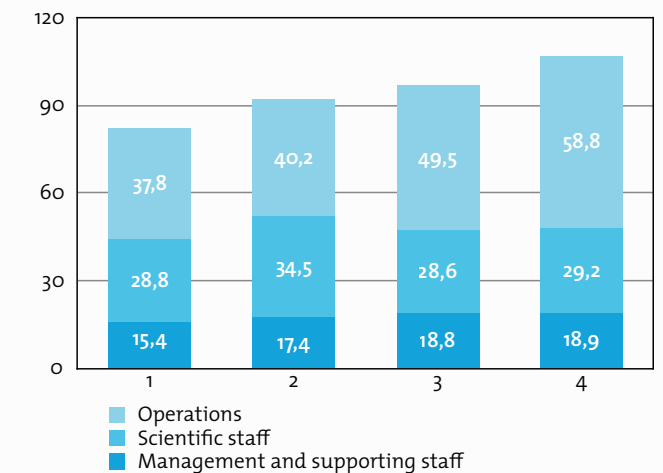


Figure 10. Summary of full-time equivalents (FTEs) at the end of each quarter in 2013, by department.



PUBLICATIONS



PUBLICATIONS

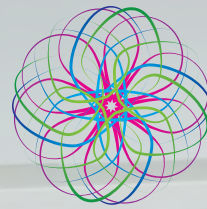
1. Boom M, Olofsen E, Neukirchen M, Fussen R, Hay J, Groeneveld GJ, Aarts L, Sarton E, Dahan A. Fentanyl utility function: a risk-benefit composite of pain relief and breathing responses. *Anesthesiology* 2013; 119: 663-674.
2. Bosch J, de Nooij J, de Visser M, Cannegieter SC, Terpstra NJ, Heringhaus C, Burggraaf J. Prehospital use in emergency patients of a laryngeal mask airway by ambulance paramedics is a safe and effective alternative for endotracheal intubation. *Emerg Med J* 2013; Epub ahead of print.
3. Cole DM, Beckmann CF, Oei NY, Both S, van Gerven JM, Rombouts SA. Differential and distributed effects of dopamine neuromodulations on resting-state network connectivity. *Neuroimage* 2013; 78: 59-67.
4. Cole DM, Oei NY, Soeter RP, Both S, van Gerven JM, Rombouts SA, Beckmann CF. Dopamine-dependent architecture of cortico-subcortical network connectivity. *Cereb Cortex* 2013; 23: 1509-1516.
5. de Kam PJ, El Galta R, Kruihof AC, Fennema H, van Lierop MJ, Mihara K, Burggraaf J, Moerland M, Peeters P, Troyer MD. No clinically relevant interaction between sugammadex and aspirin on platelet aggregation and coagulation parameters. *Int J Clin Pharmacol Ther* 2013; 51: 976-985.
6. Dillingh MR, van den Blink B, Moerland M, van Dongen MG, Levi M, Kleinjan A, Wijnsbeek MS, Lupher ML, Jr., Harper DM, Getsy JA, Hoogsteden HC, Burggraaf J. Recombinant human serum amyloid P in healthy volunteers and patients with pulmonary fibrosis. *Pulm Pharmacol Ther* 2013; 26: 672-676.
7. Franciosi LG, Diamant Z, Banner KH, Zuiker R, Morelli N, Kamerling IM, de Kam ML, Burggraaf J, Cohen AF, Cazzola M, Calzetta L, Singh D, Spina D, Walker MJ, Page CP. Efficacy and safety of RPL554, a dual PDE3 and PDE4 inhibitor, in healthy volunteers and in patients with asthma or chronic obstructive pulmonary disease: findings from four clinical trials. *Lancet Respir Med* 2013; 1: 714-727.
8. Heuberger JA, Cohen AF. World-class cyclists on EPO. *Br J Clin Pharmacol* 2013; 75: 1406-21.
9. Heuberger JA, Cohen Tervaert JM, Schepers FM, Vliegthart AD, Rotmans JJ, Daniels JM, Burggraaf J, Cohen AF. Erythropoietin doping in cycling: lack of evidence for efficacy and a negative risk-benefit. *Br J Clin Pharmacol* 2013; 75: 1406-1421.
10. Hoch M, Hay JL, Hoefer P, de Kam ML, te Beek ET, van Gerven JM, Dingemans J. Dual orexin receptor antagonism by almorexant does not potentiate impairing effects of alcohol in humans. *Eur Neuropsychopharmacol.* 2013; 23: 107-117.
11. Hoefer P, Hay J, Rad M, Cavallaro M, van Gerven JM, Dingemans J. Tolerability, pharmacokinetics, and pharmacodynamics of single-dose almorexant, an orexin receptor antagonist, in healthy elderly subjects. *J Clin Psychopharmacol.* 2013; 33: 363-370.
12. Ince I, de Wildt SN, Wang C, Peeters MY, Burggraaf J, Jacqz-Aigrain E, van den Anker JN, Tibboel D, Danhof M, Knibbe CA. A novel maturation function for clearance of the cytochrome P450 3A substrate midazolam from preterm neonates to adults. *Clin Pharmacokinet.* 2013; 52: 555-565.
13. Jobert M, Wilson FJ, Roth T, Ruigt GS, Anderer P, Drinkenburg WH, Bes FW, Brunovsky M, Danker-Hopfe H, Freeman J, van Gerven JM, Gruber G, Kemp B, Klosch G, Ma J, Penzel T, Peterson BT, Schulz H, Staner L, Saletu B, Svetnik V. Guidelines for the recording and evaluation of pharmaco-sleep studies in man: the International Pharmaco-EEG Society (IPEG). *Neuropsychobiology* 2013; 67: 127-167.
14. Khalili-Mahani N, Chang C, van Osch MJ, Veer IM, van Buchem MA, Dahan A, Beckmann CF, van Gerven JM, Rombouts SA. The impact of "physiological correction" on functional connectivity analysis of pharmacological resting state fMRI. *Neuroimage* 2013; 65: 499-510.
15. Klein RH, Alvarez-Jimenez R, Sukhai RN, Oostdijk W, Bakker B, Reeser HM, Ballieux BE, Hu P, Klaassen ES, Freijer J, Burggraaf J, Cohen AF, Wit JM. Pharmacokinetics and pharmacodynamics of orally administered clonidine: a model-based approach. *Horm Res Paediatr.* 2013; 79: 300-309.
16. Klein RH, van der Vorst MM, de Wilde RB, Hogenbirk K, de Kam ML, Burggraaf J. Evaluation of a bedside device to assess the activated partial thromboplastin time for heparin monitoring in infants. *Blood Coagul Fibrinolysis* 2013; 24: 327-331.
17. Kluff C, Meijer P, Kret R, Burggraaf J. Preincubation in the Prothrombinase-induced Clotting Time test (PiCT) is necessary for in vitro evaluation of fondaparinux and to be avoided for the reversible, direct factor Xa inhibitor, rivaroxaban. *Int J Lab Hematol.* 2013; 35: 379-384.
18. Kluff C, Skouby SO, Jespersen J, Burggraaf J. Sex hormone-binding globulin as a marker for the thrombotic risk of hormonal contraceptives: a rebuttal. *J Thromb Haemost.* 2013; 11: 394-395.
19. Klumpers LE, Fridberg M, de Kam ML, Little PB, Jensen NO, Kleinloog HD, Elling CE, van Gerven JM. Peripheral selectivity of the novel cannabinoid receptor antagonist TM38837 in healthy subjects. *Br J Clin Pharmacol* 2013; 76: 846-857.
20. Klumpers LE, Roy C, Ferron G, Turpault S, Poitiers F, Piquier JL, van Hasselt JG, Zuurman L, Erwich FA, van Gerven JM. Surinabant, a selective cannabinoid receptor type 1 antagonist, inhibits Delta9-tetrahydrocannabinol-induced central nervous system and heart rate effects in humans. *Br J Clin Pharmacol* 2013; 76: 65-77.
21. Kuepper R, Ceccarini J, Lataster J, van Os J, van Kroonenburgh M, van Gerven JM, Marcelis M, Van LK, Henquet C. Delta-9-tetrahydrocannabinol-induced dopamine release as a function of psychosis risk: 18F-fallypride positron emission tomography study. *PLoS One* 2013; :e70378.
22. Lewis LD, Somogyi A, Loke YK, Ferro A, Cohen AF, Ritter JM. Editors' Pick 2012. *Br J Clin Pharmacol* 2013; 75: 1-6.
23. Liem-Moolenaar M, Peeters P, Kamerling IM, Hogg C, Holder G, Kleijn HJ, Spaans E, Udo De HJ, de Kam ML, Franson KL, Cohen AF, van Gerven JM. Early stage development of the glycine-1 re-uptake inhibitor SCH 900435: central nervous system effects compared with placebo in healthy men. *Br J Clin Pharmacol* 2013; 75: 1455-1467.
24. Lips MA, de Groot GH, De Kam M, Berends FJ, Wiezer R, Van Wagenveld BA, Swank DJ, Luijten A, Pijl H, Burggraaf J. Autonomic nervous system activity in diabetic and healthy obese female subjects and the effect of distinct weight loss strategies. *Eur J Endocrinol* 2013; 169: 383-390.
25. Osanto S, van Poppel H, Burggraaf J. Tasquinimod: a novel drug in advanced prostate cancer. *Future Oncol.* 2013; 9: 1271-1281.
26. Secilir A, Schrier L, Bijleveld YA, Toersche JH, Jorjani S, Burggraaf J, van GJ, Mathot RA. Determination of methylphenidate in plasma and saliva by liquid chromatography/tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2013; 923-924: 22-28.
27. te Beek ET, Tatosian D, Majumdar A, Selverian D, Klaassen ES, Petty KJ, Gargano C, van Dyck K, McCrea J, Murphy G, van Gerven JM. Placebo- and amitriptyline-controlled evaluation of central nervous system effects of the NK1 receptor antagonist aprepitant and intravenous alcohol infusion at pseudo-steady state. *J Clin Pharmacol* 2013; 53: 846-856.
28. te Beek ET, Hay JL, Bullman JN, Burgess C, Nahon KJ, Klaassen ES, Gray FA, van Gerven JM. Pharmacokinetics and central nervous system effects of the novel dual NK1 /NK3 receptor antagonist GSK1144814 in alcohol-intoxicated volunteers. *Br J Clin Pharmacol* 2013; 75: 1328-1339.

PUBLICATIONS

29. van Meer L, Moerland M, Cohen AF, Burggraaf J. Urinary Kidney Biomarkers for Early Detection of Nephrotoxicity in Clinical Drug Development. *Br J Clin Pharmacol* 2013.
30. van Poelgeest EP, Swart RM, Betjes MG, Moerland M, Weening JJ, Tessier Y, Hodges MR, Levin AA, Burggraaf J. Acute kidney injury during therapy with an antisense oligonucleotide directed against PCSK9. *Am J Kidney Dis* 2013; 62: 796-800.
31. van Schinkel LD, Willemse PM, van der Meer RW, Burggraaf J, van Elderen SG, Smit JW, de RA, Osanto S, Lamb HJ. Chemotherapy for testicular cancer induces acute alterations in diastolic heart function. *Br J Cancer* 2013; 109: 891-896.
32. Wijngaarden MA, Pijl H, van Dijk KW, Klaassen ES, Burggraaf J. Obesity is associated with an altered autonomic nervous system response to nutrient restriction. *Clin Endocrinol (Oxf)* 2013; 79: 648-651.
33. Willemse PM, Burggraaf J, Hamdy NA, Osanto S. Reply to "Comment on Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors". *Br J Cancer* 2013; 109: 2503-2504.
34. Willemse PM, Burggraaf J, Hamdy NA, Weijl NI, Vossen CY, van WL, van Steijn-van Tol AQ, Rosendaal FR, Osanto S. Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors. *Br J Cancer* 2013; 109: 60-67.



Corporate photography by Michiel Plas



CHDR
Centre for Human Drug Research

