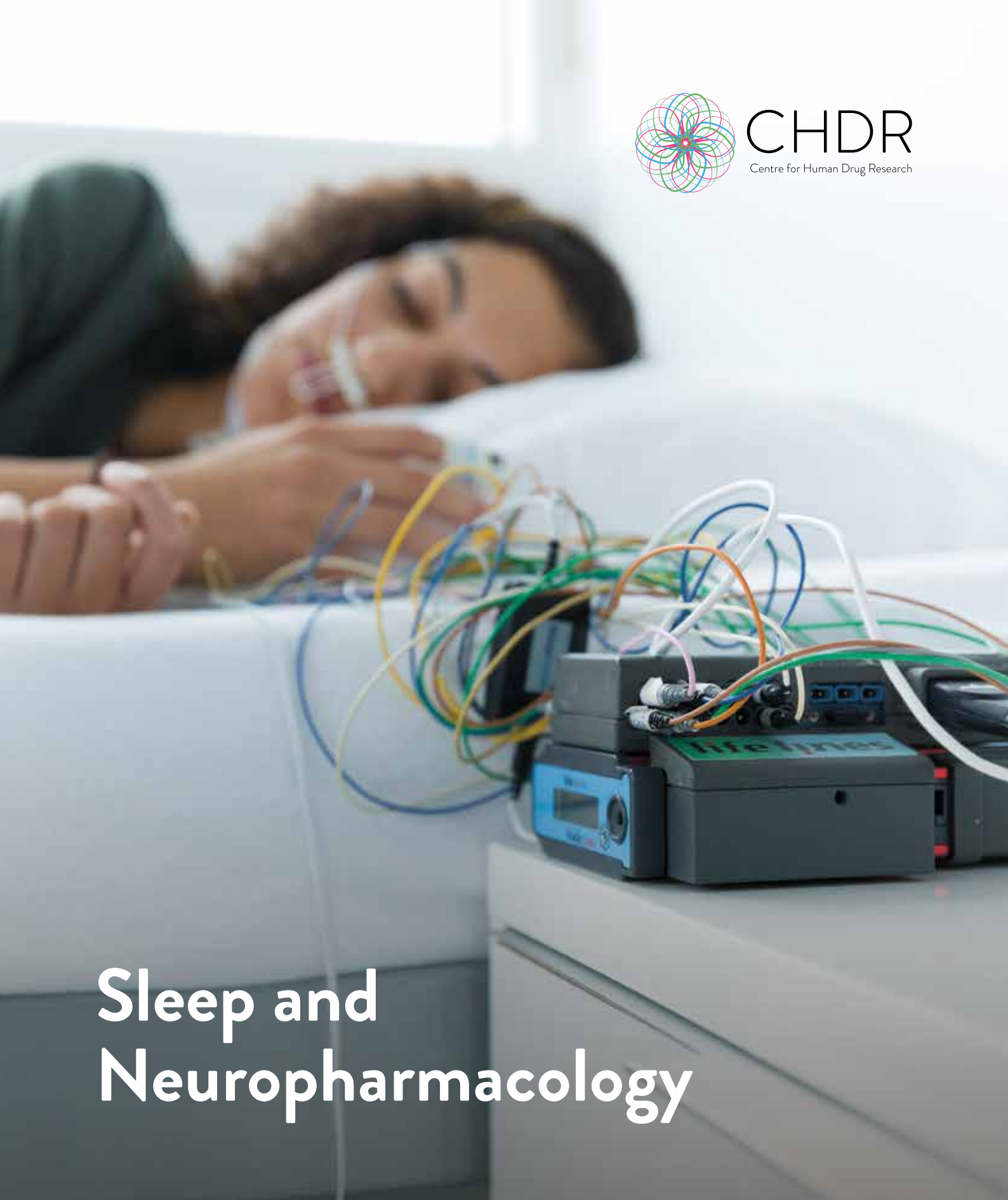
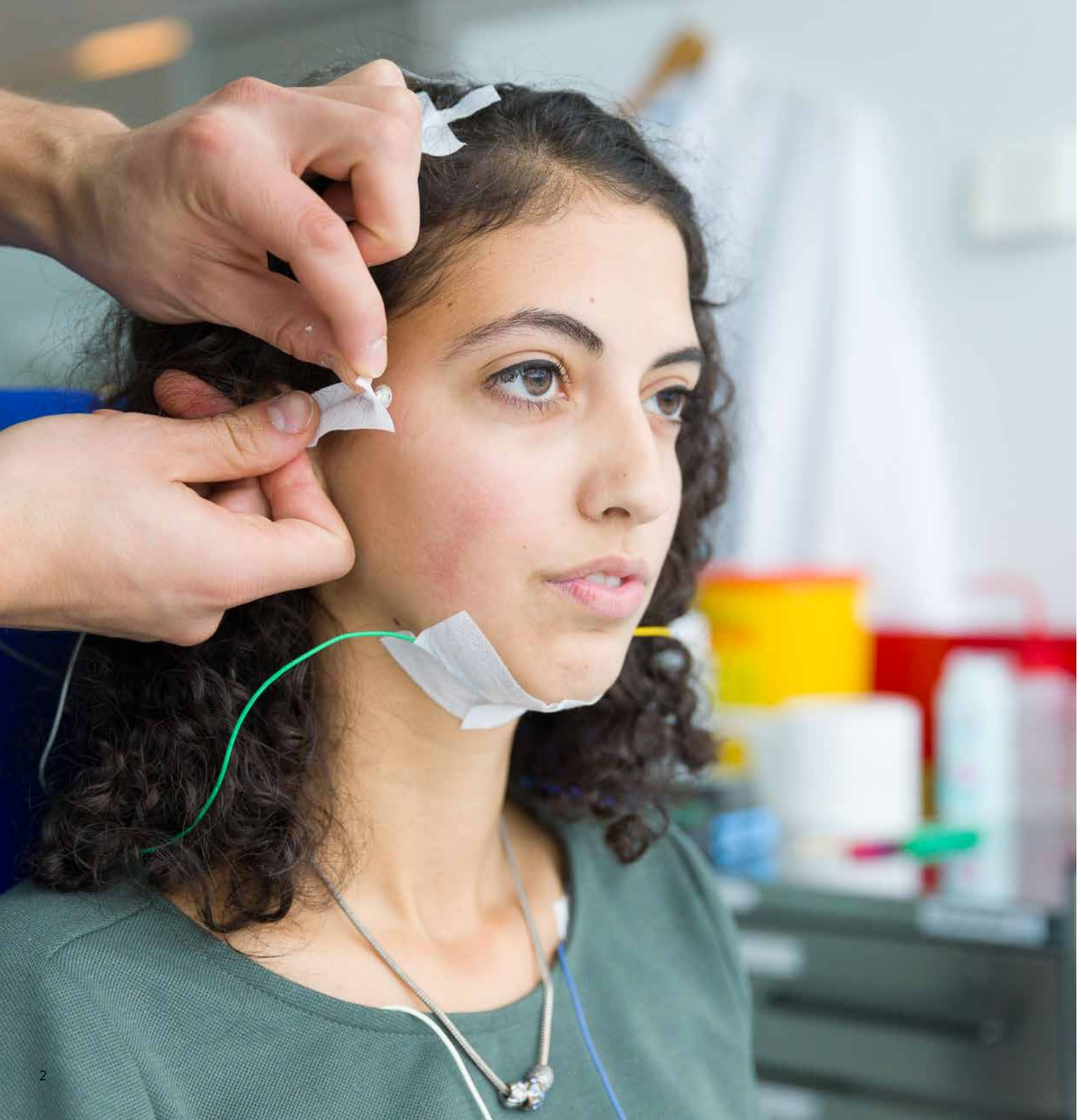


CHDR
Centre for Human Drug Research

Sleep and Neuropharmacology



Sleep and neuropharmacology: an unexpected combination

CHDR has many years of experience studying the effects of CNS drugs on sleep, including medications for patients with sleeping disorders such as narcolepsy and insomnia. However, commonly used medications against psychiatric and neurological conditions such as depression and Alzheimer's disease can also influence sleep. Therefore, studying sleeping subjects in a clinical trial can increase our knowledge regarding a compound's neuropharmacology. After all, although sleep may appear to be a passive process, it requires the coordinated activity of many neurotransmitter systems in the CNS.

Practical answers to important research questions

How does our compound compare with other sleep medications?

Using NeuroCart®, polysomnography, and driving simulators, CHDR can generate a comprehensive profile of a new sleep aid's intended and/or unintended effects. Even in the earliest stages of clinical drug development, relevant information can be collected using healthy volunteers, and these results can be compared against results obtained using established sleep aids (for example, zolpidem).

Does our CNS drug affect driving performance?

Taking a sleep aid or other CNS drug can impede driving performance. To study these effects in detail, CHDR uses a validated driving simulator in healthy subjects and patients. The driving simulator can also be used to compare the effects of a new compound with the effects of established sleep aids, alcohol, and other compounds. To quantify the intensity and duration of the drug's effects on driving performance, the simulator can be used repeatedly over the course of several hours.

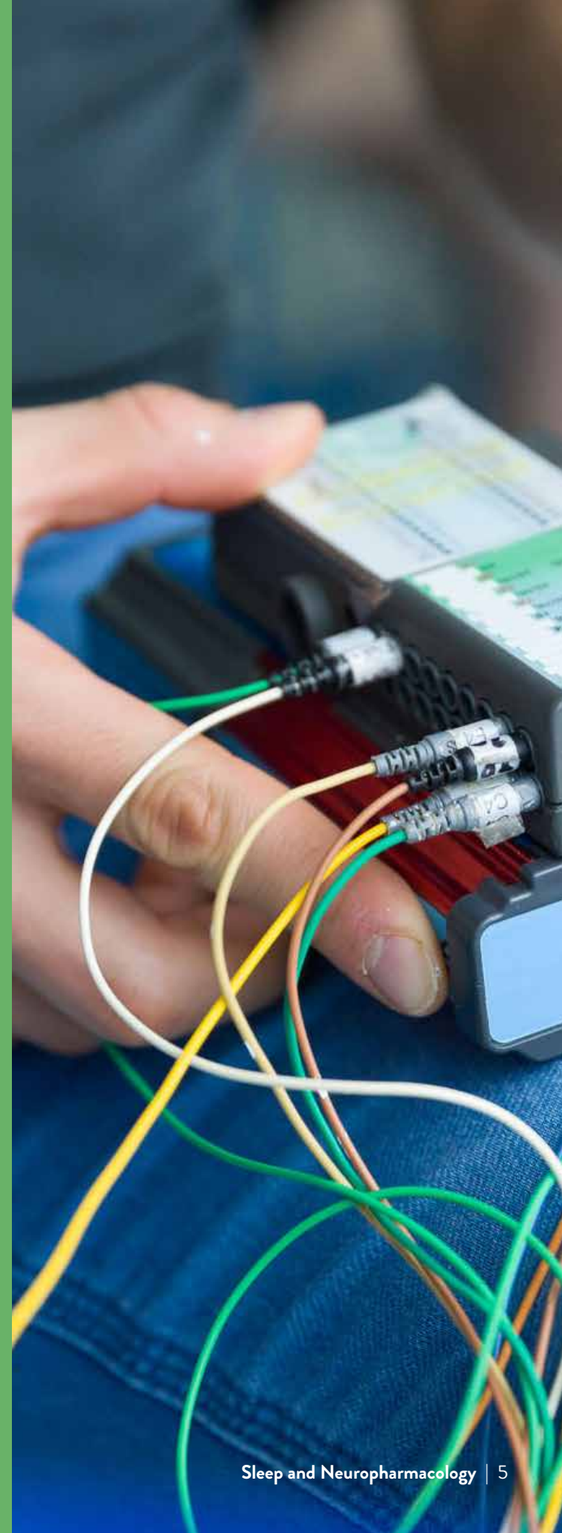
Which neurotransmitter systems are affected by our compound, and how does this affect sleep?

Polysomnography is currently being developed as a sophisticated biomarker that can be used to measure pharmacological CNS effects. Studies using healthy volunteers and patients can provide detailed information regarding the test compound's effects on both the quality and quantity of sleep, as well as providing important insight into the compound's effects on various neurotransmitter systems.

'CHDR has extensive experience with early clinical development of many CNS drugs, including novel orexinergic, histaminergic, and GABAergic compounds, providing comprehensive neuropharmacology data and PK/PD modelling based on research in both healthy subjects and patients.'

Highlights

- CHDR is a pioneer in the study of sleep-aid medications, including the first orexin antagonists.
- We have developed advanced tools for quantifying a compound's effects on the sleep cycle and to model the compound's pharmacokinetics and pharmacodynamics (PK/PD) profile.
- Using these tools, we provide sponsors with detailed information regarding the optimal dose for treating specific sleep disorders.
- Researchers at CHDR also use driving simulators to test whether a sleep medication affects driving performance.
- Combining polysomnography with NeuroCart can provide a comprehensive neuropharmacological profile of a test compound.
- Polysomnography can also be used to examine a compound's precise effects on a wide range of neurotransmitter systems.



Sleep and pharmacology: a closer look

Polysomnography: ‘eavesdropping’ on a subject’s sleep cycle

In order to have a good night’s sleep, a variety of neuronal circuits in the brain must operate harmoniously. Much like a well-conducted orchestra performing a symphony, for peak performance the brain must enter the various stages of the sleep cycle in the correct order. Changes in the brain (for example, due to ageing, biologically active substances, or pathology) can affect this process.

Polysomnography measures several physiological processes during sleep, including electrophysiology (for example, EEG, ECG, and eye movements), breathing patterns, and body movement. By combing these measurements, we can study the architecture of sleep both in healthy volunteers and in patients with common sleep disorders such as insomnia or narcolepsy. Polysomnography can also be used to study other sleep disorders such as obstructive sleep apnoea, periodic limb-movement disorder, and restless legs syndrome.

Quantifying sleep cycles using Markov chain models

The phases of sleep generally change in a stereotypical fashion during the course of the night. Because certain compounds can affect each sleep phase differently, a complex interaction can arise between pharmacokinetics and the time of night. When analysing polysomnography data, researchers can often measure the overall effects of a compound on sleep; however, the optimal release pattern is usually difficult to measure. To overcome this challenge, CHDR teamed up with the Leiden Academic Centre for Drug Research (LACDR) and Uppsala University to develop a Markov chain model of sleep. This model can be used to quantitatively follow an individual through the various stages of sleep, allowing the researcher to determine when the subject will likely transition to the next stage. Polysomnography is then used to visualise these transitions during the course of sleep.

Sleep aids can affect these transitions, and the effect can be correlated with blood levels of the compound being studied. Using the Markov chain model, researchers can predict the drug’s optimal release pattern. This approach can also be used to quantify the effects of CNS medications on specific stages of sleep (for example, the reduction in REM sleep caused by serotonergic compounds).

Profiling sleep aids that target various neurotransmitters
Insomnia and other sleeping disorders are more than just a nuisance. Patients with severe insomnia often have poor quality of life, are less productive, and are more likely to develop a psychological disorder. Yet after nearly a century of research, we’re still searching for the ideal sleep aid. Nevertheless, progress is being made every day, and several promising new compounds may outperform the last generation of sleep aids. These next-generation drugs target different neurotransmitters such as orexin, histamine, serotonin, and GABA. CHDR has extensive experience with early clinical development of many CNS drugs, including novel orexinergic, histaminergic, and GABAergic compounds, providing comprehensive neuropharmacology data and PK/PD modelling based on research in both healthy subjects and patients.

A customised strategy for early clinical development

To answer a sponsor’s specific research questions, CHDR uses a wide range of technologies, including NeuroCart (our comprehensive battery of neurophysiological and neuropsychological tests), polysomnography, PET, MRI (including our cutting-edge resting-state fMRI facility), driving simulators, CSF sampling, advanced biomarkers of inflammation, and much more.

Why choose CHDR?

The Centre for Human Drug Research specialises in early-phase clinical drug research. CHDR's overall mission is to improve the drug development process by collecting as much information as possible regarding the candidate drug in the early phases of development. This information helps sponsors make informed decisions regarding the course of clinical development for their product.

Why choose CHDR?

Research at CHDR covers a wide range of fields, including the central nervous system (CNS) and pain, the cardiovascular system, haemostasis, immunology, and dermatology. In addition, CHDR is at the forefront in developing novel biomarkers and methods for measuring drug-related effects in all of these research areas.

Pharmacology matters

Whether studying a new cognitive-enhancing drug, a next-generation painkiller, or a new monoclonal antibody designed to treat rheumatoid arthritis, the goal is to determine how the compound's effects correlate with both the dose and blood concentration at any given moment. In addition, understanding which biological systems are activated is an essential first step towards quantifying this relationship. At CHDR, our focus on pharmacology is reflected clearly in what we call question-based drug development.

Question-based drug development

CHDR actively uses question-based drug development - or QBD - as a more rational approach to drug development compared to conventional approaches. QBD can be best described as a series of questions that are addressed throughout the process. These questions often seem simple enough, but failing to answer even one question - or even addressing the questions in the wrong order - can have dire consequences. Thus, using this approach can potentially save companies millions of dollars by helping predict a catastrophic issue early in the development process, before the more expensive latter stages (for example, large-scale clinical trials or the marketing phase).

From a general perspective, the most important questions are:

1. Does the biologically active compound and/or active metabolite(s) reach the intended site of action?
2. Does the compound cause its intended pharmacological and/or functional effect(s)?
3. Does the compound cause any unintended pharmacological and/or functional effect(s)?
4. Does the compound have a beneficial effect on the disease and/or clinical pathophysiology?
5. What is the compound's therapeutic window?
6. How does any variability with respect to the drug response in the target population affect the product's development?

Contact

To learn about CHDR's full range of services, contact us today.

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