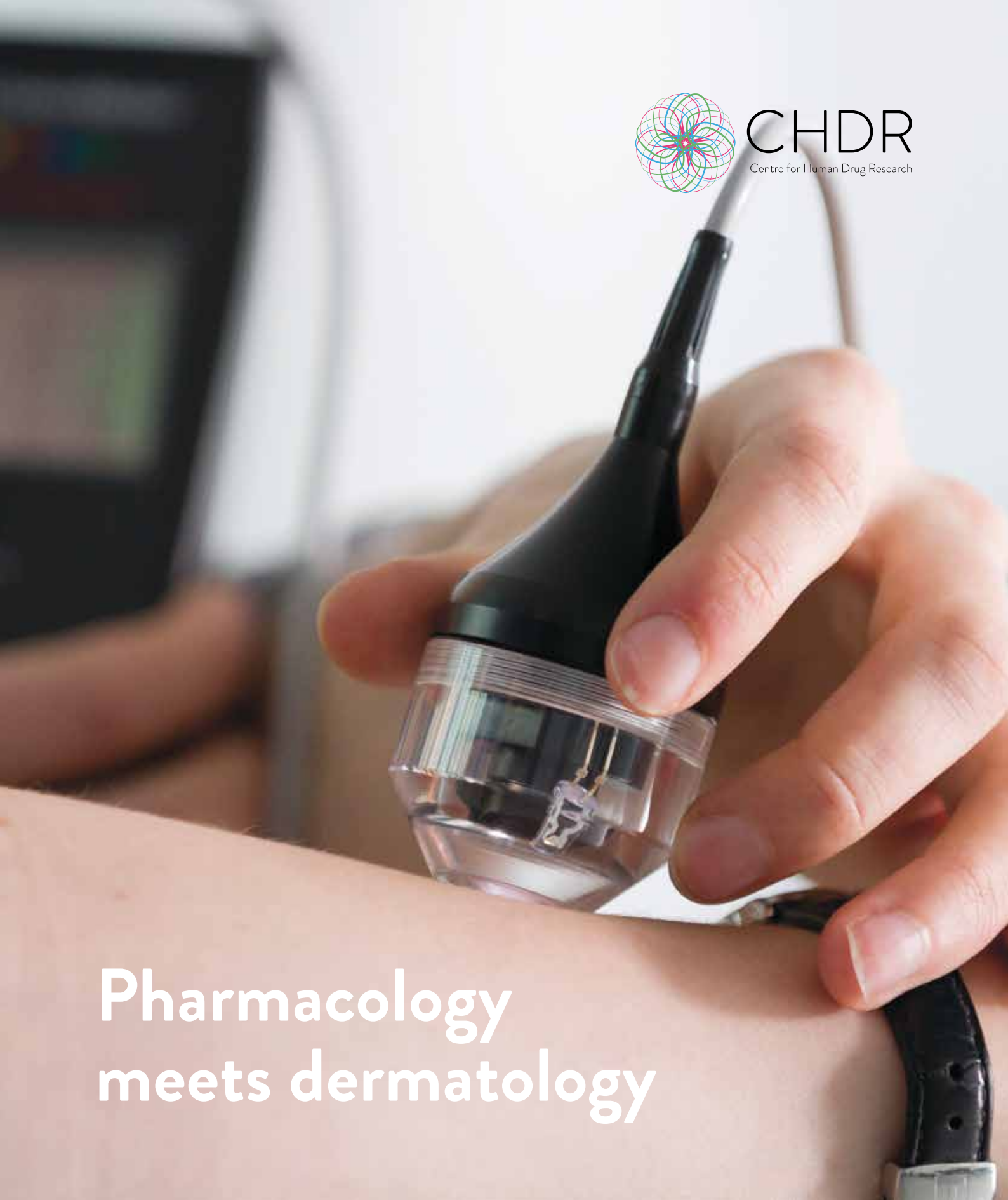

CHDR
Centre for Human Drug Research
Pharmacology
meets dermatology

Pharmacological profiling measures the efficacy of dermatological drugs

In the field of dermatology, CHDR has developed a unique approach to early-stage drug development by combining outpatient trials with innovative new measuring techniques. Although patients come to our facility for selection and follow-up visits, the trial itself takes place off-site, with the patients at home, going about their daily activities.

Our dermatology studies provide results that are more than skin deep. Because the skin is the largest and most easily accessible organ, our dermatology research also facilitates drug development in other areas, including immunology and endocrinology. In addition, CHDR is studying ways to improve wound healing. Thus, CHDR is helping meet the needs of patients everywhere.

Practical answers to important research questions

Does our compound treat the targeted skin condition?

Early in drug development, CHDR can collect a wealth of data regarding the compound's intended and/or unintended effects, even in healthy subjects. This data-intensive approach facilitates rational decision-making regarding the course of drug development. In dermatology 3D photography, total body mapping of skin lesions, objective lesion quantification and other innovative measurements can serve as robust predictors of clinical efficacy.

How well is the compound absorbed, and how is it eliminated?

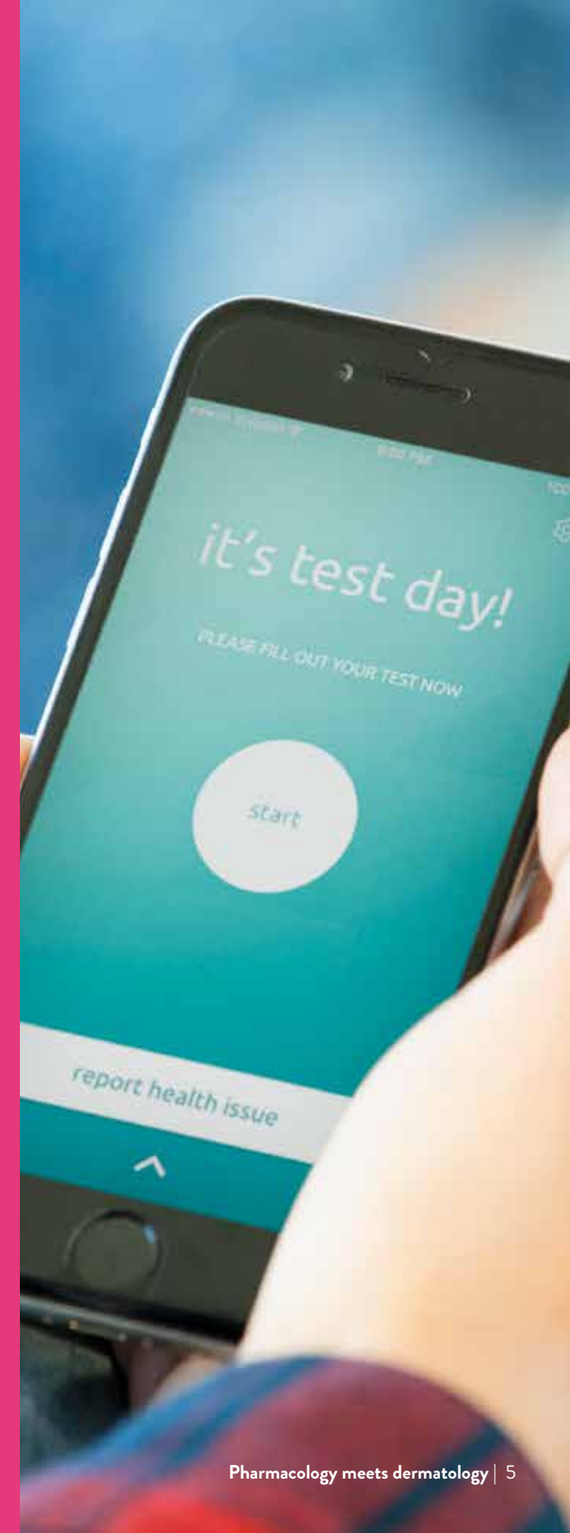
Pharmacokinetics is one of CHDR's main areas of expertise, and CHDR researchers study systemic absorption in the initial clinical phases of drug development. This proactive approach allows researchers to minimise the risk of adverse systemic effects in subsequent trials, which is particularly important when patients apply the compound at home.

Does our compound have anti-inflammatory properties?

In recent years, CHDR has selected and validated a comprehensive panel of biomarkers for measuring inflammation *ex vivo*. In addition, we have developed several pharmacological and mechanical challenge models to study inflammation. Using these approaches, we can measure the effects of both systemic and topical drugs against allergy and/or inflammation in healthy volunteers.

Highlights

- CHDR conducts clinical trials in dermatology in order to study targeted drug delivery and treatment of a wide range of dermatological conditions, including psoriasis, eczema, and premalignant lesions.
- The majority of our dermatology trials use Trial@home, our unique approach to outpatient research.
- Our customised, user-friendly apps for smartphones and tablets ensure patient compliance and help researchers monitor the lesion and the patient's daily activities.
- CHDR has a comprehensive set of tests and measurements, including 3D photography, transepidermal water loss, total body photography, Raman spectroscopy, and laser Doppler imaging. Using these techniques, the pharmacological effect of systemic compounds can be measured in the skin, including inflammation, blood flow, pain and irritation, and other parameters.
- The study compound can be applied topically transdermally, intradermally, or subcutaneously, and CHDR can study both local pharmacokinetics and the compound's effects on the skin.
- Wound healing can be studied at the biophysical, biochemical, and clinical levels, as well as from the patient's perspective.



Dermatology studies: a closer look

At CHDR, we approach pharmacology and dermatology from multiple angles. We study treatments for dermatological conditions such as psoriasis, eczema, allergic reactions, and inflammation using methods and biomarkers to objectively monitor the clinical response. Using these approaches, we can measure the effects of transdermal and intradermal drugs on the skin. On the other hand, we can also study systemic conditions by monitoring responses in the skin, for example by measuring nerve fibre conduction, surface blood vessels, and local inflammation.

Increased patient compliance and improved data quality with Trial@Home

To accurately and consistently measure the effects of a new dermatological treatment, the compound must be applied at regular intervals for several days, and each subject's compliance with the protocol must be documented. That's why CHDR developed Trial@Home. With this approach, patients visit CHDR for an initial examination. If the patient meets the study's inclusion criteria and provides informed consent, he/she then receives the study medication, instructions for its application, and an app customised to meet the specific needs of the study. This app plays a key role in ensuring:

- **patient compliance:** the app prompts the patient to apply the medication at designated times;
- **documentation:** the patient uses the app to take a picture of the treatment area, confirming that the medication was applied correctly and at the correct time; and
- **data collection:** using the app, the patient answers questions about daily complaints such as pain, itching, and/or irritation, as well as questions regarding quality of life.

All of the data collected with the app are encrypted and securely transferred to CHDR at regular intervals. If a patient does not send data for several days, he/she can be contacted by the project leader. Trial@Home has been used successfully for several clinical studies conducted in recent years, and we've found that it significantly increases both patient compliance and the quality of the data.

Objectively measure skin lesions using DermaToolbox

In addition to measuring the patient's subjective experience (for example, pain, discomfort, and ease of application), objective measurements also play a key role in assessing the effects of a new dermatological treatment. Therefore, we combined several robust techniques commonly used for dermatology research to create DermaToolbox, a comprehensive set of objective measurements and instruments used to systematically quantify subjective symptoms.

In addition to conventional clinical photography, DermaToolbox uses high-definition 3D photography to measure the lesion's dimensions, properties, and surface features. This powerful method – which was originally developed for use in the cosmetics industry – has quickly become an extremely valuable tool for studying dermatological conditions. DermaToolbox also includes a wide variety of methods for objectively measuring the compound's effects on the skin, including transepidermal water loss, lipid profiling, colorimetry, and laser Doppler imaging (see Table 1). In addition, our Biomarker group can develop biomarkers to address specific research questions.

Tool	Measures	Application
Clinical photography	Lesion size and appearance	Objectively assess the clinical course
3D photography	Lesion dimensions and surface features	Obtain additional objective information regarding the clinical course
AquaFluxTM	Transepidermal water loss	Measure the epidermis' barrier function
Colorimetry	Erythema	Measure inflammation
Laser Doppler imaging	Blood flow in the dermis	Measure erythema in inflammation, study capillary flow (e.g. in sickle cell disease)
Fourier-transformed infrared spectroscopy	Lipid organization in the stratum corneum	Measure drug penetration and the influence of interventions on skin lipids
Raman spectroscopy	The profile of the epidermal layers	Monitor the drug's penetration into the epidermis
Lipid profiling (LC-MS)	The composition of lipids in the epidermis	Monitor treatment effect
Total body photography	Lesion size and/or severity	Monitor the extent of the lesion; lesion documentation
Mobile app	Treatment compliance, adverse events, lesion status, patient-reported outcome	Take photos of the lesion off-site, Trial@home, documentation, pruritus, quality of life, monitor and document the site of administration
Thermography	Temperature (with high resolution)	Wound-healing kinetics
Transdermal patch analysis	Skin surface biomarkers	Monitor biomarkers
Punch/shave biopsy	Epidermal/dermal markers, histology	Monitor morphology and biomarkers
Transdermal penetration	Pharmacokinetics	Measure drug delivery
Skin microbiome	Cutaneous microbiome	Monitoring of the drug effect on microbiome

LC-MS, liquid chromatography–mass spectrometry

Table 1: CHDR's DermaToolbox

Pharmacokinetics at the systemic and local levels

With dermatological medicines, systemic uptake of the compound's active ingredient(s) is an important concern, particularly if the ingredient has potent systemic effects. CHDR can measure systemic penetration by applying the test compound to a 10 cm x 10 cm patch of skin, then collecting blood samples for measuring both systemic uptake and elimination.

Within the skin, treatment efficacy depends largely on the level of active molecules that reach the target receptors. Although classic pharmacokinetics – which is based on a systemic approach – has little value with respect to measuring local pharmacokinetics, it is still possible to analyse how much of the compound reaches the intended site of action. CHDR uses state-of-the-art techniques such as Raman spectroscopy to measure the concentration of the test compound in each layer of the epidermis.

Mimicking skin conditions in healthy subjects

Even in the earliest testing phases of a new dermatological compound, CHDR can generate valuable data regarding pharmacological effects using healthy subjects. We developed several so-called 'challenge models' to mimic conditions such as inflammation and allergic dermatitis (see Table 2). For example, a patch of skin can irradiated with low levels of ultraviolet light, producing mild, harmless erythema. In another model, increasing concentrations of histamine are injected intradermally, mimicking a mild allergic response. With these models, extreme care is taken to minimise the subject's discomfort. When the skin develops a clear response, the test medication is applied and its effect is measured.

DermaToolbox

Biophysical (TEWL, Raman, Thermography)	**Clinical** (standard assessments)
Biochemistry (biomarkers in biopsy)	**Patient reported** (QoL, VAS, cosmetic)
Imaging (2D, 3D, fluorescence, PET)	**Technology enhanced** mobile apps

→ **PK**

→ **Wanted effects (PD)**

→ **Unwanted effects (AE)**

TEWL: transepidermal water loss | QoL: quality of life | VAS: visual analogue scales

The skin as a route of administration

Many systemic medications, vaccines, and biologicals can be applied transdermally and/or intradermally. These delivery routes can have several distinct advantages, for example delivery without the need for an injection, which is preferred in children and patients with a fear of needles. Therefore, CHDR works closely with several research groups to develop new techniques for improving transdermal absorption.

On the other hand, delivery via the skin can also cause adverse reactions. A classic example of this phenomenon is injection-site reaction following chronic treatment with oligonucleotides. Therefore, CHDR uses DermaToolbox (see Table 1) to objectively monitor possible skin reactions and helps sponsors develop ways to prevent or minimise side effects.

Wound healing

Despite recent advances, most interventions that promote wound healing are relatively ineffective, as the wound-healing process is poorly understood. Moreover, many patients develop wounds or other skin lesions that heal extremely slowly. At CHDR, we're studying the process of wound healing, and we're developing ways to accelerate – or, if needed, slow – the healing process. For example, our researchers use immunohistochemistry to study small wounds caused by performing a skin biopsy. After the wound heals, a second biopsy is performed at the same site, providing a detailed microscopic picture of the lesion.

Together with partners in academia and industry, CHDR also studies keratinocytes in vitro and is investigating new ways to 'grow' human skin for clinical applications.

Challenge	Condition induced/mimicked	Application
Capsaicin	Erythema, hyperemia	Pain assessment
Histamine	Dose-dependent 'wheal and flare' reaction	Assess the potency and duration histamine receptor antagonists or anti-inflammatory drugs
Mechanical (tape strip/shaving)	Removal of the stratum corneum and hair	Induce local inflammation, increase drug delivery
UVB irradiation	Erythema	Pain assessment, skin sensitisation
TLR7 agonist (e.g. imiquimod)	Local inflammation	Assess the effect of anti-inflammatory compounds
PAC1 receptor agonist (e.g. maxadilan)	Local inflammation	Assess the effect of PAC1 receptor antagonists
LPS/SEB challenge	Local TLR challenge	Inflammatory response/inflammasome activation

LPS, lipopolysaccharide; PAC1 receptor, pituitary adenylate cyclase-activating polypeptide type I receptor; TLR, toll like receptor; SEB, Staphylococcus aureus enterotoxin-B; UVB, ultraviolet B

Table 2: Pharmacological challenges in skin research

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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