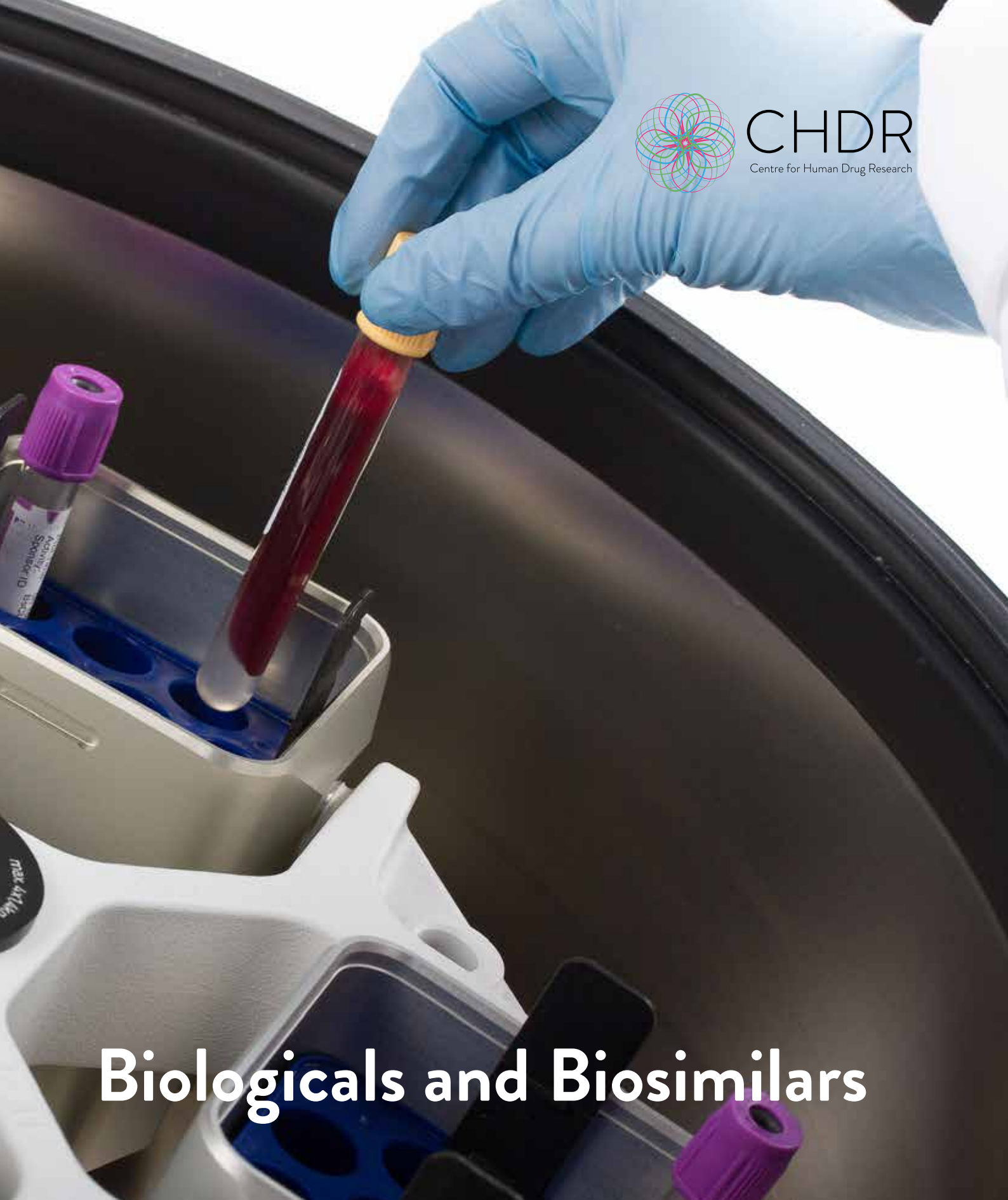


CHDR
Centre for Human Drug Research

Biologicals and Biosimilars

Adding more value to early clinical research

CHDR has more than 25 years of experience using biologicals and biosimilars. Even in the earliest stages of clinical development, we can demonstrate the pharmacological effects of biologicals and/or biosimilars in healthy subjects, thereby providing sponsors with key information for rational decision-making.

Practical answers to important research questions

What happens to our compound after it's administered?

Because most biotherapeutics are relatively large molecules, predicting their behaviour in the body can be challenging. At CHDR, we use pharmacokinetics and pharmacodynamics (PK/PD) modelling to provide sponsors with the information they need to plan the next steps in clinical research.

Are the compound's unintentional side effects due to impurities, or are they inherent to the compound's mechanism of action?

CHDR uses both *in vitro* and *ex vivo* approaches to determine whether a biological compound is likely to exert an undesired effect *in vivo*, and – if so – whether this effect is due to impurities or the compound's pharmacological activity.

Is our biosimilar equivalent to – or even better than – the original patented drug?

Confirming bioequivalence (i.e. comparable pharmacological activity) is an important step when developing a product designed to replace an existing biotherapeutic. CHDR has developed methods to test bioequivalence early in the drug development process, thereby providing important information to help guide development.

'Developing biologicals – often requires finding the right approach to answer the right questions. In this respect, CHDR has extensive experience using a wide range of approaches.'

Highlights

- Using specifically targeted biomarkers, CHDR can demonstrate the pharmacological effects of biopharmaceuticals early in clinical drug development, even in healthy subjects.
- The outcome of first-in-human studies provides a stronger basis for establishing dosage and safety profiles in future studies involving patients.
- CHDR has extensive experience addressing species specificity, immunogenicity, and unpredicted side effects, as well as establishing the starting dose, thereby optimising safety.

Biosimilars:
a closer look

Experience with a wide range of products

Biotherapeutics include a highly diverse array of biologically active compounds. Some of these compounds are produced in animals, bacteria, or cultured cells, whereas others (for example, nucleotides) are synthesised chemically. CHDR has a long history of studying biologicals, including antibodies, lipoproteins, RNA, and DNA, and many of these compounds were first administered to human subjects at CHDR.

For example, CHDR performed the first-in-human studies of a promising new drug for ApoA-1 Milano, a biologically produced apolipoprotein used to treat atherosclerosis. These studies helped establish a safe dose for use in human subjects. CHDR then studied ApoA-1 Milano in patients with stable coronary artery disease.

A wide range of approaches

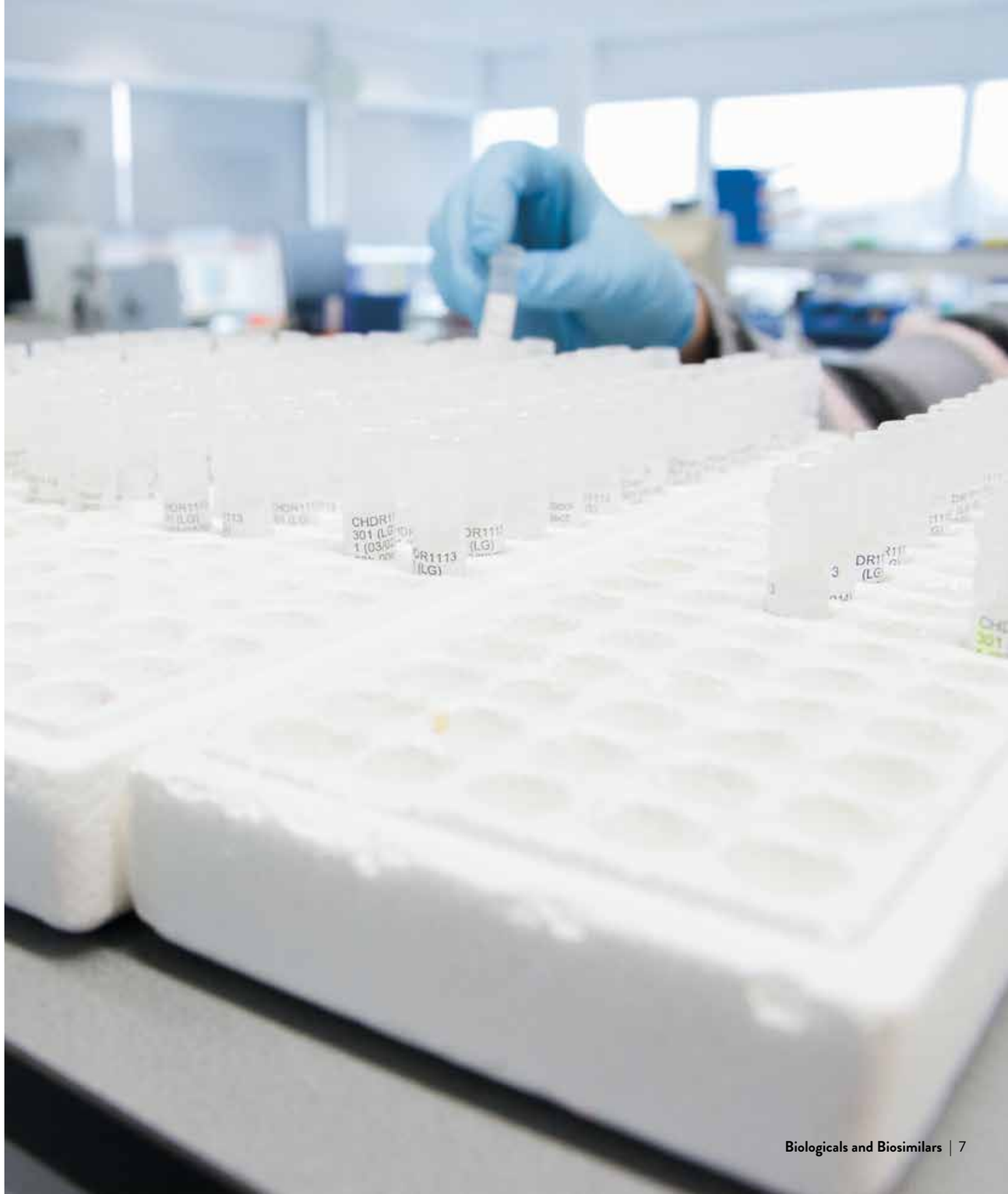
The drug development process – particularly when developing biologicals – often requires finding the right approach to answer the right questions. In this respect, CHDR has extensive experience using a wide range of approaches. Building on our expertise in clinical pharmacology, biomarkers, and study design, we work closely with the sponsor to develop the optimal approach.

Biosimilar, or 'biobetter'?

CHDR specialises in developing biomarkers that can demonstrate whether a compound is pharmacologically active, even in healthy subjects. These biomarkers can then be used to compare the activity of a putative biosimilar with the original compound. In some cases, this analysis can reveal whether a new compound is even more effective than the original. Because market authorities (e.g., the FDA and EMA) prefer early evidence of bioequivalence, obtaining this information early can facilitate future research in patients.

The naked truth: pharmacological effect or preventable impurity?

Because the process of synthesising most biotherapeutics requires the use of complex biological systems, the end product can contain small – yet biologically relevant – levels of contaminants. Moreover, some biologicals can form aggregates. These factors can cause undesired effects in subjects. If this occurs in the early stages of clinical testing, it can have serious consequences regarding the compound's clinical development. Therefore, CHDR has established a comprehensive panel of biomarkers and bioassays for detecting impurities and potential undesired effects. Importantly, CHDR has access to a comprehensive set of human immune cells that express reporter genes for monitoring the activity of immune pathways. Screening a new compound can reveal whether it might exert unwanted effects, and it can help reveal the underlying cause, thereby significantly improving early drug development.



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.

+31(0)71 524 64 00

info@chdr.nl

www.chdr.nl