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Article

Understanding the In-Vitro/In-Vivo Relationship (IVIVR): Inhaled Medicinal Products

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IVIVR modeling leverages in-vitro testing knowledge toward predicting in-vivo testing results, often reducing long-term development costs by facilitating more informed decision making during drug development.

In-vitro/in-vivo relationship (IVIVR) modeling can help researchers and product developers understand and predict clinical outcomes. IVIVR modeling, applied intuitively, allows a correlation between clinically relevant in-vitro test data and in-vivo test data with the aim of providing a more accurate prediction of the actual lung dose. These data can ultimately provide confidence in expected pharmacokinetic (PK) study outcomes for the comparison of two products or improve dose-finding study designs during early phase clinical studies, as well as potentially reduce development cost and timelines.

Standard in-vitro methodology can demonstrate product stability and provides directional information toward how much drug is delivered to the lung or deposited in the throat; however, predictions of product performance in-vivo are improved with more clinically relevant data. The emergence of new IVIVR tools and methodologies in recent years, combined with access to clinically relevant in-vitro data and significant historical and ongoing in-vivo knowledge, allows us to bridge this knowledge gap in a more meaningful way, de-risking the clinical program.

One such tool is in-silico modeling that estimates "*regional deposition of inhaled aerosols in the human respiratory tract*," information used to model PK outcomes. The use of in-silico modeling also advances our understanding of the impacts of inhalation profiles, the timings of dose release, and variances in physiology from patient to patient (i.e., the effects of different absorption and clearance rates).

IVIVR modeling applies to the development of any inhaled dosage form since it closes knowledge gaps, speeding up the development process. This methodology has been most effective in the development of products requiring bioequivalence (BE), wherein a PK outcome can be modeled using clinically relevant data to "close the loop" — to understand the clinical data, redevelop the product, re-run simulations, and minimize the number of PK studies necessary; refer to Figure 1.

As illustrated in Figure 1, prudence dictates having as much in-vitro confidence as possible before conducting the PK study to avoid another product design loop that requires another PK study. Accordingly, an approach that utilizes clinically relevant in-vitro data for in-silico modeling, using the findings to run smaller-scale PK studies, is a powerful tool to guide product development.

IVIVR in Practice

Consider an inhaled drug delivery product in development. *Clinically relevant in-vitro testing* is conducted to analyze, for example, various inhalation profiles and *anatomical throat models*, as well as different firing angles and dose release timing. These data are used as inputs for in-silico modeling to generate regional deposition data. In turn, these regional deposition data are used to model the PK outcome, which is dependent on several factors linked to the individual compound properties and a patient's physiology.

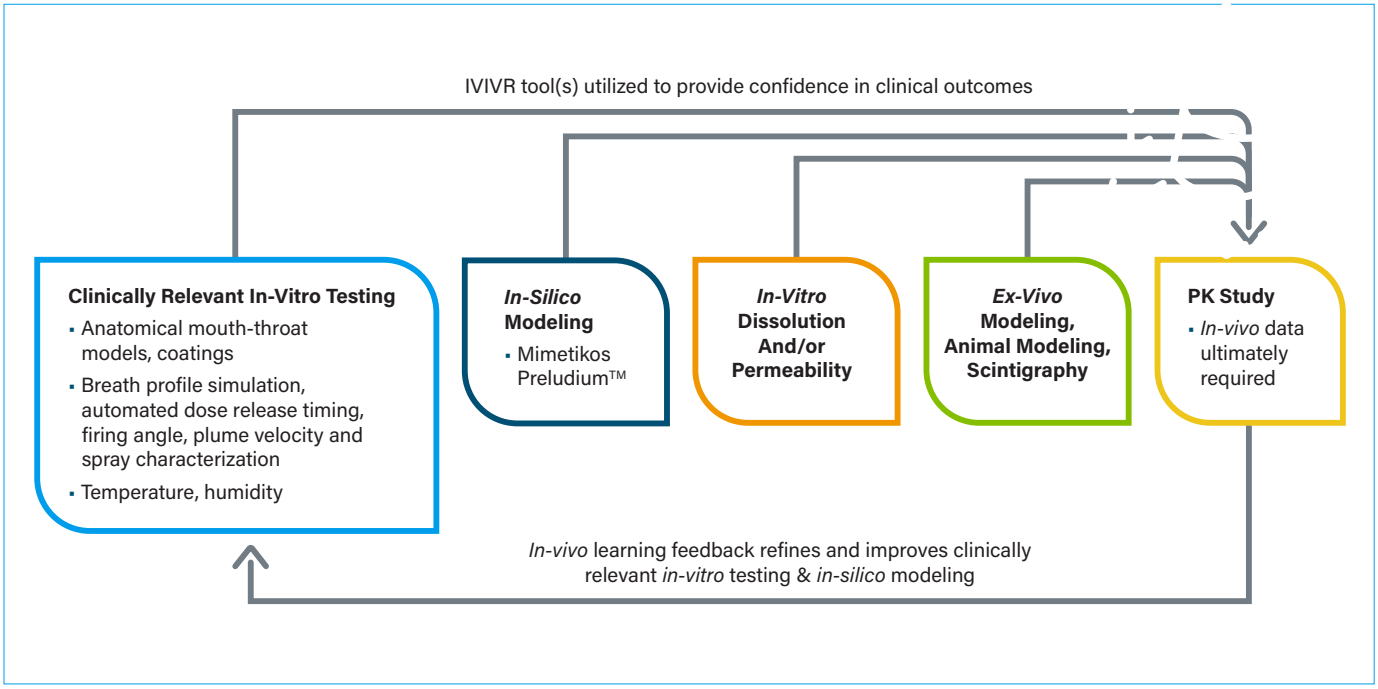
Clinically relevant testing and IVIVR also apply to drugs delivered systemically — perhaps even more so than local delivery — because of the information they provide up front and their potential to reduce the sponsor's clinical work to define the target dose. The vital factor is when such testing would be most beneficial to the development program (e.g., to inform the design of dose-finding studies).

While it remains difficult to reduce the clinical work associated with new product development (as opposed to generic product development), using these tools can inform better design of those studies. Whether used to evaluate novel excipients, formulations, or novel devices, in-silico modeling can enhance product understanding and achieve outcomes that were planned for in the clinical study.

As these techniques develop, regulatory agencies are likely to begin acknowledging their benefit to a greater extent, bolstering their usefulness for both generic and new product development. In recent years, regulators have started discussing the use of in-vitro data packages to show bioequivalence and whether tools like in-silico modeling would help regulators accept such a data package.

In 2019, the FDA issued *a draft guideline on beclomethasone dipropionate* inhalation aerosol in which the agency has suggested that alternative in-vitro and in-silico methods, such as those described in this article, may be used in place of the

FIGURE 1. Integration of IVIVR modeling into the development process



traditional comparative clinical endpoint study. While the example is specific, it is a step in the right direction and reinforces the FDA's commitment to increasing access to generic alternatives for complex drugs, noted as a key area of focus for the agency in its 2021 *Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science (FARS)* report.

Kindeva's IVIVR Expertise

Kindeva can demonstrate a client's product is capable of being developed into an inhaled product supporting all aspects of feasibility, development, regulatory approval, through to commercialization. While other organizations offer some specialist services in this area, Kindeva can provide the unique capability to holistically integrate a combination of clinically relevant in-vitro testing, in-silico modeling, and clinical feedback within a development program. Understanding the impact of variability in the clinic helps study designers develop advantageous clinical controls and protocols that minimize subject variability to isolate the drug's impact.

While historically Kindeva's focus has been metered dose inhaler (MDI) development, we apply a range of tools to thoroughly comprehend and aid the development of diverse inhalation products, including dry powder inhalers (DPIs) and soft mist inhalers (SMIs). This broad experience supports an understanding of how we can improve or change product performance.

Consider, for example, Kindeva's *development of an MDI to match an SMI*. We were able to depict the relationship, through in-vitro testing, between a chlorofluorocarbon (CFC) MDI, a hydrofluoroalkane (HFA) MDI, and an SMI. We used these data to develop a product, which subsequently underwent clinical testing to generate PK data. BE was exhibited for the HFA MDI, showcasing the ability to repurpose existing active pharmaceutical ingredients (APIs) in other delivery device formats.

Kindeva is expanding its in-silico modeling expertise through a knowledge transfer partnership (KTP) project with Loughborough University (U.K.). The project seeks to understand the physics involved in spray generation using computational fluid dynamic (CFD) simulation of more sustainable propellants with lower Global Warming Potential (GWP) than existing currently marketed HFAs. The partnership's goal is to "predict spray parameters and characteristics from first principles, such as regional deposition, droplet size, and velocity … to design faster and more reliable low-GWP pharmaceutical products." Eventually, a combination of CFD and in-silico modeling that estimates regional deposition of inhaled aerosols could lead to a completely virtual prediction of clinical study outcomes.

Final Thoughts

IVIVR modeling is not just about progressing from point A to point B in a drug development process. It is a means to apply knowledge gleaned during in-vitro testing — conducted in a laboratory with a cascade impactor and ancillary equipment — toward emulating a patient taking that drug product. It provides value in the form of sound scientific knowledge explaining that data, often reducing long-term development costs by preventing additional product design cycles.

Kindeva's capability to perform IVIVR modeling in-house, supported by our in-vitro testing and in-vivo experience, provides our clients an unmatched opportunity to evaluate their products. It also makes Kindeva a partner well-positioned to guide clients through novel approaches and the use of alternative methodologies to support inhaled product development, as well as product registration, in the most efficient manner possible.

About the Authors

Neha Patel is a chemistry, manufacturing, and controls (CMC) specialist with a track record in the successful development and approval of multiple inhaled products over the last 20 years. More recently, she has taken leadership of Kindeva's IVIVR effort with the aim of keeping abreast of industry and regulatory advances in this area for the benefit of future development projects and clients.

Andy Cooper is a research specialist responsible for driving new ideas and providing broad subject matter expertise to resolve critical issues during complex inhalation product development. He has nearly 20 years of experience within the inhalation field. Andy represents Kindeva on multiple sub-teams of the European Pharmaceutical Aerosol Group (EPAG) and has contributed to several peer-reviewed publications.