The Pebble Drug Evaluation Hub

Executive Summary

Pebble are disrupting and modernising the drug development roadmap from the lab to clinical trial approval with the **Drug Evaluation Hub**. Our **LIVING-ORGAN** systems closely replicate human physiology so accurately that you can expect a significant increase in preclinical research efficiency, reducing both time and costs **x10**. We bypass animal testing approaches, far exceeding ethical standards while providing better human-relevant data. This white paper explains how the future of drug development will be precision, speed, and ethics.

Introduction

The transition from preclinical assessment to approved drug is one of the most challenging passages in drug development, with a success rate of **less than 1%**. The foundational tools for preclinical testing - namely, in-vitro assays and small animal models - have long been the bedrock for initial evaluations. Yet, these methods present significant **limitations** in **translational validity** when predicting human outcomes. While small animal studies offer convenience and cost-effectiveness, they often fail to replicate human physiological responses due to interspecies differences. Consequently, promising therapeutic candidates may be prematurely discarded or, conversely, advanced without sufficient understanding of their potential effects in humans.

On the other end of the spectrum, large animal models offer **greater physiological resemblance** to humans and are considered more predictive. However, these models come with their own set of challenges. Not only are they associated with **higher financial costs** and longer study durations, but they also raise complex **ethical** considerations that necessitate rigorous justification under the principles of humane scientific research. The balancing act between predictive accuracy, ethical responsibility, and the economic and temporal expense of large animal studies has created a **bottleneck** in the progression of drug candidates.

As the drug development industry confronts these challenges, the call for a **new paradigm** is clear. A more effective toolbox is urgently needed - one that bridges the gap between traditional preclinical models and human biology. This new suite of tools must not only predict clinical outcomes more accurately but also operate within an ethical framework that aligns with the growing emphasis on animal welfare. It is within this context that **Pebble's Drug Evaluation Hub** will redefine the landscape of preclinical drug development.

Advancing Preclinical Models

Our **LIVING-ORGAN** systems enable a direct analysis of how therapeutic agents behave in human-like physiological conditions. By simulating drug responses across isolated or systemically connected organs, we provide crucial data that can **predict clinical efficacy** and **safety** with greater accuracy. Our systems represent a significant step forward, allowing researchers to observe the effects of drugs on organ physiology, in real time.

A Standardised Approach

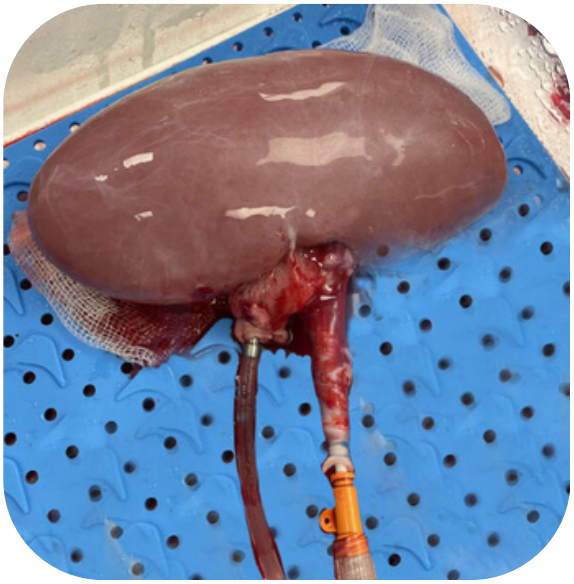
We can undertake standard drug development processes - pharmacokinetics (PK), pharmacodynamics (PD), toxicology, safety assessments, and drug-drug interactions - with a level of **precision** and **translational relevance** that small animal models cannot match.

Our PK assessments provide a detailed view of a drug's journey through the body. We can track how drugs are **absorbed**, **distributed**, **metabolised**, and eventually **excreted**, offering data that closely predicts human responses. With PD studies, we map out the therapeutic effects of drugs, observing their **efficacy** and integrating **biomarker analyses** to understand mechanisms at play. Toxicology studies elucidate the **pathophysiological changes** underlying these effects, beyond simple toxicity, thereby providing deeper insights for safer drug design. Our safety evaluations encompass a comprehensive assessment of potential **adverse reactions** across various organ functions, ensuring drugs that advance to clinical trials are backed by solid safety profiles. We can also explore **drug-drug interactions** in an integrated multi-organ context, reflecting the true nature of human metabolism and excretion.

The superior translational value of the data generated through our LIVING-ORGAN systems means that researchers can make informed decisions **earlier** in the drug development process, improving the **predictability** of clinical trial outcomes and enhancing the overall **efficiency** of drug development. Our approach represents a leap forward in preclinical research, setting a new standard for developing safe, effective therapeutics with an assurance that comes from our systems' closeness to human biology.

Fail - Iterate - Repeat

A globally unique element to the LIVING-ORGAN system is that it allows **iterative testing** in the initial stages without the need for regulatory reporting in the future. This means that compounds can be **rapidly optimised** based on robust scientific evidence. Our approach not only speeds up the development cycle but also does so in a way that maintains **confidentiality** and **integrity** of the research process.



A Uniquely Ethical Approach

The Hub's strategy aligns with the industry drive towards more predictive and humane research methods. By utilising organs that are ethically sourced, we maintain a focus on **reducing animal usage** in line with the 3Rs principle. Our data serves as a valuable bridge between in-vitro studies and clinical research, ensuring that promising drug candidates are given the best chance for successful development.

After Non-Reportable Analysis - The Regulatory Pathway

Regulatory agencies are increasingly attentive to the contributions of ex-vivo systems in providing predictive and human-relevant data, beyond what traditional in-vitro or animal models can offer. All components within Pebble's LIVING-ORGAN systems are universally **approved for human use**, which reinforces the reliability and applicability of the data produced.

The FDA's Centre for Drug Evaluation and Research (CDER) and European counterparts like the EMA and MHRA are advocating for alternative testing methods that **reduce** or **replace animal use**. The LIVING-ORGAN systems can therefore serve as pivotal tools for safety and efficacy assessment, adhering to the **3Rs principle** (Replacement, Reduction, Refinement) by utilising organs sourced from the food industry in a responsible manner.

We can produce integrated data that aligns with the FDA's **Predictive Toxicology Roadmap** and **EURL ECVAM's** support for advanced models in risk assessment, bolstering the weight-of-evidence approach. Moreover, regulatory bodies accept pharmacokinetic and pharmacodynamic (PK/PD) data from such innovative models, with Pebble's platforms poised to become integral in PK/PD modelling due to their close mimicry of human responses.

Furthermore, the identification and validation of **biomarkers** through these systems are seen as a significant advantage, as evidenced by the FDA's biomarker qualification programs. The LIVING-ORGAN system has consistently mirrored human responses to stimuli, indicating its potential for recognizing new biomarkers that could be pivotal in drug development and regulatory submissions.

For Advanced Therapy Medicinal Products (ATMPs), which often lack established preclinical models, these ex-vivo systems offer invaluable insights into **safety** and **efficacy**, with regulatory frameworks already in place to consider such innovative approaches.

As the industry moves forward, Pebble is committed to ensuring that the data generated by their LIVING-ORGAN systems are recognized and valued by regulatory authorities, further emphasising the need for early engagement with these bodies to **align preclinical data** with **regulatory expectations**.

Conclusion

Pebble are **disrupting** and **modernising** the drug development roadmap from the lab to clinical trial approval with our Drug Evaluation Hub. Our LIVING-ORGAN systems closely replicate human physiology so accurately that you can expect a significant increase in preclinical research efficiency, reducing both **time** and **costs x10**. We bypass animal testing approaches, far exceeding ethical standards while providing better human-relevant data. The future of drug development is **precision**, **speed**, and **ethics**.