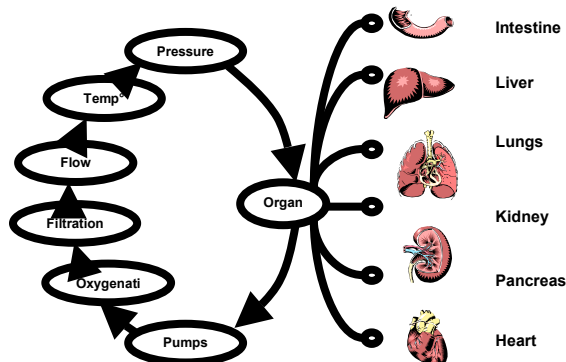


## Ex Vivo Metrics™ by Bowman Research Inc

Bowman Research (Bowman) is a research-based organization that provides a unique service to Pharmaceutical and Biotechnology companies. Bowman conducts whole organ perfusion studies for drug development using its proprietary Ex Vivo Metrics™ technology. Such studies can markedly improve decisions on lead product candidates and speed up development of new medicines. Through perfusions of human kidney, liver, intestine or lung, information may be derived on the absorption, disposition, metabolism, excretion, efficacy and toxicity of candidate drugs and that information will be highly relevant to the way in which the molecule is likely to behave in human clinical trials and beyond.



Bowman uses ethically-donated-for-research human organs that are made available through the transplant program in the United States and that are unsuitable for transplant

To date, Bowman has concentrated its efforts on establishing viable perfusion systems. The organs selected for study are those principally involved in absorption (gut and lung), metabolism (liver, gut and lung), tissue accumulation and clearance (liver, gut and lung) or those which could be key sites for efficacy (lung) or toxicity (liver).

Ex Vivo Metrics works on ex-vivo organs with intact blood supply that, apart from aspects of innervation and inter-organ dependence, mimic the in vivo state with few extrapolations or assumptions. The studies are designed to provide test systems, as close to the clinical situation as possible, to permit investigation of particular aspects of the development of candidate drugs without the need for human dosing and any

*As a predictive tool for drug candidate selection Ex Vivo Metrics may*

- *Confirm authenticity of in vitro data*
- *Overcome uncertainties of species differences*
- *Early benefit / risk assessment of alternative drug candidates*

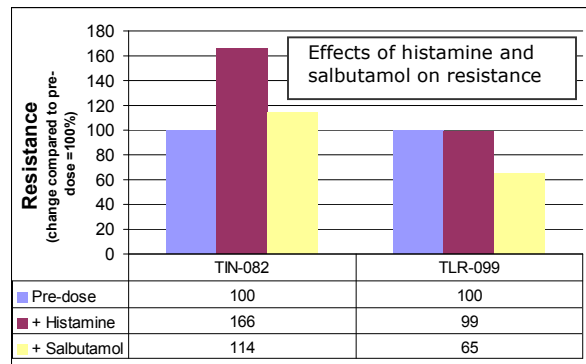
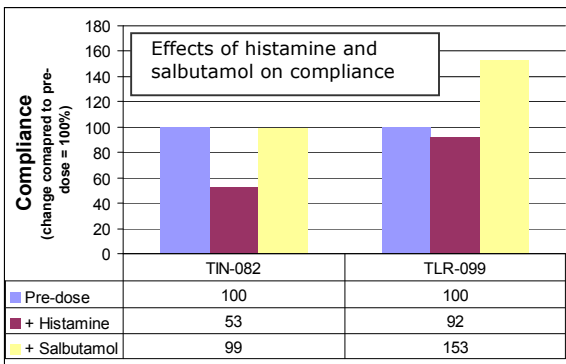
attendant risks. Such studies are individually designed to provide answers to specific issues arising during the development of particular compounds by many, if not most companies.

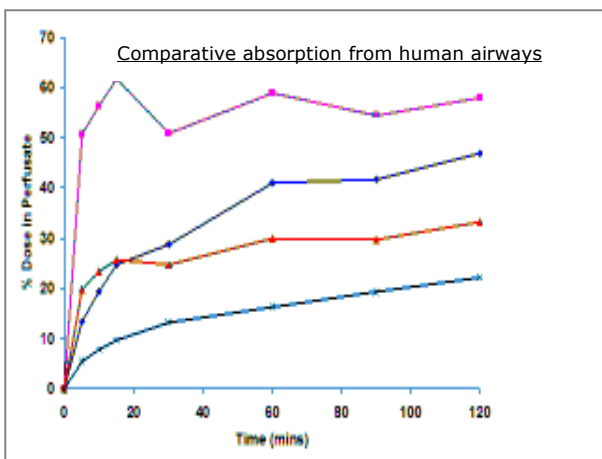
The following table illustrates the advantages of Ex Vivo Metrics relative to other test systems that are commonly used. Ex Vivo Metrics is functionally superior to tissue and cell-based assays, more relevant to humans than studies using whole animals and arguably the next best thing to a human clinical trial without actually doing one.

	Human Ex Vivo Metrics™	Whole animal	Animal Ex Vivo Perfusion	Organ Baths	Tissue Slices	Cells	Sub-cellular systems
Relevance to Human Species	●			●	●	●	●
Physiological functions	●	●	●				
Nervous	○	●	○				
Hormonal	●	●	●	●			
Vasculature	●	●	●				
Full cell complement	●	●	●	●	●		
Extracellular Matrix	●	●	●	●	●		

### Ex Vivo Metrics Protocols

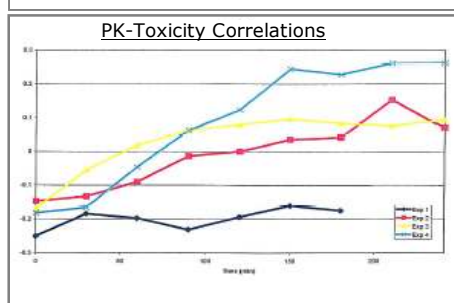
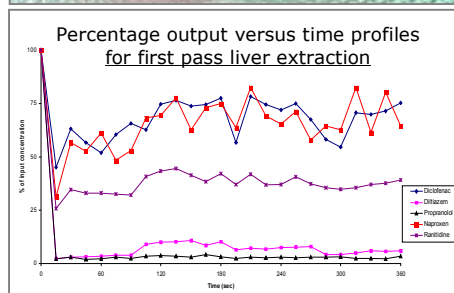
**Human lung** - We can mimic inhaled delivery of drugs and measure effects on functional performance in perfused human lung preparations. For example changes in compliance and resistance can be measured following histamine challenge as shown below, as well as the performance of a drug designed to reverse these effects (in this case salbutamol).





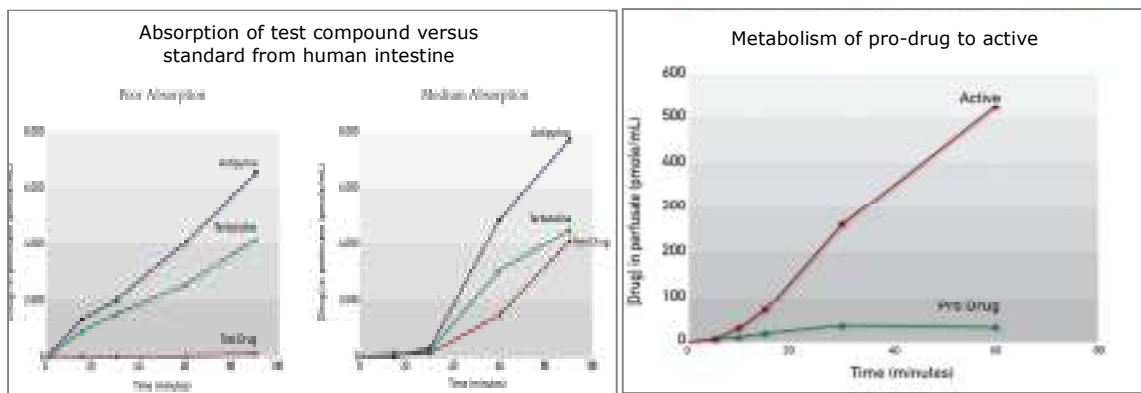
By measuring the concentration of drug (and metabolites if appropriate) in the blood perfusate over time, it is also possible to explore comparative absorption kinetics of different drug candidates (or different formulations of the same drug candidate) from the airways, an important feature when inhalation is the intended route of delivery.

**Human liver** – using Ex Vivo Metrics it is possible to explore pharmacokinetics, including biliary excretion, potential interactions and aspects of toxicity. First pass extraction can be quantified and related to systemic exposure to parent drug and metabolites. We also have data which indicates that Ex Vivo Metrics produces unequivocal metabolism data (qualitative and quantitative) consistent with known metabolism in vivo, and also describes the Phase II conjugate excreted in the bile. Standard markers of hepatotoxicity such as elevations in  $K^+$ , liver enzymes (GGT, ALT, AST) and BUN can be detected in the perfusate and release of cytokines and other relevant mediators can also be monitored. Certain 'false positive' effects observed in hepatocyte preparations (such as with BHT) are not observed in the intact perfused liver.



**Human intestine** – the perfused human intestine, with peristaltic function maintained, is a powerful aid to understanding the absorption, disposition and local metabolism of candidate drugs intended for oral administration. Absorption of different drugs or different formulations can be quantified. In this case the drug can

be administered to the gut lumen at clinically relevant concentrations and presented for absorption in a way that closely mimics the in vivo situation. The concentration of the drug and metabolites can be measured in the perfusate giving a clear indication of the efficiency of the absorption process unaffected by secondary phenomena (such as hepatic metabolism and re-circulation) that may occur in vivo. This allows molecules or formulations with superior absorption characteristics to be selected for development and examination of pro-drug performance.



***In summary....*** Ex Vivo Metrics facilitates a number of important investigations using integral systems directly relevant to humans, some of which would not be possible even in a clinical trial setting. The various Ex Vivo Metrics protocols, used cohesively, provide a powerful basis for early profiling of drug candidates and selection of those with the best overall profiles. A number of important questions can be addressed in relation to:

- Uptake by target tissue from blood and plasma:tissue concentration ratios
- Absorption, metabolism and bioavailability
- Efficacy and plasma concentration
- Toxicity and clinically relevant concentrations
- Drug-drug interactions
- Novel biomarkers and 'signatures' for disease states

By testing compounds on functional human organs Ex Vivo Metrics can potentially provide unequivocal, relevant organ-specific human data earlier in the R&D process. For example, by identifying and avoiding surprise human metabolites which may otherwise become apparent only after extensive clinical trials in humans, Ex Vivo Metrics may save not just money but time to market. Ex Vivo Metrics is expected to

provide the greatest value from testing compounds in Pre-Clinical and Phase I because of the high value of being able to evaluate and select compounds early. The expected value of cost savings tends to be greater for problems in Pre-Clinical than in later phases because reducing the number of trials and not having to repeat trials has a greater effect when done earlier in the process.

*Ex Vivo Metrics:*

- A novel humanized pre-clinical test system for drug development
- Can be used to generate unequivocal and relevant human 'clinical' data in functional perfused human organs prior to formal clinical trials
- Can be carried out early at an early stage whereas clinical trials first require completion of extensive pre-clinical safety evaluation of candidate drug(s)

*Successful application of Ex Vivo Metrics at the correct time could improve the efficiency of the selection process, reduce overall attrition rates and improve the risk profile by allowing resources to be focused on the most promising candidates and reducing redundant expenditure.*

### **Experienced Team**

Bowman's competent core team of isolated organ perfusion scientists, whose aggregate experience in problem solving the field of drug discovery and development exceeds 50 man-years, covers the wide range of experience required to optimize and maintain the physiology, pharmacology and biochemistry of organs ex vivo for predicting the fate and effects of drug candidates in vivo.

Bowman Research welcomes the opportunity to discuss Ex Vivo Metrics with you. Following an introductory presentation seminar the typical process is as follows:

- Workshop-style meeting usually held at client premises to clarify, as required, specific aspects of Ex Vivo Metrics and to review potential applications
- Identification of specific project(s)
- Drafting of protocols, reporting specifications, schedules and budgets
- Protocol approval and initiation of work at Bowman

Please contact us to arrange a call or meeting at your convenience.

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