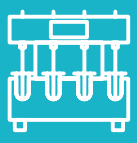
Small Molecule –
Technical Insights Series

Biopharmaceutics Assessment: Identifying the correct approach for in vitro studies

As part of our small molecule insights series we review the growing importance of biopharmaceutics assessment with Dr. Mark McAllister, Chief Scientific Officer of Biowaived (UK). Mark shares his perspectives on how to identify the correct approach, avoid common pitfalls, and leverage in vitro testing to accelerate successful outcomes in drug product design and clinical exposure/efficacy.

Introduction

As drug molecules become increasingly complex and formulation strategies more sophisticated, the importance of robust biopharmaceutics assessment has never been greater. These assessments essentially combine the knowledge of drug substance and drug product attributes and how these ultimately determine how they release and perform after administration (think about it as where **physiology meets pharmaceutics!**). A risk assessment can help understand the critical factors influencing absorption and pharmacokinetic profiles, support model development and guide decision making for dosage form design and clinical dosing.



Biopharmaceutics data which accurately profiles performance with biorelevant systems is the key to selecting an appropriate formulation approach to optimise absorption.

1. How has the role of in vitro biopharmaceutics studies evolved in recent years, and why does this matter for outsourcing partners?

Studies which help development teams understand the critical bioavailability attributes of their formulation are really important to guide drug product design and get it right first time. As molecules have become increasingly more challenging from a delivery perspective, biopharmaceutics data which accurately profiles performance with biorelevant systems is the key to selecting an appropriate formulation approach to optimise absorption.

2. For those designing development programmes, what are key differences when considering biopharmaceutics assessment for new molecular entities, drug substances to be repurposed or generic development activities?

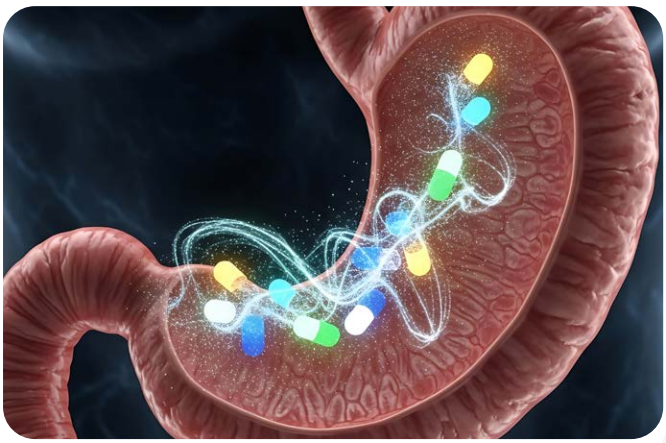
With NMEs, we are always starting on a new journey of discovery and collating knowledge as the compound progresses through preclinical testing to clinical development. Throughout this evolving biopharmaceutics picture, we need to be mindful of the level of uncertainty which can be associated with key physicochemical, biopharmaceutics and ADME parameters.

For example, cell-line permeability is often measured early in a high-throughput screen and we need to be mindful around some of the potential limitations which may be associated with this type of data (e.g. compound recovery or concentrations used).

There's also variability associated with the GI tract and it can be complex to take all of this into account when assessing risks for oral absorption. At Biowaived, we often look at the interplay between API properties and GI physiology using a global systems analysis approach which allows us to evaluate the impact of relevant ranges of variability for both API and relevant physiological system parameters on absorption.

This can be used to inform early versions of the risk assessment and create a biopharmaceutics risk register for a team to manage and update as the compound progresses through development. For drugs which are repurposed or being developed as a generic medicine, the situation is clearly very different. In this instance, we start from a relative position of strength in terms of the data available.

However, for some older molecules, finding accurate permeability or solubility in biorelevant media can be a challenge. Equally, it may be that all the data required to connect drug product composition and processing with PK data are not easily accessible which can complicate an assessment. In such cases, we can generate new data or use a model-based approach to assess parameters such as particle size impact on dissolution and absorption.



3. What are the critical outputs of biopharmaceutics risk assessments and how do they influence in vitro study design at various project milestones?

Pre-clinical, post phase one read out, end of phase two or products aiming to apply for a biowaiver?

In the preclinical phase, we are looking to consolidate the available data, identify critical gaps to address prior to the next milestone and map the most important parameters for absorption so that the challenge of formulation technology selection can be a data driven process rather than one which is driven by institutional practice or access to a particular technology. We can also consider the likelihood of food effects or interactions with acid reducing agents such as H2 receptor antagonists or PPIs.

The Phase I update is often one of the most critical in the life-cycle of a project, it's when we find out if our knowledge of absorption potential and disposition processes translates to human physiology. We also have that most valuable of datasets– human PK data – and we can use this to update and refine our predictive models for absorption and assess the accuracy of some of the assumptions a team will have made for dosage form design for their phase 2 study.

We can be more definitive at this stage in terms of food effect or acid-reducing agent potential. Formulation bridging between Phase 1 and 2 is often a focus of the risk assessment at this stage, particularly in those instances where a team has chosen a resource sparing pathway to the clinic for Phase 1 such as an extemporaneous formulation or API in capsule.

At the end of Phase 2, or proof of concept studies, the biopharmaceutics risk assessment is relatively mature and begins to focus on the forward plan to registration for aspects such as dissolution method capability, formulation variant design to establish dissolution discriminatory ability and the potential for modelling to support product specifications such as particle size and dissolution.

Overall, the biopharmaceutics risk assessment is now viewed as a key process to link dosage form design with performance and because of this, it forms the foundation for assessing dissolution method capability and framing expectations for 'biodiscrimination' across the product life-cycle.

4. What are the most common mistakes companies make when selecting or outsourcing in vitro studies?

It is having a preconceived idea of what the study should be. The test needs to account for API properties, dosage form design and relevant physiology. We also need to consider what the data will be used for and if we can expect it to provide data to answer the question of interest e.g. supporting formulation design during development or guiding internal decision making for formulation selection for a clinical study.

5. From your experience, what differentiates a strategic biopharmaceutics partner from a standard testing provider?

I think a strategic biopharmaceutics partner takes time to understand the biopharmaceutics design space for the project – this covers API properties, formulation design and clinical administration conditions so that the in vitro testing (and in silico modelling) is designed with the context of use clearly in mind.

6. How do you ensure the chosen in vitro approach is tailored to the molecule, the dosage form and the development stage?

I think this starts with the biopharmaceutics risk assessment, it is essential to get this holistic understanding of biopharmaceutics properties mapped out so that the in vitro approach can be correctly selected and appropriately parameterised. Critical dissolution attributes can be identified via a biopharmaceutics risk assessment and should be considered when designing stage-appropriate in vitro approach.

7. Can you share an example where selecting the wrong in vitro method led to misleading or costly outcomes, and how this could have been avoided?

Over the years, I've seen teams take two different approaches to select in vitro methodology to help guide formulation development. In one case, a team thinks that going for a complex in vitro system gets them closer to physiology so it's the best approach to progress.

This can be true in some instances but there are also some I can think of where the system complexity is not warranted or indeed makes it difficult to pinpoint the critical dissolution processes which ultimately determine in vivo performance. In such cases, the team's progress is slowed and their ability to interpret the data is lost in the 'fog' of system complexity.

On the opposite side of the coin, I've seen teams think that a really simple method is all they need, it could be the first compendial dissolution method they've adopted for example. This can overlook the importance of incorporating physiological parameters such as pH change or in vivo relevant hydrodynamics.

Vast arrays of dissolution data are generated as the test is simple and quick, every formulation is tested and along the way there can be false correlations in terms of formulation performance.

Teams can be reluctant to take a step back, reconsider what is critical for the performance of their drug product and start again. In both cases, the solution is relatively straightforward, it's that simple equation which defines biopharmaceutics risk as the net result of API, drug product properties and their interaction with physiology. It requires a combination of formulation understanding and biopharmaceutics experience to get this right.

8. How do you define "biorelevant" testing in practice, and how important is it for sponsors to invest in these approaches?

That's quite a nuanced question and in some respects those of us working in this area haven't helped ourselves by blurring the boundaries for definitions in this area through the interchange use of terms such as biorelevant, physiologically based or biopredictive testing. For me, biorelevant is defined as the minimal set of test properties which are needed to capture the performance of a dosage form after administration.

This doesn't need to be complex, for example, a simple acidic buffer which captures gastric conditions in the fasted state may be all that is needed for a compound with good solubility but for a weak base, with precipitation potential, then a more complex transfer test which accounts for aspects such as gastric pH after co-administration of a 240 ml glass of water and transfer to a bile salt rich intestinal media may be needed. I think sponsors often appreciate a discussion on the design aspects of a biorelevant test and why it's important for their product.

9. When working with outsourcing partners, how should companies balance cost, speed, and physiological relevance?

It's that concept of warranted complexity again, the balance is driven by the question being asked and how the test can be designed to ensure the critical elements are incorporated so that the performance data produced is relevant to both the formulation and the proposed use conditions.

10. How can in vitro data be integrated with PBPK modelling or other predictive tools to provide confidence in decision making?

This is an area which has been evolving at a rapid pace over the last few years. Looking back to the IMI OrBiTo project, the largest pre-competitive public-private partnership we had in the biopharmaceutics world, we were very interested in how we could use dissolution within PBPK models to improve predictions of formulation performance.

How this is done though has a huge impact on the ability of a model to propagate subject variability in a relevant way. Simply providing dissolution data as an input which strictly defines formulation performance relies on the inherent biopredictive capability of the method and can limit the ability to propagate relevant variability associated with GI tract parameters within the model. There is a lot of work in this area and many interesting publications which demonstrate that if the appropriate approach is selected, dissolution performance can be accurately described within a model and be a cornerstone for complex assessments such as virtual bioequivalence.

Another example in this space is with solubility data and using a set of more complex media to describe and parameterise the solubilisation of a poorly soluble molecule with endogenous bile salts and fatty acids in the GI tract. This concept goes beyond simply measuring values in media which approximate the average physiology and extends it to cover a relevant range of physiological variability.

11. What role does scientific interpretation play compared to simply generating data, and how does Biowaived add value in this area?

I think it is vital and adds significant value to the data we generate. From our time in large pharma, we are very used to answering the question around what does this mean for the next step in a project when we review a dataset. The data are only useful with interpretation and our background and experience across early and late-stage formulation development make us ideally equipped to help with what are often challenging decisions.

12. How early in development should sponsors engage with experts to define their biopharmaceutics strategy?

I think the ideal starting point is in the early preclinical phase. During lead development can be an appropriate starting point to initiate the conversation with a focus on building out the biopharmaceutics design space for the chemistry series of interest.

13. What are regulators expecting today in terms of justification for in vitro study design, and how can outsourcing partners help meet these expectations?

That's a very timely question as expectations are evolving quickly in the space. At the start of May, I travelled to attend the M-CERSI meeting in Washington which focused on the role of biopharmaceutics risk assessment for determining the requirements for a clinically relevant dissolution test. It was clear from the multiple FDA presentations that expectations for the role of dissolution in regulatory decision making have shifted significantly with a clear movement beyond the traditional quality control paradigms toward a predictive, patient-centric science-led approach.

The future of dissolution testing is looking like one which is underpinned by a holistic understanding of API, drug product properties and clinical performance – very different from the space we've been accustomed to over the last few years which was very much focused on discriminatory power for critical formulation variables, material attributes and process parameters.

14. For companies with limited in-house expertise, what should they look for when selecting a partner for biopharmaceutics assessment?

I would suggest that they look for a partner who has a deep understanding of the drug development process and what is needed to help make decisions to move a project forward. They should also look for a partner who can articulate why and what value biopharmaceutics assessment brings, it's not a science which anyone studies at graduate level so for many, the integrative nature of biopharmaceutics can be viewed as a bit of mystery, the ideal partner should be able to de-mystify this and help with internal communications of why the data matters for project teams.

15. What key questions should sponsors ask themselves, or their CRO, before initiating an in vitro study?

I think the starting point is always the question **"what are we are trying to understand and then, what are the gaps we need to address so we can move forward?"** This is a great starting point for a conversation with their CRO.

16. Looking ahead, how is Biowaived positioning itself to help clients navigate emerging challenges and innovations in biopharmaceutics assessment?

We are always looking to grow our array of dissolution technologies so that we can offer a relevant test to our clients. Also, we are very mindful that in the new world of evolving regulatory expectations, the in vitro data are only useful when linked to an outcome which relates to product performance and for this we need to be able to continue to grow our modelling capabilities.

Looking longer term, we are also interested in growing our offer in the parenteral space with the new dissolution approaches now available which enable a biorelevant assessment of products switched from the intravenous to subcutaneous route of administration.

It's an exciting time to be working in biopharmaceutics and we feel we are well placed to grow the company's capabilities to meet the evolving needs of our clients.

Biowaived

Biowaived Ltd is a contract research organisation focused on delivering tailored biopharmaceutics and dissolution support for drug product design and development.

We are based at Discovery Park, Sandwich, Kent where we have established a state-of-the-art dissolution laboratory with a range of compendial dissolution equipment (including USP 1, 2, 3 and 4 equipment), non-compendial dissolution platforms (including Pion MicroDiss, Pion MicroFlux and the Artificial Stomach Duodenum model), HPLC and UPLC analytics and additional characterization techniques such as PXRD, surface tension measurement, microscopy and particle sizing.

We have PBBM modelling capabilities which are used to predict how changes in dissolution performance will translate to product performance after administration to patients. With our background experience coming from many years of pharmaceutical product development in large pharma spanning preclinical to commercial development, we have expertise in analytical, materials sciences, formulation design and biopharmaceutics.

Overview of biopharmaceutics services at Biowaived

- **Consultancy and modelling services** including biopharmaceutics risk assessment and physiologically based biopharmaceutics modelling
- **We use a structured, stage appropriate approach for dissolution method design and development.** Our framework for dissolution method design evolves through the drug product life-cycle to deliver a robust method with defined discriminatory capabilities suitable for regulatory submission.
- **We specialise in designing biorelevant dissolution studies** to define the critical attributes which determine drug product performance in the GI tract. Our biopredictive methods can be adapted to simulate in vivo conditions by considering media composition, pH, mixing and gastrointestinal transit.
- **Physicochemical profiling including pKa, LogP, Ksp, solubility and intrinsic dissolution rate testing** can help evaluate and inform biopharmaceutics risks during drug product design and formulation development.