BIOIVT

Navigating New Regulatory Guidelines for Drug Interaction and Metabolism Studies

Designing ADME Studies With Purpose

Using strategic program design to identify potentially dangerous interactions between experimental drugs and other substances helps advance the most promising compounds more safely.

The development program for a new drug from the research bench to human trials includes multiple *in vitro* evaluations to help predict its safety and efficacy. To probe whether an experimental drug can effectively enter circulation, exert a targeted therapeutic effect, and undergo metabolism and clearance, researchers rely on absorption, distribution, metabolism, and excretion (ADME) studies, which include drug metabolism and pharmacokinetics (DMPK) (1,2). As the new drug progresses through preclinical development, scientists also use ADME studies to carefully examine potential interactions between the new compound and other medications. These studies play a critical role in identifying red flags, such as low efficacy and toxicity concerns, that need to be considered before making substantial investments in a drug's development (3).

The impact of drug-drug interactions

Cocomitantly administered drugs can alter the metabolism of medications, impacting their safety and effectiveness. Some drugs either induce expression or inhibit the activity of other drugs' metabolizing enzymes, which can reduce therapeutic effect or lead to toxicity. They can also inhibit or be the substrates of transporters for other drugs, altering their excretion or their distribution to target tissues. Data on a drug's metabolizing enzymes and transporters are key for predicting dangerous drug-drug interactions (DDIs), and constitute a critical component of the investigational new drug (IND) application that researchers must submit to regulatory agencies like The Food and Drug Administration (FDA) before testing a drug in human volunteers. DDIs are a significant concern for researchers, considering that more than two thirds of American adults over 65 take five or more medications concurrently (4). Information on potential DDIs helps clinicians determine which drugs they can coadminister during a human trial and how to adjust drug doses to prevent undesired drug effects.

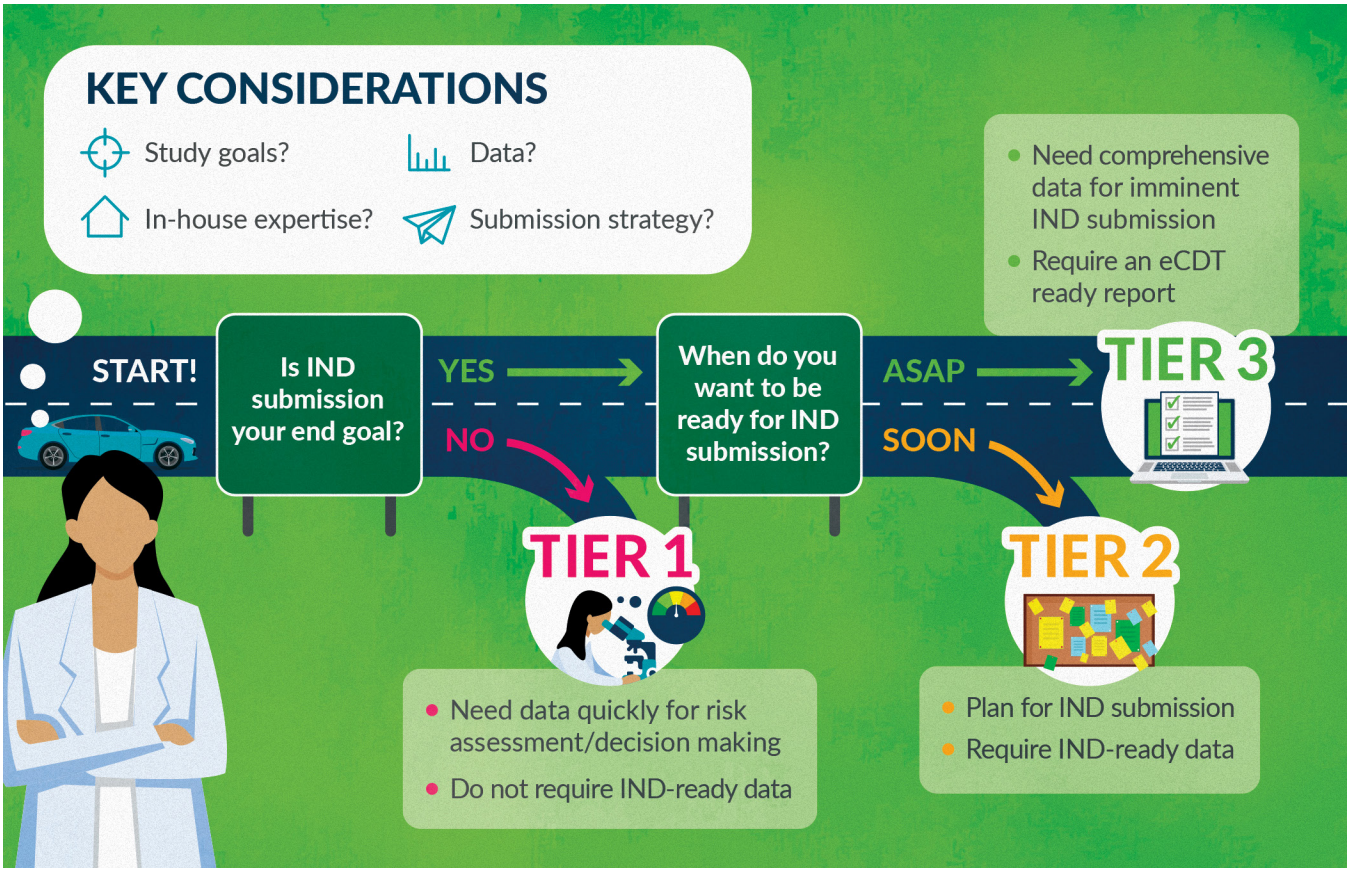
Harmonized guidelines for understanding DDI potential

Researchers conducting FDA-mandated DDI experiments can secure approval for first in-human studies in the United States, but they might encounter challenges obtaining regulatory clearance elsewhere due to disparate, region-specific standards. Starting in 2024, drug developers will design DDI studies based on new, unified Drug Interaction Studies Guidelines (M12) developed by the International Council for Harmonization (ICH) (5). The ICH is an international organization that brings together regulatory authorities and pharmaceutical industry representatives, including those from the United States, the European Union, and Japan, to develop harmonized standards for pharmaceutical product development (6). Harmonized guidelines ensure the quality, safety, and efficacy of pharmaceuticals while reducing regulatory barriers on a global scale. This harmonization simplifies the drug development and approval process, reducing the need for multiple, region-specific studies and documentation.

The new ICH M12 guidelines offer broad recommendations for *in vitro* experiments to evaluate the DDI potential of an investigational drug, including drug interactions mediated by the inhibition or induction of enzymes or transporters (5). The guidelines recommend that researchers examine a drug candidate's potential to induce or inhibit a standard panel of seven cytochrome P450 enzymes and nine major transporters that metabolize and distribute most drugs (4), and potentially investigate a variety of other enzymes and transporters depending on the results of initial studies or the specifics of the compound. ICH M12 guidelines also recommend determining which enzymes are responsible for the formation and elimination of metabolites that could cause DDIs.

Aligning study design with study goals

The new harmonized ICH M12 guidelines save researchers valuable time as they can avoid performing studies to simply satisfy disparate regional requirements. Instead, they can focus their ADME strategy to meet specific goals, including seeing their drug through the regulatory approval process or licensing the drug to a biopharmaceutical company for further development. Although the new guidelines standardize a once complex process, aligning study design with drug development goals remains a challenge for many researchers. This can lead to frustration, as scientists may find themselves spending excessive time performing unnecessary experiments or trying to decipher unexpected or unusual data to determine if a candidate compound is worth pursuing.



A three-tiered solution for solving key drug development needs: *BioIVT's three-tiered program adapts to the unique needs of scientists, whether they want to gather IND-ready data or obtain a quality risk assessment of their compound for future study planning.*

BioIVT experts have extensive experience advising scientists with unusual data and helping them efficiently advance new drugs through the research and development pipeline. Researchers have different objectives when implementing ADME programs. To accommodate clients' needs and requirements, BioIVT developed three standard, "fit-to-purpose" study designs that follow the latest ICH guidelines. Tier 1 leverages BioIVT's expertise to aid in risk assessment and strategic decision-making, quickly providing quality data that can shape future study design. Tier 2 is an IND-enabling program that helps scientists examine a drug's ADME and DDI potential and provides IND-ready data. It is suitable for those planning future IND submissions or desiring complete data to prevent later rework. For those with immediate IND submissions in mind, Tier 3 examines a drug's DDI potential and offers a full report formatted as an electronic common technical document (eCTD), the standard, ICH-compliant format for submitting IND applications to the FDA. Additionally, BioIVT's expert team provides guidance with custom study designs and deliverables catering to each research team's specific needs.

A standard pathway to drug regulatory approval

The harmonization of regulatory guidelines marks a pivotal moment in drug development, offering a consolidated framework that standardizes the design and interpretation of DDI studies and the path to regulatory approval. The three-tiered ADME study options provide a strategic and flexible approach that abides by the current guidelines, allowing researchers to select the pathway most aligned with their specific goals and the unique characteristics of their compound. These structured options, ranging from rapid data acquisition for strategic decision-making to comprehensive IND-enabling programs, accommodate the varying needs and preferences of scientists. This combination of harmonized guidelines and tailored study options significantly optimizes the drug development landscape, enabling more innovative therapeutic solutions and streamlining the process of developing new pharmaceuticals that improve patients' lives.

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A Q&A with Dr. Brian Ogilvie: Getting Drug Design Right

In vitro drug testing helps determine how a new drug is metabolized and transported, a prerequisite for human trials.

Brian Ogilvie, Vice President of Scientific Consulting at BioIVT, guides scientists of all levels through the crucial investigational new drug application process.

A major concern during drug development is accurately predicting possible adverse side effects based on how an investigational drug interacts with other medications. Regulatory agencies require *in vitro* drug testing to address this, but newly trained toxicologists are often uncertain how to properly perform these studies in accordance with federal agency regulations.

Since 2006, Brian Ogilvie, Vice President of Scientific Consulting at BioIVT, has expertly guided both novice and veteran scientists through the investigational new drug application process, a crucial step for companies aiming for first in-human trials.

Can you explain how your team helps scientists develop new therapeutics?

Scientists often already have a large body of data about their drug. We counsel them, review their data, and help fill any gaps depending on their goal. If the scientist wants to get to a first in-human study through the investigational new drug process, we need data showing how the drug is metabolized and transported. For clinical studies in patients, we need data about what other drugs might interact with the new compound because patients in a clinical trial may have comorbidities that require other medications.

What are some examples of problematic drug-drug interactions?

If drug A is metabolized through one pathway by a certain enzyme, and drug B, which inhibits that enzyme, is given with it, drug A will build up to potentially toxic levels. When we do metabolism studies, the ideal situation is that drug A is metabolized by several enzymes or transported by several transporters so that a single drug cannot cause toxicity. On the other hand, if drug B increases the expression of drug A's metabolizing enzyme, the effect of drug A is diminished. This can also occur with transporters. If the target for drug A is in the liver but drug B inhibits one of the transporters that pulls drug A into the liver, drug A will not have an effect.

What are some pitfalls that scientists fall into when designing metabolism studies?

One of the first questions I ask is, "What is the structure of the compound?" After 26 years of experience, I can usually look at the structure and know which enzyme systems will metabolize it. If the structure has a phenolic group, the drug will likely get conjugated rapidly by enzymes like UDP-glucuronosyltransferases (UGTs) or sulfotransferases. In those cases, the compound should be tested in hepatocytes, so all the enzymes and transporters are present. I have seen cases where people test their compound directly in subcellular fractions from human hepatocytes (microsomes) and see it is metabolized by cytochrome P450 enzymes. When they get to the clinic, they find their compound is rapidly conjugated by UGTs or other enzymes that are faster than the P450 enzymes. They expected their compound to have a longer half life because they ignored the effect of other enzyme systems.

Can you describe a time you assisted a client with navigating regulatory requirements?

We had a client who successfully went through a new drug application with the FDA. Two years later, the client wanted approval in Europe. Even though they had clinical data, the European Medicines Agency (EMA) asked for additional *in vitro* studies. We explained they were unnecessary. Eventually they agreed, and our client got approval without spending another $200,000 USD doing studies that would not have added value.

What are the implications of the new ICH guidelines on study design?

Researchers bring us compounds, such as peptides, that are not typical small molecule drugs. However, the EMA treats them as small molecule drugs, and requires additional studies. The new ICH drug-drug interaction guidelines may allow more flexibility. We can focus on the science rather than just checking a box. Because we now have one guidance document for all the agencies, we do not have to design different studies for the FDA and the EMA; it can just be one study.

How does your consulting approach vary based on research group size and drug stage?

We have worked with many small pharmaceutical companies with fewer than ten people who want to get data on their compound to attract investments. In those cases, we have tiered services. Tier one is a basic study to show investors that the new drug is worth developing further. If the drug is further in development, or the pharmaceutical company is larger and has a pipeline, we suggest a tier two approach, or even a tier three study to get a full, good laboratory practice-compliant report. Our subject matter experts tailor studies based on researchers' needs and compound properties.

This interview has been condensed and edited for clarity.