Drug-drug interaction studies

WHITEPAPER

From protocol to practice: The basics of drug-drug interaction studies

Introduction

Drug-drug interactions (DDIs) refer to the alteration of a drug's effect due to the presence of another drug. These interactions can lead to diminished therapeutic effects or increased toxicity, causing adverse drug reactions.

While accurate prediction of DDIs and their mechanisms is not always possible, it is important to assess these potential interactions and their risk during the clinical development program of any new drug. This whitepaper aims to provide pharmaceutical professionals with a comprehensible overview of DDI studies within a clinical development program, highlighting their significance, methodologies, regulatory landscape and practical applications.

Contents

1. Importance of DDI studies

The purpose of conducting DDI studies on novel medicinal products in the development phase is to acquire insights into how the new medicinal product impacts the safety and efficacy of other medicinal products, and vice versa. This process is fundamentally anchored by three key pillars that constitute the foundation of all DDIs: ensuring patient safety, maintaining drug efficacy and adhering to regulatory compliance.

PATIENT SAFETY

Ensuring patient safety is the foremost reason for conducting DDI studies. Unanticipated, unrecognized, or mismanaged DDIs can cause morbidity and even mortality associated with prescribed drug use. By identifying potential interactions early, pharmaceutical professionals can mitigate risks of adverse effects, safeguarding patient health and well-being based on the Summary of Product Characterization (SmPC) including the DDI information. Treatment recommendations are developed based on the clinical relevance of the DDI and the possibility of making dose adjustments or treatment monitoring. Especially in populations such as the elderly or those with comorbid conditions, the risk of developing an adverse drug reaction (ADR) secondary to a DDI increases significantly with the number of medications a patient is receiving.

DRUG EFFICACY

Understanding DDIs is essential for maintaining the therapeutic efficacy of drug regimens. DDIs can cause partial or complete abolishment of treatment efficacy. Effective DDI studies help in optimizing drug combinations, ensuring that patients receive the maximum benefit from their treatments.

REGULATORY COMPLIANCE

Regulatory agencies, such as the European Medicines Agency (EMA) and the Food and Drugs Administration (FDA), mandate comprehensive in vivo DDI data as part of the drug approval process in order to provide information about metabolic routes of elimination and potential contributions to metabolic DDIs as described in ICH M12. Compliance with these requirements is essential for the successful market introduction and continued monitoring of new pharmaceuticals.

2. Essential concepts in DDI studies: metabolism-mediated and transporter-mediated interactions

First of all, there are several types of drug interactions. In this paper, we will discuss the metabolism-mediated and transporter-mediated interactions. These are two of the most understood and commonly known interactions. Additionally, these are the ones described in the FDA Clinical Drug Interaction Studies Guidance.

Understanding the roles of cytochrome P450 (CYP) enzymes and transporters in drug metabolism and transport is essential for predicting variable pharmacokinetics and drug responses. Knowledge of these interactions aids in optimizing therapy, managing drug interactions and personalizing medicine to enhance patient outcomes.

A metabolism-mediated interaction is when there is inhibition or induction of a drug-metabolizing enzyme, such as CYP. Transporter-mediated interactions are interactions that involve transporters like P-glycoprotein (P-gp) that move drugs across cell membranes.

2.1 METABOLISM-MEDIATED INTERACTIONS

Metabolic interactions are a significant type of DDI involving enzymes such as the CYP family, which play a crucial role in the metabolism of many drugs and other substances within the body. These enzymes are primarily found in the liver but also present in the lungs, kidneys and intestines. Additionally, the uridine 5'-diphospho-glucuronosyltransferase (UGT) enzyme family contributes to drug metabolism. However, in this paper, we will focus on the CYP enzymes.

(I) CYTOCHROME P450 ENZYMES (CYP)

STRUCTURE AND FUNCTION

CYP enzymes are a large superfamily of heme-containing enzymes, categorized into different families and subfamilies based on their amino acid sequences. The primary families involved in drug metabolism are CYP1, CYP2 and CYP3. These enzymes mainly perform oxidation reactions, which increase the water solubility of lipophilic substances, facilitating their excretion through the kidneys.

GENETIC VARIABILITY

There is significant genetic variability in CYP enzymes, resulting in different capacities for drug metabolism among individuals. This variability can lead to differences in drug efficacy and the risk of side effects. The main CYP enzymes responsible for the metabolism of most clinically used drugs include CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

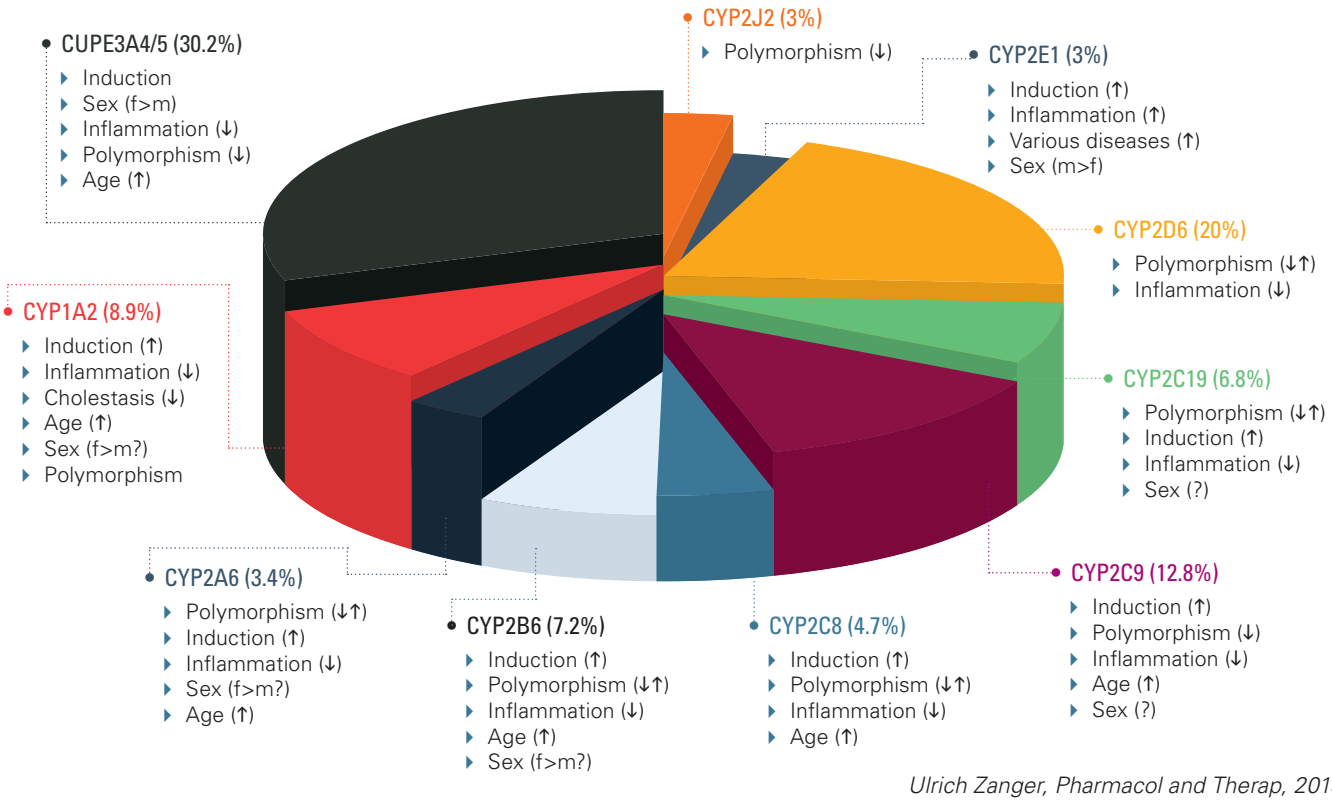
FACTORS INFLUENCING CYP ACTIVITY

Knowledge of the intrinsic and extrinsic factors that influence the expression and function of the responsible enzymes is essential for predicting variable pharmacokinetics and drug response.

Several factors can influence the expression and activity of CYP enzymes, including:

- Genetic polymorphisms: genetic variation between populations and individuals
- Induction and inhibition: certain drugs and other xenobiotics can modify the activity of CYP enzymes through induction or inhibition. Induction increases enzyme production and activity, thereby accelerating the metabolism of the CYP substrates. In contrast, inhibition decreases enzyme production and activity, slowing down the metabolism of the CYP substrates
- Regulation by cytokines and hormones: inflammatory cytokines and hormones can modulate CYP expression
- Disease states: illnesses can affect enzyme levels and activity
- Sex and age: differences have been observed between males and females, and between ages

This pie chart presents the primary CYP enzymes responsible for metabolizing most clinically administered drugs. It also demonstrates the varied mechanisms and factors that can impact the expression of each CYP enzyme, with each enzyme being influenced uniquely.



Ulrich Zanger, Pharmacol and Therap, 2013

(II) CLINICAL SIGNIFICANCE

Many DDIs result from the induction or inhibition of CYP enzymes. Drugs that induce CYP enzymes can increase the metabolism of co-administered drugs, potentially reducing their efficacy. Conversely, drugs that inhibit CYP enzymes can decrease the metabolism of co-administered drugs, leading to higher drug levels and the risk of toxicity.

For drugs with a narrow therapeutic index (NTI), such as warfarin, it is crucial to monitor plasma concentrations to ensure both effectiveness and the avoidance of toxicity. NTI drugs are those where small differences in dose or blood concentration can lead to serious therapeutic failures or adverse drug reactions, which may be life-threatening. Therefore, understanding the involvement of CYP enzymes in the metabolism of these drugs is essential for effective therapeutic drug monitoring.

Genetic testing can help identify CYP enzyme variants, allowing for personalized dosing recommendations. This approach helps minimize side effects and maximize drug effectiveness.

2.2 TRANSPORTER-MEDIATED INTERACTIONS

Transporter-mediated interactions involve proteins that facilitate the movement of drugs across cell membranes. These interactions can greatly impact the pharmacokinetics of drugs by affecting their absorption, distribution and excretion. The most studied and well-known transporters involved in DDIs include:

- Efflux transporters: P-gp and BCRP (breast cancer resistance protein)
- Hepatic transporters: OATP1B1 and OATP1B3
- Renal transporters: OAT1, OAT3, OCT2 and MATE

In the following sections, we will delve into each of these transporters in more detail.

(I) EFFLUX TRANSPORTERS: P-GP AND BCRP

FUNCTION

P-gp and BCRP are efflux transporters that pump drugs out of cells against their concentration gradient, using energy from adenosine triphosphate (ATP) hydrolysis. They are found in various tissues, including the intestines, liver, kidneys and blood-brain barrier. These transporters play critical roles in:

- Protecting tissues from toxic substances
- Reducing drug absorption in the intestines
- Facilitating drug elimination through bile and urine
- Limiting drug penetration into the brain

SUBSTRATES

P-gp and BCRP transport a wide variety of substrates, including:

- Chemotherapeutic agents (e.g. doxorubicin, paclitaxel)
- Antiretrovirals (e.g. protease inhibitors like ritonavir)
- Immunosuppressants (e.g. cyclosporine, tacrolimus)
- Cardiac drugs (e.g. digoxin)
- Antibiotics (e.g. erythromycin)

(II) HEPATIC TRANSPORTERS: OATP1B1 AND OATP1B3

FUNCTION

OATP1B1 and OATP1B3 are organic anion transporting polypeptides which function as hepatic transporters involved in the uptake of a wide variety of endogenous compounds and xenobiotics, including many drugs, into hepatocytes.

SUBSTRATES

- OATP1B1: statins (e.g. atorvastatin, simvastatin), angiotensin II receptor blockers (e.g. valsartan), and certain antibiotics (e.g. rifampicin)
- OATP1B3: taxanes (e.g. paclitaxel), certain anticancer drugs and some peptides

(III) RENAL TRANSPORTERS: OAT1, OAT3, OCT2 AND MATE

FUNCTION

OAT1, OAT3, OCT2 (organic cation transporter 2), and MATE (multidrug and toxin extrusion protein) are renal transporters involved in the excretion of various endogenous compounds and drugs.

SUBSTRATES

- OAT1: antiviral drugs (e.g. tenofovir) and antibiotics (e.g. penicillins), NSAIDs
- OAT3: methotrexate, furosemide and certain antihypertensives
- OCT2: metformin, cisplatin and beta-blockers (e.g. atenolol)
- MATE: metformin, cimetidine and cisplatin

(IV) CLINICAL SIGNIFICANCE

The inhibition or induction of transporters can significantly impact the pharmacokinetics of their substrate drugs, leading to changes in drug efficacy and potential toxicity. For instance, overexpression of P-gp in cancer cells is a common resistance mechanism against chemotherapeutic drugs, as it pumps these drugs out of the cells, thereby reducing their effectiveness.

Genetic variants can also affect transporter activity and influence individual responses to medications. Genetic testing for these variants can help guide personalized dosing of drugs, such as statins, to minimize adverse effects and optimize therapeutic outcomes.

3. Setting up a DDI study

ASSESSING PRE-CLINICAL DATA
In vitro & animal models

DEFINING STUDY DESIGN
In line with research objectives

REGULATORY CONSIDERATIONS
For study results

3.1 STEP 1: ASSESSMENT OF PRECLINICAL DATA

Before embarking on a clinical DDI study, it is essential to integrate preclinical data to inform the study's design and objectives. This phase involves synthesizing information from in vitro drug metabolism and drug transporter studies to evaluate the potential for interactions at the clinical level.

INTEGRATION OF PRECLINICAL DATA

1. In vitro studies: begin by reviewing results from in vitro drug metabolism studies, which provide insights into how the investigational drug is metabolized by enzymes such as CYP3A4 and others. Identify any potential for the investigational drug to act as a substrate, inhibitor or inducer of these enzymes
2. Drug transporter studies: evaluate findings from drug transporter studies to understand the role of transporters such as P-gp, BCRP and others in the absorption, distribution, metabolism and excretion (ADME) of the investigational drug. Determine if the drug interacts with these transporters or if it is a substrate for them
3. Safety data: consider the available safety data for the investigational drug. If the drug has not been tested in humans previously, prioritize gathering safety information before conducting DDI studies. This ensures that the investigational drug is safe for use in clinical studies involving interactions with other drugs

DECISION-MAKING FOR CLINICAL DDI STUDIES

Based on the integration of preclinical data, you can then make informed decisions regarding the need for and timing of clinical DDI studies:

- Prioritization of interactions: utilize guidelines from regulatory agencies such as the EMA and FDA to prioritize interactions based on the risk assessments of preclinical data. For instance, if the investigational drug shows significant metabolism via CYP3A4 and is likely to be co-administered with strong inhibitors or inducers of this enzyme, prioritize testing these interactions first
- Study design considerations: determine the appropriate study design based on preclinical findings. For example, if the investigational drug is susceptible to significant inhibition or induction effects, plan for crossover or parallel design studies to assess these interactions comprehensively

- Regulatory guidance: consult regulatory guidelines to understand the expected outcomes of DDI studies and the thresholds for clinical significance of interaction effects on pharmacokinetic parameters such as area under the curve (AUC), Cmax and Tmax

3.2 STEP 2: CHOOSING STUDY DESIGN

Once the need for a DDI study is established based on preclinical data, the next step involves defining the study objectives and selecting an appropriate study design.

The primary objectives in a DDI study are typically to quantify the impact of the interacting drug on the pharmacokinetics (PK) of the investigational drug (e.g. changes in AUC, Cmax) or vice versa.

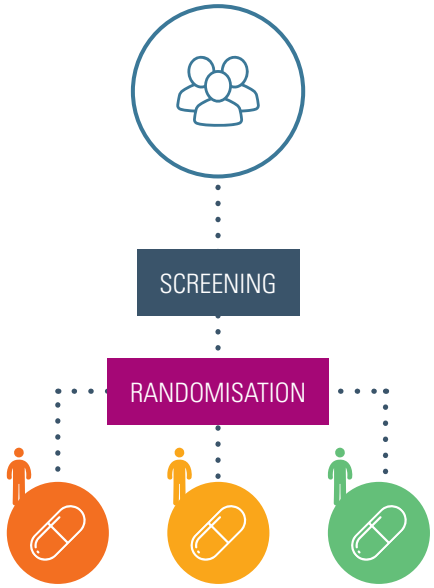
(I) STUDY POPULATION

Typically, DDI studies are conducted using healthy volunteers, unless there are notable safety concerns or if assessing pharmacodynamic endpoints is more suitable in a patient population. The number of subjects in a DDI study should be adequate to ensure a dependable assessment of the interaction's magnitude and variability. While guidelines do not specify exact numbers, SGS studies typically involve 12 to 45 volunteers.

(II) SINGLE OR MULTIPLE DOSES

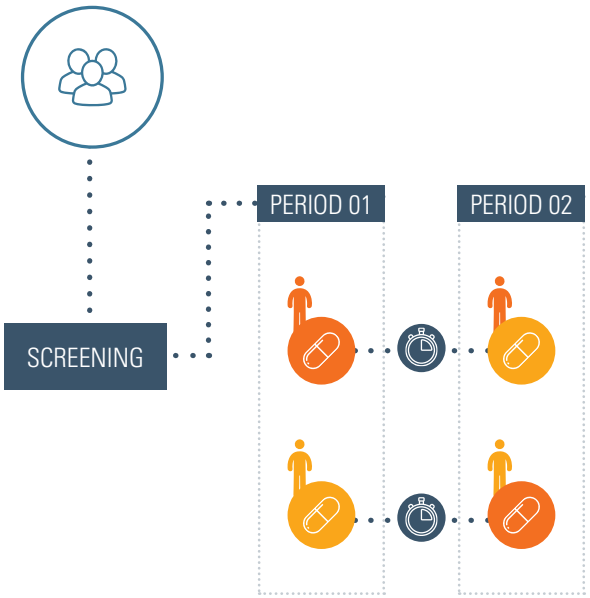
The decision between single or multiple dosing depends on the drug's characteristics. For substrates, a single dose is typically adequate unless the drug exhibits time-dependent pharmacokinetics, such as auto-inhibition or induction.

PARALLEL TRIAL



In a parallel study design, one group of participants receives only the substrate (drug being studied), while another group receives both the substrate and the inducer (another drug known to affect the metabolism or activity of the substrate)

CROSS-OVER TRIAL



Typically, in a crossover study, each subject undergoes two experimental periods: one where they receive the substrate alone and another where they receive the substrate with the perpetrator drug

LEGEND: *Treatment A* *Treatment B* *Treatment C* *Washout period*

In the case of inhibitors, a single dose may suffice if it produces a similar effect on the enzyme or transporter as observed during steady-state conditions with multiple doses.

However, if the substrate has a prolonged half-life, multiple dosing is preferred to capture its entire exposure profile.

When studying inducers, multiple dosing is necessary to ensure maximum induction of the specific metabolic pathway.

(II) PARALLEL OR CROSSOVER STUDY

When planning a DDI study, researchers can opt for either a crossover design or a parallel design.

Each design choice balances the need for reducing variability and ensuring study feasibility based on drug characteristics and safety considerations. Crossover design is preferred for most DDI studies, because all subjects will receive all treatments reducing intersubject variability.

Parallel, two-arm studies are suitable when a crossover design is impractical, such as when one drug has a prolonged half-life and therefore long washout period or when the investigational drug cannot be administered more than once safely.

A crossover study can utilize a randomized crossover (e.g. substrate followed by substrate + inhibitor/inducer, or vice versa), a one-sequence crossover (e.g., substrate followed by substrate + inhibitor/inducer fixed), or a parallel design (e.g., substrate in one group and substrate + inhibitor/inducer in another). Crossover studies, whether randomized or one-sequence, are generally preferred over parallel designs to minimize variability between subjects. The duration of the washout period is determined by the pharmacokinetics of both the substrate and perpetrator drugs, the expected impact on the substrate's half-life, and the time required for enzyme activity or pharmacodynamic effects to return to baseline.

	Pros	Cons
Parallel design	• Simple execution • Drugs with long half-lives or those that have residual effects after dosing	• Higher inter-subject variability may require a larger sample size • Requires more subjects compared with crossover designs
Crossover design	• Reduces inter-subject variability • Requires fewer subjects compared with parallel designs	• Longer study duration due to washout periods • Potential for carryover effects if the washout period is not sufficient

(IV) TYPES OF DDI STUDY

Different types of DDI studies are crucial for evaluating both the presence and magnitude of DDIs in clinical settings. These study types are not mutually exclusive and should be chosen based on specific study goals.

STANDALONE VERSUS NESTED

Standalone studies focus solely on assessing drug interactions as the primary objective. In contrast, nested studies incorporate DDI assessments within broader studies that may include single ascending dose (SAD), multiple ascending dose (MAD), food effect and other pharmacokinetic evaluations.

INDEX DRUGS

These studies involve potent inhibitors or inducers and sensitive substrates (metabolized by a single CYP enzyme). Known as "index drugs," these perpetrators and substrates have well-characterized pharmacokinetic and DDI profiles regarding inhibition, induction or metabolic pathways.

Index studies aim to estimate the greatest interaction magnitude for specific metabolic pathways. Results from these studies can often be extrapolated to predict interactions with other drugs of similar potency and metabolic pathways without needing additional studies. Regulatory guidelines provide a list of known index drugs.

EXPECTED CONCOMITANT MEDICATION

These studies investigate interactions between the investigational drug and drugs commonly co-administered in the target population. They are particularly relevant when a drug is used as an add-on therapy or in fixed-dose combinations. Drug selection considers the mechanistic understanding of potential DDIs and the frequency of co-administration. While informative, results from these studies may be challenging to apply to other drugs due to the lack of index substrates or perpetrators for certain metabolic and transporter pathways (e.g. UGTs, CYP2B6).

COCKTAIL APPROACH

A cocktail study involves administering substrates of multiple enzymes and/or transporters simultaneously to study subjects. The Geneva cocktail is an example; including substrates like caffeine (CYP1A2), bupropion (CYP2B6), flurbiprofen (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6) and midazolam (CYP3A4). This approach allows for the concurrent evaluation of a drug's potential to inhibit or induce multiple metabolic pathways if appropriately designed and executed.

Each study type serves distinct purposes in evaluating DDIs, emphasizing the importance of selecting an appropriate study design based on specific study objectives and regulatory guidance. These studies provide critical insights into drug safety and efficacy, helping to inform clinical decision-making and optimize therapeutic strategies.

(V) SELECTING INHIBITORS, INDUCERS AND SUBSTRATES

When selecting perpetrator or victim drugs for DDI studies, several considerations should guide choice, building upon aspects discussed regarding the type of DDI study:

- Potency: opt for potent inhibitors or inducers with well-established inhibition or induction profiles. Index drugs serve as exemplary choices
- Clinical relevance: opt for those commonly used in clinical trials, possessing extensively documented pharmacokinetic profiles and well-characterized effects
- Specificity: select substrates that are specifically metabolized by the enzyme or transported by the transporter of interest. Similarly, for inducers and inhibitors, choose those that specifically affect the enzyme or transporter of interest. This approach offers numerous advantages over nonspecific drugs: it simplifies and enhances the interpretation of pharmacokinetic results, reduces the risk of confounding factors and provides a clearer understanding of the drug's metabolic pathways in the body

3.3 STEP 3: INTERPRETING STUDY RESULTS AND REGULATORY CONSIDERATIONS

Following the completion of a DDI study, the interpretation of results is crucial for determining the clinical significance of interactions and as input for regulatory submissions. Interpreting the results involves several critical steps:

(I) ASSESSMENT OF INTERACTION

Evaluate whether the observed interactions are clinically significant based on changes in pharmacokinetic parameters, such as AUC and Cmax. These parameters reflect alterations in drug metabolism due to enzyme or transporter inhibition or induction.

Comparing PK parameters with and without the interacting drug provides initial insights. Significant changes in exposure are typically defined as an increase in AUC or Cmax of more than 25-30%; or a decrease of more than 20-25%. Statistical methods, often applying 90% confidence intervals (CI), are used to evaluate the significance of these changes. A 90% CI within the range of 0.8-1.25 is generally considered nonsignificant by regulatory standards (EMA and FDA guidelines).

(II) LABELING RECOMMENDATIONS

Based on these findings, appropriate labeling recommendations are provided, which may include safety monitoring, therapeutic monitoring or necessary dose adjustments. For instance, increased exposure due to an inhibitor might necessitate a dosage reduction.

(III) REGULATORY SUBMISSION

Prepare and submit a detailed report to regulatory authorities, including study design, methodology, results and conclusions. This report should address all aspects of the DDI study to ensure comprehensive regulatory review and approval.

4. SGS expertise in DDI studies

Over the past decade, SGS has conducted more than 35 DDI studies, providing comprehensive support throughout different stages of drug development. This extensive experience allows us to support our clients in making informed decisions regarding DDI studies in their clinical development programs.

In the preclinical phase, SGS offers expertise in evaluating the inhibition or induction capacities of investigational medicinal products (IMPs), helping to assess their potential impact on metabolism and interaction with other drugs.

This includes detailed analysis and interpretation of preclinical data, crucial for informing decisions as studies progress. During the design phase, SGS assists in developing robust study protocols tailored to specific project needs, ensuring methodological rigor and alignment with regulatory requirements. This proactive approach ensures that DDI studies are strategically planned and executed to deliver meaningful insights into drug interactions early in the development process.

5. Case studies

To better understand the theoretical background, we would like to discuss two clinical development programs in which SGS provided consultancy and executed DDI studies for our clients at our Clinical Pharmacology Unit in Edegem, Belgium. The preclinical data shows a lot of DDI potential, so DDI studies will definitely have their place in the clinical development of both of these drugs.

5.1 CASE STUDY A

Study A is an umbrella study that combines multiple parts, including a DDI cohort. The initial step involves testing the drug (drug A) as a substrate. After thorough safety assessments, additional DDI studies may be conducted.

(I) STEP 1: PRECLINICAL DATA

- Metabolism: CYP3A4
- Inhibition: CYP2C8, OATP1B1, OATP1B3
- Induction: CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19

IMP: substrate

- Perpetrator: strong inhibitor of CYP3A4

Drug A is a drug that has never been tested on humans. Therefore, we first need other safety data before it is even possible to set up different DDI studies. In a nested DDI, the drug will be tested as a substrate of CYP3A4 together with a strong inhibitor.

Drug A is primarily metabolized by CYP3A4. Inhibition of this enzyme is expected to prolong the elimination and increase the exposure of the drug. The dose used for the DDI studies is 30 times lower than the highest dose given to humans, ensuring a clear safety margin.

(II) STEP 2: STUDY DESIGN

This phase 1 study is a randomized, double-blind, placebo-controlled, single and multiple ascending dose investigation in healthy participants, to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of drug A.

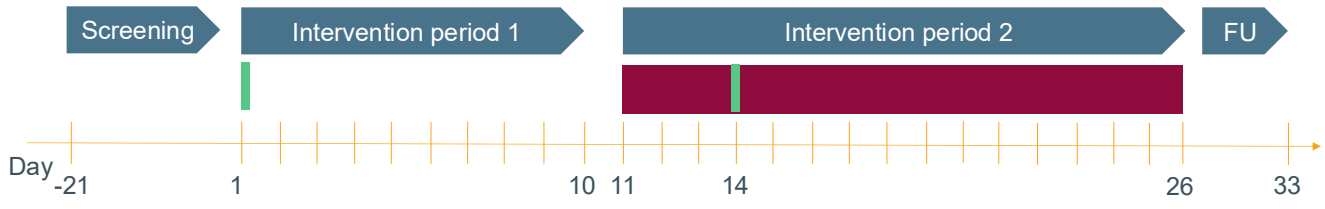
The DDI component is an open-label, fixed-sequence, two-period, standalone single-cohort study to evaluate the effect of multiple doses of a strong CYP3A4 inhibitor, itraconazole, on the single-dose PK of drug A. This involves:

- Healthy volunteers
- Multiple dosing of a strong inhibitor (using an index drug)
- Checking the interaction on a single dose of drug A, the substrate
- A cross-over, one-sequence design
- A nested DDI study approach

(III) STEP 3: SELECTING CHEMICAL INHIBITORS, INDUCERS AND SUBSTRATES

In this case, selecting chemical inhibitors, inducers and substrates is straightforward due to the availability of well-known index drugs. However, this is not always the case, and sometimes further research and literature review are necessary to select appropriate probe drugs.

Study A: Study design



PHASE 1:
Drug A is administered alone. A sufficient washout period follows

PHASE 2:
Itraconazole is administered once daily for approximately two weeks

PHASE 3:
Drug A is administered again on the third day of itraconazole dosing (in combination with the inhibitor)

LEGEND: *CYP3A4 inhibitor* *Drug A*

5.2 CASE STUDY B

Study B is a standalone study that only assesses the interaction between IMP (drug B) and three different probe drugs. Drug B is tested both as an inducer and an inhibitor, following EMA and FDA guidelines. It has demonstrated the highest induction value for CYP3A4 and the highest inhibition value for BCRP and CYP2C8.

(I) STEP 1: PRECLINICAL DATA

- Metabolism: BCRP, CYP
- Inhibition: CYP2C8, BCRP
- Induction: CYP3A4, CYP2B6, CYP1A2, CYP2C8

IMP: inducer and inhibitor

- Induction: affects CYP3A4 substrate
- Inhibition: affects BCRP and CYP2C8 substrates

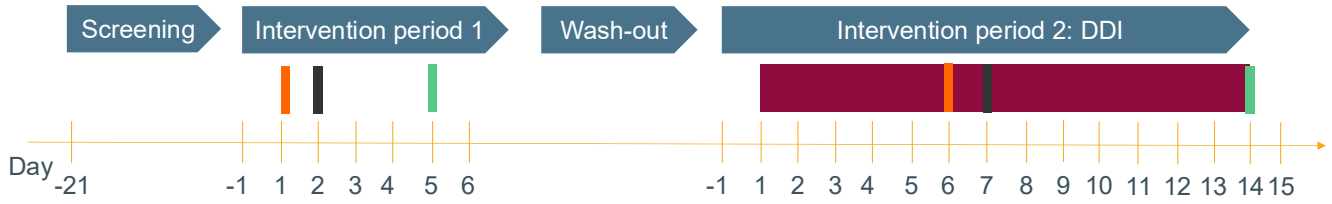
Drug B is currently being tested only as an inducer and inhibitor, not as a substrate. Drug B has been tested before, so more safety data is available, which means more possibilities. This drug induces and inhibits a couple of enzymes and transporters.

(II) STEP 2: STUDY DESIGN:

- Healthy volunteers
- Multiple dosing of drug B to evaluate its role as an inhibitor and inducer
- Assessment of interactions with single doses of sensitive substrates (using index drugs)
- A cross-over, one-sequence design
- A standalone DDI study approach

An open-label, nonrandomized, 2-period DDI study to evaluate the effect of multiple doses of drug B on the single-dose pharmacokinetics (PK) and a transporter substrate in healthy subjects.

Study B: Study design



PHASE 1:
Administer the three index substrates (repaglinide, midazolam and rosuvastatin) alone without drug B

WASHOUT PERIOD:
Allow sufficient time for the elimination of the substrates

PHASE 2:
Administer drug B daily for two weeks until a steady state is reached. Then co-administer the substrates with drug B

LEGEND: *Drug B* *CYP2CB substrate* *BCRP substrate* *CYP3A4 substrate*

(III) STEP 3: SELECTING CHEMICAL INHIBITORS, INDUCERS AND SUBSTRATES

In this study, selecting the chemical inhibitors, inducers and substrates is straightforward, due to the availability of well-known index drugs.

However, this is not always the case, and further research and literature review may be required to select appropriate probe drugs.

When you need to be sure

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