Reducing adverse event risk with informed, data-driven decisions about DDIs

PharmaPendium’s Drug–Drug Interaction Risk Calculator can predict the risk of drug–drug interactions, guiding decisions about which drugs to prioritize or eliminate from trials.
Here, the senior scientist of a global biopharmaceutical group discusses how they use PharmaPendium’s Drug-Drug Interaction Risk Calculator (DDIRC) in the prioritization of drug candidates and the planning of clinical trials. They state that the DDIRC helps to save considerable time and effort by demonstrating which DDI-focused clinical trials are not essential and that it increases trial safety by identifying risks with co-medications at higher doses.

Challenge

Drug–drug interactions (DDIs) account for 3 to 5% of all reported adverse drug reactions (1). Their incidence is increasing, primarily because patients are being prescribed more drugs, meaning the likelihood of taking a combination of drugs is higher.

In 2012, the U.S. Food and Drug Administration (FDA) provided draft guidance for the industry on drug interaction studies (2), stating that “pharmacokinetic interactions between an investigational new drug and other drugs should be defined during drug development, as part of an adequate assessment of the drug’s safety and effectiveness”.

Identifying potential DDIs and assessing their risk is a priority for pharmaceutical manufacturers and regulatory authorities. Assessments should be performed as early as possible in development to minimize health risks to clinical trial subjects and patients who may already be on a medication, and to prevent considerable spending on a drug that will fail during the most expensive stage of development, reach the market with severe prescribing restrictions, or be subject to a costly recall.

Solution

The Drug–Drug Interaction Risk Calculator (DDIRC) in PharmaPendium is fully compliant with the FDA’s 2012 draft guidance for drug interaction studies.

As a mechanistic static model calculator, the DDRIC can be used early in drug development, before anything is known about the elimination routes of the victim compound or the role of gut extraction for the victim and/or inhibitor in humans.

It also provides important insight in later stages of development when these parameters are already known.

Examples of DDIRC applications include:

• Informing decisions on which DDI-focused clinical trials are needed and which can be omitted to save time and effort
• Revealing the risk of interaction with drugs that clinical trial participants are already taking
• Helping to identify alternative drugs that would be safer to use as co-medications in clinical trials and post-market
• Evaluating the risk of interaction with common drugs, such as analgesics and antihistamines

Thanks to clear visual output data (Figure 1), the DDIRC makes it easy to see drugs with high risk of interaction, even when hundreds of drugs are under consideration.

Business Impact

At one global biopharmaceutical group, the DDIRC is already in use for drug candidate selection and clinical trial planning for oncology treatments. The group’s senior scientist reports that the DDIRC helps to save time and resources by showing which drugs to prioritize. It also helps to minimize risk to participants.
“If the risk of interaction is low for one drug and high for another, that information helps us to prioritize candidates. It’s also important to assess DDI risk with co-medications that can’t be avoided in the clinic. This is often the case in oncology trials, when even in phase 1, study participants are already on medications.”

They give a specific example. “In a recent trial, the DDIRC predicted no risk of interaction with substrates of six metabolizing enzymes but significant risks with some substrates of a seventh. We prohibited all co-medications that were known substrates of that enzyme to make a safer and more successful trial.”

The advantage with the DDIRC is its type of result. “The results provided by DDIRC are easier to work with than those from base DDI prediction models, which require very little input data to predict DDIs but can predict a long list of prohibited drugs. That may over-complicate clinical trials.”

The DDIRC is also used for supporting discussions with regulatory bodies. “During an end-of-phase I meeting for an investigational drug entering phase II of clinical development, we met with the FDA to agree on the scope of the clinical pharmacology program. PharmaPendium’s DDIRC was used to assess the risk of DDI due to inhibition of metabolizing enzymes. The in vitro data showed weak-to-moderate inhibition of four CYP enzymes, and the DDIRC predicted that the change in AUC ratio at the dose proposed for phase II was not clinically significant. We obtained a similar prediction at a theoretical higher dose and longer exposure. The FDA agreed with our conclusion that there was no risk of clinically significant inhibition, and we saved considerable time and money by not having to assess these factors in a clinical DDI study.

Another example, looking at dose assessment, is also significant. “We used the DDIRC to reveal significant risk of DDI when higher doses of the investigational drug were used. For this reason, we recommended that the co-medication dose would have to be adjusted if the investigational drug was to be given at ≥ 400mg. Having this predictive knowledge leads to better risk mitigation and ultimately leads to improved safety.”

The Drug–Drug Interaction Risk Calculator provides unique and actionable insights into the behavior of drugs in humans. In all applications at this global biopharmaceutical group, it has helped to inform decisions that have saved the company time, money and resources, and most importantly, have reduced the risk of adverse events caused by drug–drug interactions.

Figure 1 The DDI Risk Calculator enables risk assessment of multiple drugs simultaneously. The graph shows therapeutic classes where available drugs can be safely used as co-medications.

References
PharmaPendium®
PharmaPendium informs critical drug development decisions on safety and efficacy, risk assessments and mitigation and study designs with fully searchable FDA and EMA drug approval documents and FAERS data, a drug-drug interaction risk calculator and comparative safety, pharmacokinetic, efficacy, and metabolizing enzyme and transporter data.

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