# AN EVIDENCE-BASED APPROACH FOR MANAGING DDI RISK FOR PATIENTS IN CLINICAL TRIALS.

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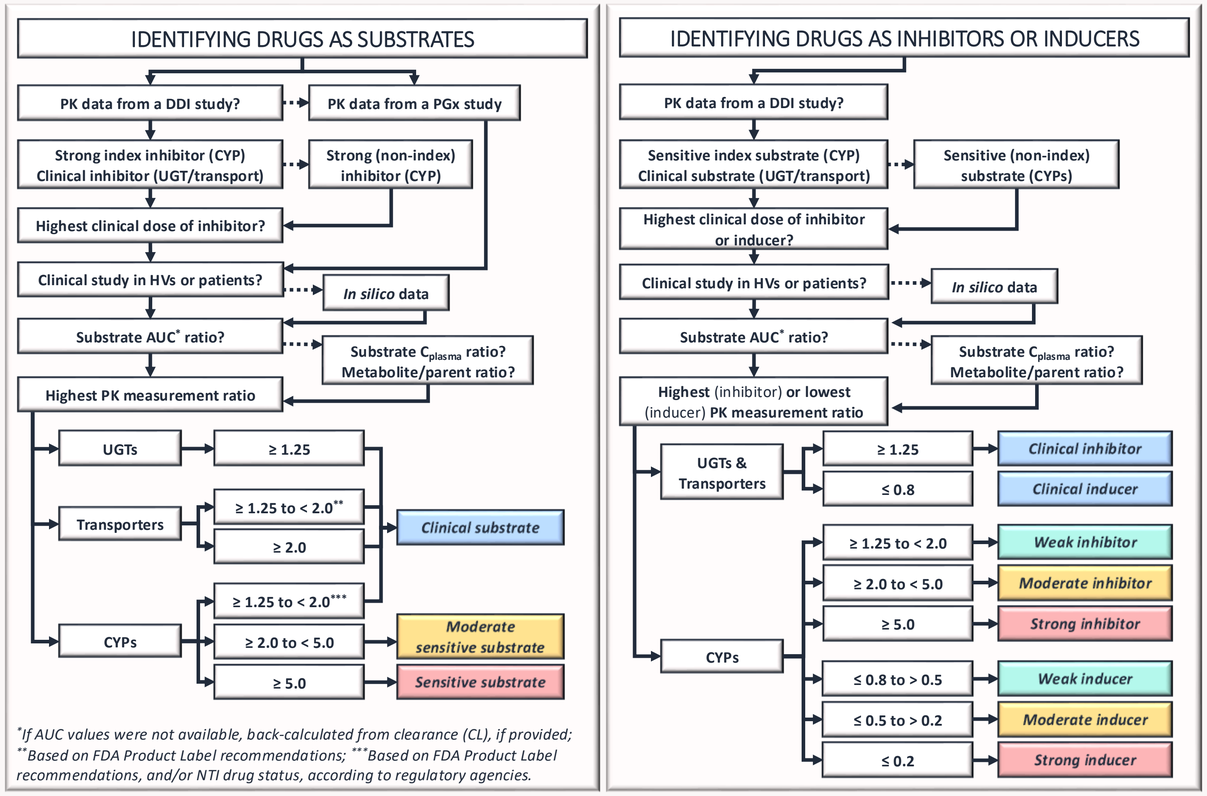
## Background and Objectives

There is a need for guidance and best practices for improved drug-drug interaction (DDI) management in clinical trials. Inadequate DDI management may not only lead to adverse events, but could also influence clinical evaluation of the unlicensed investigational medicinal product by leading to loss of efficacy.[1,2] Here, we propose that a systematic evidence-based approach leveraging regulatory-approved characterizations per the ICH M12 Guideline for Drug Interaction Studies[3] and clinical DDI and/or pharmacogenetic (PGx) data can be used to generate dynamic lists of potential concomitant medications for use in a particular clinical trial.

## Methods

Clinical pharmacokinetic (PK) data were compiled from the literature and FDA new drug application (NDA) reviews using the the Certara Drug Interaction Database (DIDB®). When clinical evaluations were not available, simulated (*in silico*) data were used. Sensitive and moderate sensitive substrates for CYPs as well as clinical substrates for UGTs and transporters were identified based on available AUC ratios (AUCRs) obtained from DDI studies. For polymorphic enzymes and transporters, available PGx data were also considered to identify substrates. DDI evaluations were conducted with clinical index inhibitors for CYPs, and clinical inhibitors for UGTs and transporters. Additional strong inhibitors were applied when index inhibitor studies were not available for CYP enzymes. Inhibitors and inducers were also identified and classified based on the available AUCRs obtained from DDI studies. These evaluations were conducted with clinical index substrates for CYPs, and clinical substrates for UGTs and transporters. When index substrate studies were unavailable for CYP enzymes, additional sensitive substrates were used. The highest AUCR was used to represent the worst-case scenario. Substrate sensitivity and inhibitor and inducer potency classifications were applied to CYP enzymes, but not to UGTs or transporters. When AUCR values were not provided, other PK measurements such as plasma concentrations (e.g., $C_{max}$, $C_{avg}$) and the metabolite/parent ratio were used when appropriate. Other drug properties, PK parameters, fraction metabolized, narrow therapeutic index (NTI), and QT prolongation potential were also considered. Decision trees were developed to characterize substrate sensitivity, and inhibitor and inducer potency (**Figure 1**).




*If AUC values were not available, back-calculated from clearance (CL), if provided; **Based on FDA Product Label recommendations; ***Based on FDA Product Label recommendations, and/or NTI drug status, according to regulatory agencies.*

**Figure 1.** Decision trees to assign characteristics for (left panel) substrates, (right panel) inhibitors and inducers. In accordance with the ICH M12 DDI guideline, inhibitor and inducer potency classifications are applied to CYP enzymes, but not to UGTs or drug transporters.



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*"Strategies for the evaluation of an investigational drug need to be developed early in drug development and **continually updated** as new data become available."*[2]

## Results

The systematic evidence-based approach identified a total of 1944 characteristics for 946 drugs, as presented in **Table 1**. To highlight the utility of this approach, we present the example of a hypothetical new molecular entity (NME) identified during development as a **CYP3A sensitive substrate.** This process would generate an evidence-based lists of 188 CYP3A inhibitors and 118 CYP3A inducers to review in the context of the NME's clinical trial population, considering its PK and safety profile. An example of the strong inducers of CYP3A is presented in **Table 2**.

**Table 1.** Drug characteristics identified.

| Category | Substrates | Inhibitors | Inducers |
|---|---|---|---|
| **CYP enzymes** | 298 moderate sensitive<br>186 sensitive<br>8 clinical | 328 weak<br>144 moderate<br>81 strong | 151 weak<br>70 moderate<br>17 strong |
| **UGT enzymes** | 56 clinical | 7 clinical | 12 clinical |
| **Transporters** | 199 clinical | 360 clinical | 27 clinical |

**Table 2.** A direct output list of all **strong inducers** of **CYP3A** identified.

| Drug | Therapeutic class | Study type | Marker drug | Lowest AUCR | Lowest $C_{max}R$** | Citation | Date |
|---|---|---|---|---|---|---|---|
| **apalutamide** | Antiandrogens | Clinical DDI | midazolam* | 0.08 | 0.23 | NDA 210951 | 2018 |
| **avasimibe** | Antilipemics | Clinical DDI | midazolam* | 0.07 | . | PubMed 12766253 | 2003 |
| **carbamazepine** | Anticonvulsants | Clinical DDI | quetiapine | 0.13 | 0.20 | PubMed 16390352 | 2006 |
| **encorafenib** | Kinase Inhibitors | Clinical DDI | midazolam* | 0.18 | 0.26 | NDA 210496 | 2018 |
| **enzalutamide** | Antiandrogens | Clinical DDI | midazolam* | 0.14 | 0.23 | NDA 203415 | 2012 |
| **ivacaftor and lumacaftor** | Respiratory Agents | Clinical DDI | itraconazole | 0.18 | 0.10 | NDA 206038 | 2015 |
| **lumacaftor** | | Clinical DDI | ivacaftor | 0.20 | 0.24 | | |
| **ivosidenib** | Cancer Treatments | PBPK DDI | midazolam* | 0.17 | 0.26 | NDA 211192 | 2018 |
| **mitotane** | Cancer Treatments | Clinical DDI | midazolam* | 0.06 | . | PubMed 21220434 | 2011 |
| **phenytoin** | Anticonvulsants | Clinical DDI | nisoldipine | 0.11 | 0.18 | PubMed 8917062 | 1996 |
| **rifampin** | Antibiotics | Clinical DDI | budesonide | 0.003 | 0.009 | PubMed 15726657 | 2005 |
| **rifapentine** | Antibiotics | Clinical DDI | midazolam* | 0.07 | 0.11 | PubMed 22472995 | 2012 |
| **st. John's wort (*Hypericum perforatum*)** | Herbal Medications | Clinical DDI | midazolam* | 0.20 | . | PubMed 16341856 | 2006 |

*FDA clinical index substrate for CYP3A. **Value observed or simulated in the study that yielded the lowest AUCR*

## Discussion

This process provides a robust and consistent evidence-based method for identifying concomitant medicines that need to be considered in the context of clinical trials of new drug products. A limitation of this approach is that it relies heavily on the sensitivity, potency, and specificity of index drugs. Use of static or dynamic DDI prediction models can be used as a follow-up to help decide whether a concomitant medication should be included or excluded from a particular clinical trial.

## References

1. Burger et al. Patients in Clinical Trials are Sub-Optimally Protected for Drug-Drug Interactions: A Call for Action. J Clin Pharmacol. 2025 May;65(5):654-657.
2. Lohy Das et al. Navigating Drug–Drug Interactions in Clinical Drug Development: A Tutorial. Clin Transl Sci. 2025 Sep 22;18(9).
3. ICH Harmonised Guideline: Drug interaction Studies M12 (2024).