Supplementary Protocol

Protocol for DDI-OI Data Collection

Source: UW DIDB, Drugs@fda (published NDA reviews and drug labelings), Goodman and Gilman, and other published papers

1. For collection of fe, list fe,iv and fe,po (fraction of the administered dose excreted unchanged in urine) in two different columns:

* First check data availability in NDA reviews and drug labelings for both fe,iv and fe,po.
* If not available, check Goodman and Gilman for either fe,iv or fe,po.
* If not available, look for other published sources to obtain fe,iv. If fe,iv is not found, then look for fe,po.
* If the statements in the source documents included the following;
* “xx% of the dose was excreted unchanged in urine”, enter “xx/100”.
* “the range of fe” is available, enter “xx-yy”. Use average of xx and yy for plotting.
* “less than xx% of the dose was excreted unchanged in urine”, enter the number as “<xx/100”.
* “less than xx% of the dose was excreted as total radioactivity in urine” and fraction of the unchanged drug is not available, enter “<xx/100” with a footnotes (need to be specifically flagged).
* “minimally/negligibly/trace amount excreted in urine”, enter “minimal”, “negligible”, or “trace”.
* If only Clr and Clsys values after IV administration are available in the clinical pharmacology section, enter “fe,iv” as calculated as Clr/Clsys.

1. For collection of %F (absolute oral bioavailability)

* If from the FDA labeling, the information is usually is available under the absorption subsection of the “Clinical Pharmacology” section of the FDA labeling, or published papers and an absolute bioavailability study using iv and po, has been conducted. If it is clearly stated “the absolute bioavailability is xx%”, then enter “xx/100”.
* If it is not stated, look for info like Clsys and Cloral values, %F can be calculated as 100\*Clsys/Cloral. If no information, then enter “NA” “not available”.
* If the ADME data is available (e.g., at least xx% based on percent unchanged in urine following oral administration), enter “>xx/100”.

1. For determination if renal excretion is a significant route of elimination (“renal pathway significant”), the following determination is utilized:

* If fe,iv >= 30% or fe,po >= 30%, enter “yes”.
* If the fe,iv <30% or fe,po/F<30%, enter “no”.
* If fe,po<30% in the absence of F, or if fe unknown, enter “NA(not available)”.

1. For determination if nonrenal elimination is a significant route of elimination (non-renal pathway significant):

* Enter “yes” if the entry for “3” above is “no”.
* Enter “yes” if fe,iv <= 70% or fe,po/F <= 70%
* Enter “yes” if a human mass balance study after iv administration shows that >=30% of the dose is metabolized by liver enzyme.
* Enter “yes” if a human mass balance study after intravenous administration shows >=30% of the drug is excreted unchanged in feces.
* Enter “yes” if a human mass balance study after oral administration shows >=30% of the dose is excreted as metabolites in the urine.
* Enter “no” if fe,iv or fe,po>70%.
* If none of the above fits, enter “NA (not available)”.
* Specifically flag if “non-renal pathway” clearly involves pathways other than liver or intestine (e.g. bone metabolism).

1. Metabolic enzymes:

* List all metabolic pathway specified in PL.
* If they were described as "major", "main", or “primary” in PL, bold these enzymes.
* When PL says metabolic pathway is not major, describe as “Metabolism is not a major pathway”.
* When PL says a compound is not metabolized, describe as “Not metabolized”.
* If PL does not describe any enzymes, describe as “Not specified”.
* If PL is not available, DIDB or publications should be queried.

1. Transporters:

* Collect in vitro information as substrate using UW DIDB and the FDA labeling.
* List all the transporters described in DDI guidance from FDA, EMA, and PMDA (P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1/2K, OAT1/3).