Comments on CT inclusion criteria

General comments: As you know, I do not like the use of “perpetrator / victim” to describe the drugs involved in a ddi. Precipitant / object is my preference. As you will see, there is a fair amount of ambiguity in the criteria. Unless criteria are obvious and easily evaluated, I would not include them since it would encourage evaluators to guess if the criteria are met or not.

Criteria number

1. The use of the term “time-dependent” inhibitor may be problematic for some users. The FDA draft does not provide a definition of time-dependent. I can think of at least two examples where multi-dose regimens would be important: precipitant drug is converted to a metabolite that inhibits the object drug; precipitant drugs with long half-lives that require loading doses or repeated administration to get to steady state.
2. While the use of the listed index inhibitors would be desirable, it does not eliminate the use of alternative drugs as appropriate precipitant drug. Some of the index inhibitors, ie fluvoxamine, are known to inhibit multiple enzymes. If the exact metabolic pathways of the object drug are unknown to the investigators, they may inhibit a pathway different than the one they think is being evaluated. The same applies to transport inhibitors – several drugs inhibit multiple transporters. This is probably more of an issue than when dealing with CYP inhibitors because many drugs are also substrates for multiple transporters. Bottom line, did investigators choose a precipitant / object pair that limit the mechanism to a single pathway?
3. I do not get this. If a drug has linear kinetics, it is linear at all doses. That is the definition of linear kinetics. This one could be deleted from the list.
4. As written, it sounds like the object drug administration should be delayed. However, it is not clear what “delayed” means. Does this mean after steady state of precipitant is reached, or some period of time after precipitant dose is administered – ie not simultaneously. There are so few examples were this is important- the rifampin example in the FDA draft is the primary one- that I would remove this criteria from your list.
5. Consider alternative wording: If the object or precipitant drug displays non-linear or dose dependent kinetics, was the drug dosed to steady-state?
6. Instead of “relevant pharmacokinetic pathway” I suggest “relevant metabolism or transporter pathway”.
7. This makes sense. However, this is a rather complex issue. The effect of food can range widely. Knowing what specific conditions should be used is probably beyond the ability of typical readers to evaluate. Perhaps an alternative guide would be: if the drugs are not administered fasting, did the authors provide adequate rational for the variation?
8. As written, this assumes only 2 enzymes are acting on the object drug. Perhaps a more general criteria would be; “If a study uses an object drug metabolized by more than one pathway, is the precipitant drug a selective inhibitor or inducer of only the primary metabolism pathway of the object drug?”
9. See #2 above. That applies to precipitant drugs as well as object drugs. Bottom line, did investigators choose a precipitant / object pair that limit the mechanism to a single pathway?
10. This reads well.
11. Not sure how one would know if maximum inhibition was achieved. Assessing the plasma concentration of the precipitant drug and comparing that to therapeutic concentrations would make sense, but inhibition magnitude will be variable between patients. I doubt many studies will try to meet the recommendation in lines 261-5. Would likely be easier to simply dose precipitant drug to steady state before administering object drug. I would take this single dose criteria out.
12. Again the issue is how would one determine if the dose of the precipitant drug was sufficient to produce a measurable interaction? What if there is NO interaction? The FDA guidelines note that maximum dose of precipitant drug should be used. I would assume this means maximum therapeutic dose. Perhaps the Drive criteria should state the criteria in those terms. “Was the dose of precipitant drug similar to the maximum therapeutic dose?” The FDA criteria re “shortest dosing interval” does not make much sense. Do they mean the interval between doses of the precipitant drug or total duration of precipitant drug administration? How about: “Was the dose of precipitant drug similar to its maximum therapeutic dose and was it administered for an adequate duration to reach steady-state?”
13. Reads ok as is.
14. This refers to non-linear object drugs. The FDA guidance does not suggest what “therapeutic dose is most likely to demonstrate a DDI”. I cannot offer any guidance either. An interaction could be seen with the object drug in either the linear or non-linear concentration range. If the object drug is in the nonlinear range, a smaller change in clearance will result in a larger change in AUC vs doing the study with the object drug levels in a linear concentration. This seems to be rather odd. I would recommend removing this criteria since no one can predict where a drug’s clearance becomes non-linear in any given patient.
15. Non two-way crossover studies (ie parallel group) should not be relied upon for DDI evidence. This criteria could be simplified to: “Does the study design account for the pharmacokinetic properties of both the object and precipitant drugs? Has an adequate washout period been provided to allow complete elimination of the object and precipitant drugs between trial arms?
16. This is a study power question. It is difficult for most readers to know if adequate sample size was used. Thus, one should rely on the study design section of the report to provide a sample size estimate to adequately power the study for the statistical endpoints.
17. The criteria should specify that the AUC measurements are for the object drug. This criteria seems ok, but it is missing the important criteria that at least 3 half-lives of concentration-time data for the object should be provided to estimate AUC0-inf.
18. This is ok as written.
19. This is ok as written.
20. Again, most readers will not be able to judge if the sample size is adequate. I would suggest that parallel, two arm studies only be accepted when it is not possible to do a cross over design. Study authors must justify the use of parallel design; convenience is not a good reason. Adequate justification of sample size must be presented.
21. There is a typo: geometric mean ration should be geometric mean ratio. I am not clear what “observed variability” means. Is that min – max effect? Standard deviation? Percent of subjects exceeding some set mean ratio? Without definition, I would delete the observed variability criteria.