FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

FDA Perspectives on Regulatory Guidance on Drug-Drug Interactions

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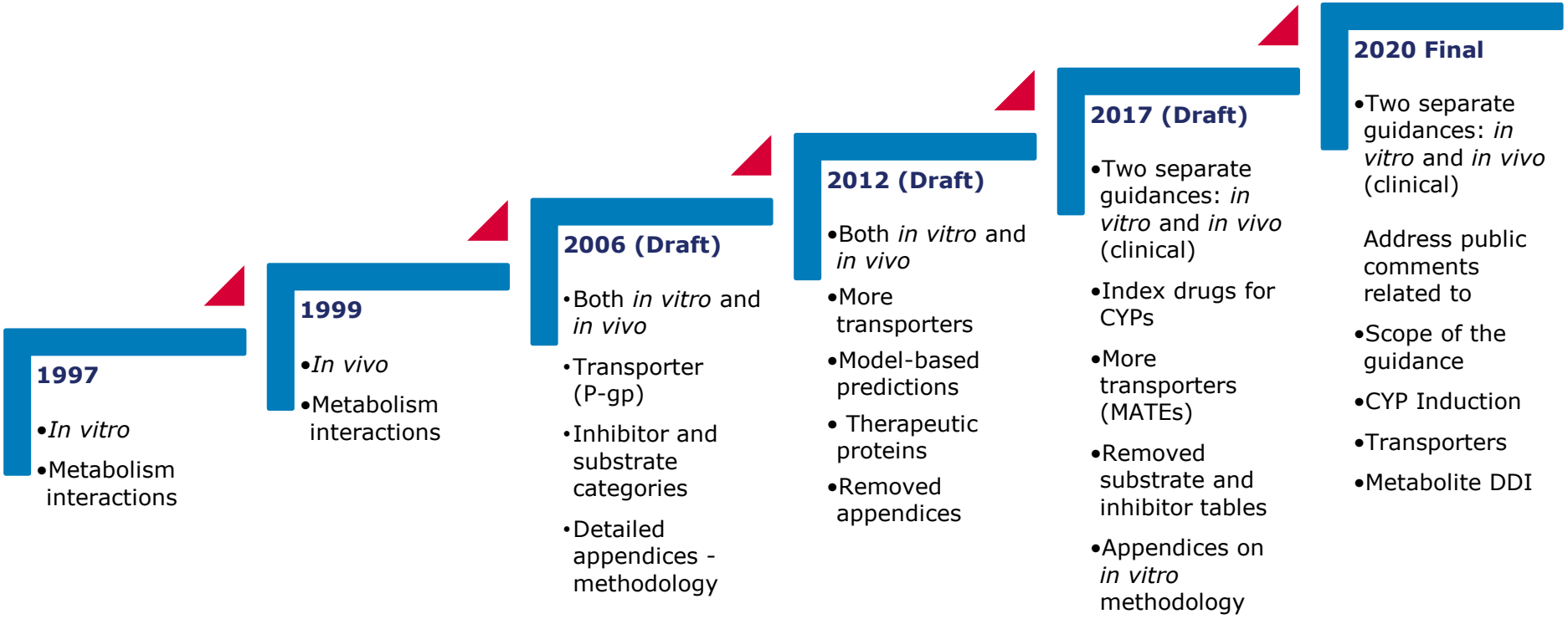
Evolution of FDA DDI Guidances



FDA Website: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (periodically updated)
https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

2020 DDI Guidances: Scope

- Scope: Evaluation of cytochrome P450 (CYP)- or transporter-mediated DDIs
- Topics not addressed in the 2020 guidances
  - Therapeutic protein DDIs (draft guidance issued Aug, 2020)
  - DDIs involving oral contraceptives (draft guidance issued Nov, 2020)
  - Gastric pH -dependent DDIs (draft guidance issued Dec, 2020)
  - Phase 2 enzyme-mediated DDIs
  - Plasma protein displacement-mediated DDIs
  - Pharmacodynamic DDIs
  - Detailed guidance on product labeling language
- PBPK:
  - PBPK Analyses — Format and Content (Aug, 2018)
  - The Use of PBPK Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls (draft guidance issued Sep, 2020)

Outline

- How to evaluate induction potential of an investigational drug on CYP2C enzymes

- Impact of nitrosamine impurities of rifampin products on DDI assessment of inducer effect on an investigational drug

Evaluate Induction Potential of CYP2Cs

- Induction potential is typically evaluated for CYP1A2, 2B6, and 3A4 first in vitro. If a drug doesn't induce CYP3A, no need to evaluate CYP2Cs, since they are co-regulated by PXR agonists and less inducible than CYP3A. If CYP3A4 is induced, there is a need to further evaluate induction effect on CYP2Cs.

- It is not uncommon that positive controls have limited induction effects on CYP2C8, 2C9, or 2C19, making it difficult to interpret the in vitro data.

- An approach is to leverage in vivo DDI study results with a sensitive CYP3A substrate.

- Negative DDI can rule out induction potential of a drug on CYP3A and also CYP2Cs, *as long as* the possibility of CYP3A inhibition by the drug and its metabolite(s) can be excluded (avoid situations where inhibition and induction of CYP3A counteract each other).

Evaluate Induction Potential of CYP2Cs

Several scenarios

- A drug (and metabolite) doesn't inhibit CYP3A in vitro or R values less than corresponding thresholds.

- A drug as a reversible inhibitor cannot be ruled out with CYP3A inhibition potential due to R_1 or $R_{1,gut}$ over the threshold. An in vivo study may add a period where a sensitive CYP3A substrate will be given shortly after or simultaneously with a single dose of the drug. If there is no significant effect, it rules out inhibition. Thus, a negative DDI after multiple doses of the drug on CYP3A substrate indicates no induction, either.

- This approach might not work for a drug/metabolite with long t1/2 and significant accumulation after multiple dosing. It may not work for a drug that is also a time-dependent inhibitor.

- The strategy may also be applicable for evaluating induction potential on P-gp and UGTs

Ramsden D, et al. Drug Metab Dispos . 2019 Oct;47(10):1206-1221.

Nitrosamine Impurities in Rifampin and Rifapentine Products

- MNP (1-methyl-4-nitrosopiperazine) and CPNP (1-cyclopentyl-4-nitrosopiperazine) belong to nitrosamine class of compounds, some of which are classified as probable or possible human carcinogens, based on tests such as rodent carcinogenicity studies.

- The acceptable intake limits are 0.16 parts per million (ppm) for MNP in rifampin and 0.1 ppm for CPNP in rifapentine in humans.

- The Medical Policy and Program Review Council of CDER decided that use of rifampin products with MNP impurity above 0.16 ppm in healthy volunteers is not acceptable.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamines-rifampin-and-rifapentine

What's the Impact on DDI Assessment?

- Rifampin is a well-known inducer of multiple enzymes (e.g., CYPs, UGTs) and transporters (e.g., P-gp, OATP1B). It is the most often used inducer in DDI studies to evaluate the impact of inducer drugs on the PK of investigational drugs.

- Rifampin (single-dose) is also a potent inhibitor of OATP1B and has been used in DDI studies to examine the effect of OATP1B inhibition on the PK of drugs that are OATP1B substrates.

- Now, we need to find an alternate inducer because of impurities exceeding the acceptable limit for rifampin products.
  Since Dec 2020, 7 INDs from several sponsors have encountered this issue.

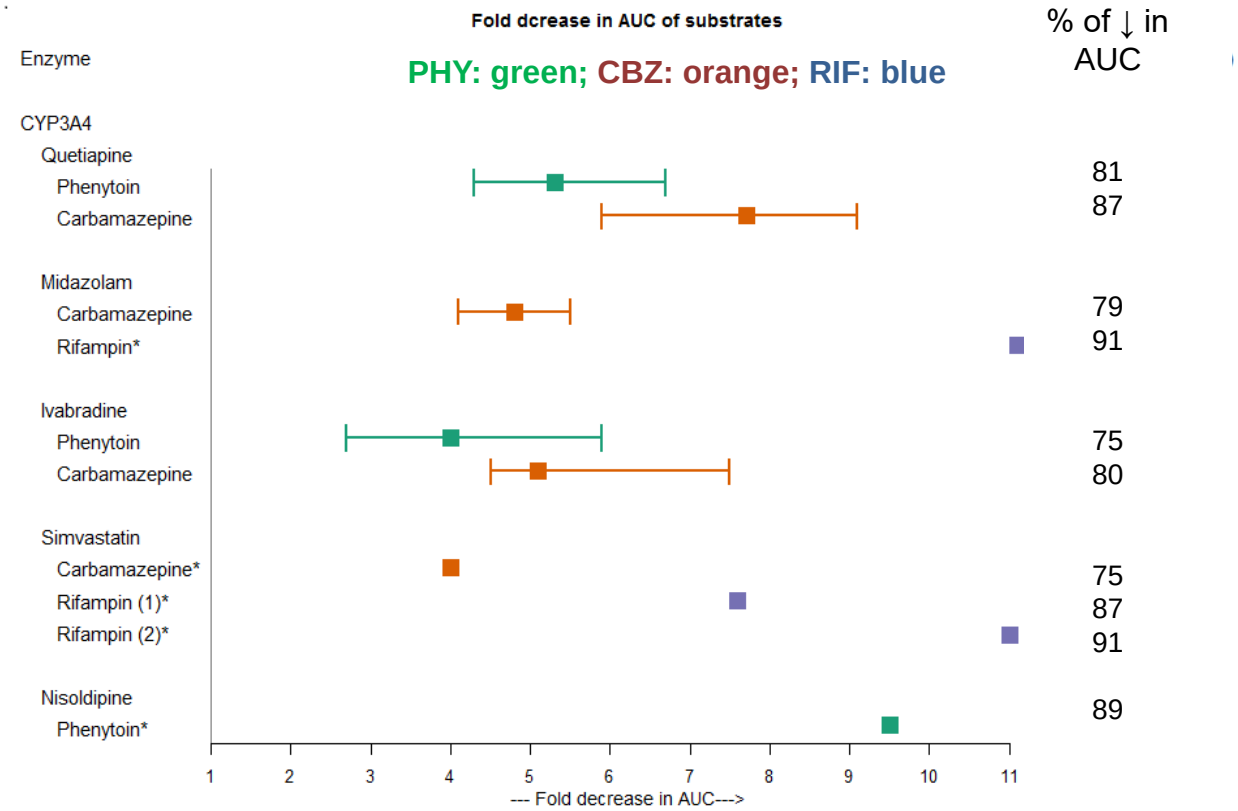
What may be an Alternative Drug for Rifampin for DDI Studies

- Carbamazepine (CBZ) as the primary choice to evaluate the impact of CYP3A inducers. Dosing of CBZ
  initiated from a lower dose(e.g., at 100 mg bid and titrated in 100 mg increments to 300 mg BID over 3-7 days);
  and then maintained at 300 mg BID for 14 days

- Phenytoin (PHY) as a secondary alternative to evaluate the impact of CYP3A induction. PHY dosing regimen is 300 mg/day (qd, bid, tid) for 14 days. A period of up-titration may not be needed.

Why Carbamazepine or Phenytoin?

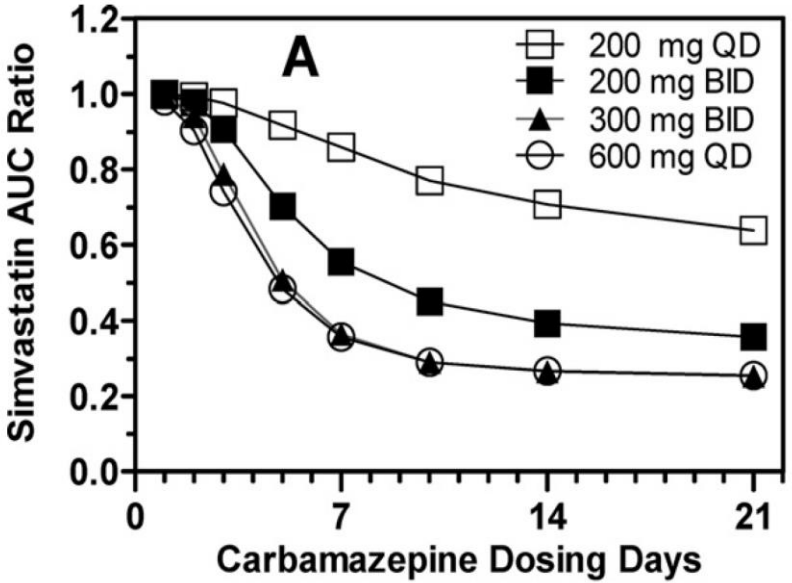
Examples of CYP3A strong inducers: apalutamide, enzalutamide, mitotane, rifampin, St. John's wort, CBZ, PHY



strong inducers ↓ AUC of a sensitive substrate by 5-fold or more, i.e., AUC substrate is decreased by 80% or more

Dosing Regimen of Carbamazepine for DDI Studies (Dose Level)

- Literature studies conducted in healthy subjects used CBZ doses from 200-1200 mg/day, with majority studies conducted with 400 mg/day or 600 mg/day.
- Based on PBPK simulations, 600 mg/d dose approaches plateau.



Xu Y, et al. Drug Metab Dispos. 2011 Jul;39(7):1139-48.

Dosing Regimen of Carbamazepine for DDI Studies

- *Duration:* CBZ treatment ranged from 5 to 42 days, with a median value of 16.5 days. PBPK simulations indicated that 14 days are sufficient to reach the maximal effect.

- *Dosing schedule:* Titration may be needed to improve tolerability and reduce drop-out rate. CBZ was usually initiated from 100 mg bid (in a few studies started from 200 mg qd or bid).

– *Recommendation:* Initiate CBZ from a lower dose (e.g., at 100 mg bid and titrate in 100 mg increments to 300 mg BID over 3-7 days), and then maintain at 300 mg BID for 14 days

May need to consider screening subjects with East Asian ancestry for carriers of HLA-A*3101 or HLA-B*1502 alleles to reduce the risk of severe AEs (e.g., Steven-Johnson Syndrome)

Dosing Regimen of Phenytoin for DDI Studies

- There were fewer DDI studies with phenytoin.
- *Dose:* most commonly used was 300 mg total daily dose given as qd or tid (in a few studies as bid).
- *Duration:* ranged from 5 days to 22 days, with a median of 14 days.
- *Dosing schedule:* There was no titration in most studies.

- *Recommendation:* PHY dose is 300 mg/day (qd, bid, tid) for 14 days. A period of titration is not needed.

Other Scenarios

- Could a moderate CYP3A inducer be an option for drugs extensively metabolized by CYP3A?

  A study with a moderate inducer may confirm the anticipation of significant effect of strong inducers and also characterize the effects of moderate inducers. This may reduce the need of post-marketing requirement/commitment studies.

- What is an alternative for rifampin as OATP1B inhibitor?

  Cyclosporine is also a potent inhibitor (it also inhibits P-gp, BCRP, and MRPs). Rifampin also inhibits P-gp.

- What is an alternative for rifampin as an inducer for drugs mainly metabolized by CYP2C8/2C9/2C19 or UGTs or transported by P-gp/OATP1B?

  Less studies with other inducers

Other Products with Nitrosamine Impurities

- Certain valsartan, losartan, and irbesartan products were recalled due to nitrosodimethylamine (NDMA) or N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) over the acceptable limit.

- FDA requested removal of all ranitidine products from the market because of NDMA impurity. Certain nizatidine products were also recalled.
  Consider other H2 blocker (e.g., famotidine) in gastric pH-dependent DDI (pH-DDI) studies

- Metformin extended-release products were recalled by a number of manufacturers due to NDMA impurities
  Metformin is used as a substrate in DDI studies with OCT2/MATEs inhibitors.
  IR products of metformin are not affected and still available for DDI studies.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan
https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine
https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-metformin-products?utm_medium=email&utm_source=govdelivery

Perspective

- Drug interactions is one important factor in determining the drug and dose for individual patients. An integrated approach can be used to leverage available in vitro/in vivo information and in silico to evaluate DDI potential of a drug.

- CYP induction is more complicated than inhibition. While significant advances have been made, there are still areas that need further research (e.g., criteria for IVIVE based on mRNA data, how to utilize activity data) and also think about study design of in vivo DDI studies.

- Although rifampin has been most often used, there may be scenarios where an alternative inducer is appropriate, with a balance of clinical relevance and utility to extrapolate findings to other inducers.

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