Endogenous Biomarkers for the Evaluation of CYP3A-mediated Drug Interactions

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Evaluation of Drug-Drug Interactions

In Vitro DDI Assessment

How to assess the DDI potential?

What should be my clinical DDI assessment strategy?

Which clinical DDI studies should I conduct?

Focuses on enzyme- and transporter-based DDI

Clinical DDI Studies

When to conduct needed clinical DDI studies?

How should clinical DDI studies be conducted?

How should results from clinical DDI studies be analyzed, interpreted, managed and communicated?

Model-based DDI Prediction and Simulation

Modified from Dinko Rekić, ASCPT 2016

Goals of Drug Interaction Evaluation

- Determine the potential for clinically significant DDIs

- Determine management strategies for clinically significant DDIs

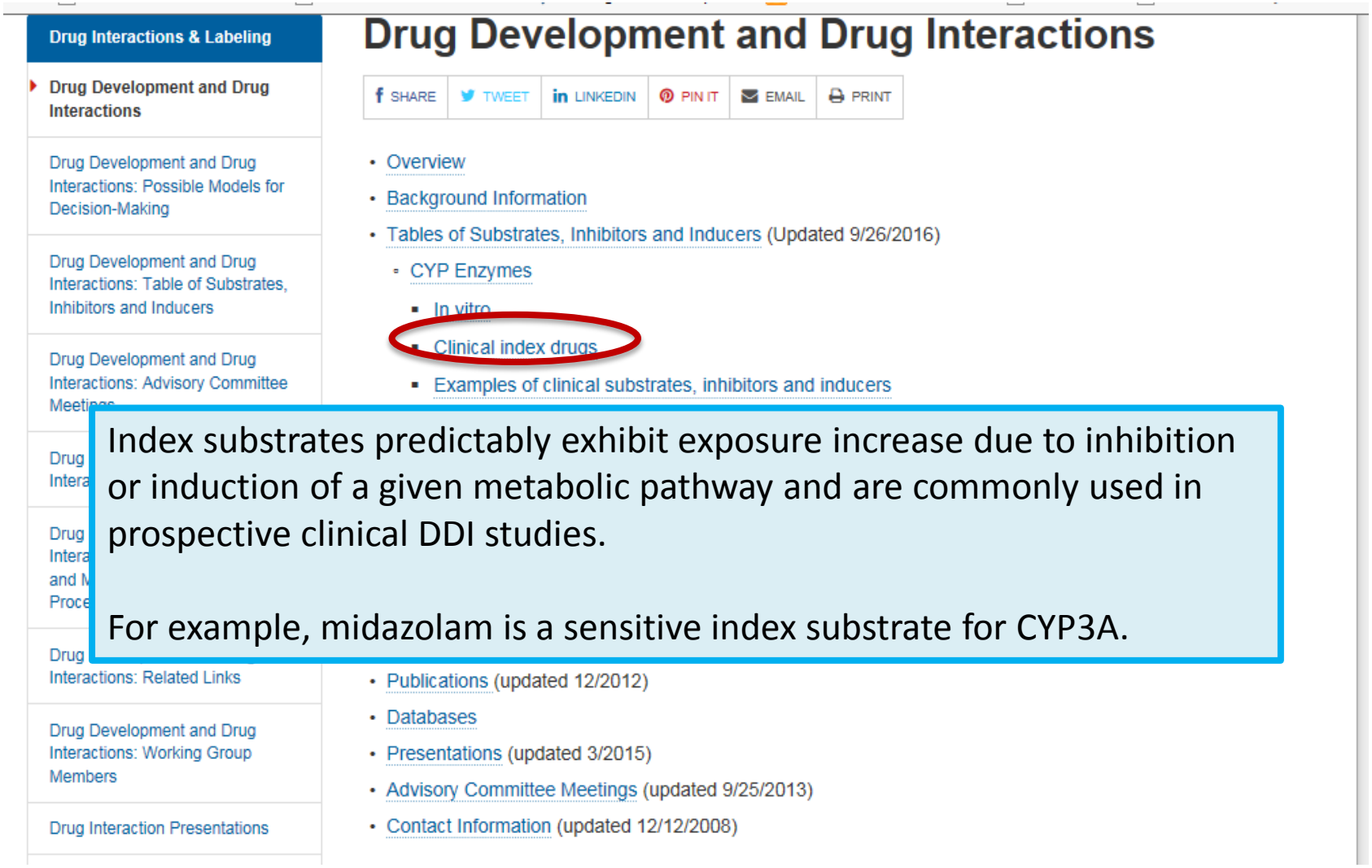
Types of DDI Studies

- In vitro
  - Inhibition
  - Induction
  - Mixed
- Clinical
  - Prospective or Retrospective
  - Index studies (studies with index perpetrators and index substrates)
  - Concomitant use studies
- In silico

Index studies

- Use perpetrators or substrates with **well defined properties** (level of inhibition, induction, and metabolic pathway)
- **Extrapolate** to other substrates and perpetrators
- May not be clinically relevant for intended patient population

FDA Drug Development and Drug Interactions Website



Index substrates predictably exhibit exposure increase due to inhibition or induction of a given metabolic pathway and are commonly used in prospective clinical DDI studies.

For example, midazolam is a sensitive index substrate for CYP3A.

Endogenous Biomarker (vs. Probe Substrate) for DDI Evaluation

Advantages:

- Obviates the need to administer a probe drug
- Patient population

Challenges:

- May not be used to evaluate gut enzymes
- Variability (baseline, diurnal variation)

Biomarkers of CYP3A activity Questions

- *What have we learned?*
- *Are we ready to utilize biomarkers to replace clinical DDI studies?*

4β-Hydroxycholestrol (4β-HC) for CYP3A DDI Evaluation

- 5 NDA submissions (2013-2016)

	Purpose	Conclusion
NME as CYP3A modulator (1 case) In vitro-inhibitor and inducer for CYP3A In vivo-no effect on CYP3A	4β-HC was used along with a sensitive CYP3A substrate to study the effect of multiple dose NME on CYP3A activity	Both 4β-HC and CYP3A substrate results showed that CYP3A levels did not change significantly in the presence of NME. DDI results with the CYP3A substrate were included in the labeling. (Results of biomarker were not included in the labeling.)
NME as CYP3A substrate (4 cases)	4β-HC was used to show CYP3A change in the presence of the known inducer (e.g., rifampin or phenytoin)	Supportive to show that CYP3A was induced in the presence of known inducer.

NME: new molecular entity

Urinary 6β-Hydroxycortisol (6β-OHC) for CYP3A DDI Evaluation

- 7 NDA submissions (2013-2016)

	Purpose	Conclusion
NME as CYP3A inducer (5 cases) in vitro/in vivo→labeling 1 +/- → n/a 1 +/+ (*+)→ + 1 +/? (in vivo dose was not high enough) → n/a 1 -/± (variable) (*-) →negative in vitro data 1 -/- → -	6β-OHC was used to study the effect of multiple dose NME on CYP3A activity 2 cases had separate studies with *CYP3A substrates 3 cases no other studies with CYP3A substrates	Conclusions in the labeling were generated from overall assessments. The sources of information (e.g., biomarker) were not mentioned in the labeling.
NME as CYP3A substrate (3 cases)	6β-OHC was used to show CYP3A change in the presence of the known inducer (e.g., rifampin)	Supportive to show that CYP3A was induced in the presence of known inducers.

NME: new molecular entity; n/a: not available (drug was not approved).

Comparison of 4β-HC and Midazolam for DDI Evaluation

	4β-HC	Midazolam (oral)
Selectivity for CYP3A	Good	Good
DDI type and sensitivity	-Induction -Not sensitive to inhibition (long-half life)	Sensitive to both inhibition and induction
DDI magnitude and quantification	Smaller dynamic range	Change in CL larger
DDI site	Hepatic	Intestine and hepatic

Comparison of 4β-HC and Midazolam with Varying Induction Potencies

Table 1. Inducer Classification and Corresponding Model-Predicted 4βHC Biomarker Changes

Regulatory CYP3A Inducer Classification[a]	Midazolam AUC GMR[b]	Model-Predicted Plasma 4βHC Increase: Population PK/PD[c]	Model-Predicted Plasma 4βHC Increase: E_{max}-I_{max}	Model-Predicted Plasma 4βHC Increase: Bayesian Mechanism–Based PK/PD[d]
Weak	0.50–0.80	<1.13	1.09–1.37	1.05–1.20
Moderate	0.20–0.50	1.13–2.10	1.37–2.46	1.20–2.05
Strong	0.20	>2.10	>2.46	>2.05

[a]FDA Guidance for Industry—Drug-Drug Interaction Studies, 2012; EMA Guideline on the Investigation of Drug Interactions, 2012.
[b]AUC, area under plasma concentration-time curve; GMR, geometric mean ratio.
[c]From Ref. 8.
[d]From Ref. 7.

Mangold, et al, Clin Pharm in Drug Develop, 2016

Table 2. Model-Predicted 4βHC[a] Increase From Baseline Median (5th and 95th Percentiles) After 14 Days of Treatment With Rifampicin

Rifampicin Dose (mg)	Predicted Median (5th, 95th Percentiles)
10	1.13 (1.04, 1.44)
20	1.28 (1.10, 1.71)
100	2.10 (1.45, 3.49)
500	4.43 (2.63, 6.77)
600	4.76 (3.00, 6.77)

[a]4βHC, 4β-hydroxycholesterol.

Jiang et al, *Clin Pharm in Drug Develop*, 2016

When May 4β-HC be Used for DDI Assessment

- Determine the potential for clinically significant DDIs

- May detect NMEs that are "stronger" CYP3A inducer

- May miss NMEs that are "weaker" CYP3A inducers
- May not provide an accurate DDI assessment for NMEs that are mixed CYP3A inhibitors/inducers
- Cannot be used to study for CYP3A inhibition

- Determine management strategies for clinically significant DDIs

How to extrapolate the results <u>"quantitatively"</u> to other CYP3A substrates to inform dosing adjustment?

Conclusions

- New research has been conducted in the biomarker area
- We have limited regulatory experience on the use of endogenous biomarkers (e.g., 4β-HC) for DDI evaluation.
- There are areas that endogenous biomarkers can be used to assess DDI
  - For example, 4β-HC for qualitative assessment of hepatic CYP3A induction
  - Limitation and scope of each marker need to be well understood with proper validation to fit the intended purpose of the evaluation.
- Currently, 4β-HC study alone is unlikely to replace an oral midazolam study as an "index" substrate
  - Can 4β-HC data coupled with PBPK modeling be able to quantitatively predict the effect on CYP3A induction?

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What is an Ideal Universal DDI Biomarker?

- **Selectivity**-Good specificity
- **DDI Type and Sensitivity**-Sensitive to changes in enzyme activity (either inhibition or induction)
- **DDI magnitude and quantification**-Quantitative correlation with the known index substrate change in a similar magnitude in response to enzyme activity change
- **DDI site**-Can detect both intestinal and hepatic enzyme changes