Survey: Drug-Drug Interactions Between Hormonal Contraceptives and Drugs with Teratogenic Potential

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Disclaimer

- I have no conflicts of interest

- The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the United States Food and Drug Administration (FDA)

Background

- When females of reproductive potential (FRP) need to take teratogenic drugs, prevention of pregnancy is critical to mitigate teratogenic risk
- Several factors may decrease contraceptive effectiveness
  - Drug- Hormonal Contraceptive (HC) Interaction

    Impact on HC is the key information to recommend reliable contraceptive methods

Background-cont.

- **Current FDA Drug-Drug Interaction (DDI) Guidance:**

  There may be mechanisms of induction that are presently unknown

  ⇩

  a potential human teratogen needs to be studied in vivo for effects on contraceptive steroids if the drug is intended for use in fertile women, regardless of *in vitro* induction study results

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf

Objective of the Survey

Understanding the Current Practices for

- Conducting clinical DDI study between HC and potentially teratogenic drugs
- Using clinical DDI results to inform effective contraception methods in clinical trials and product labels

Methods

Recently approved new molecular entities (NMEs) with teratogenic potential

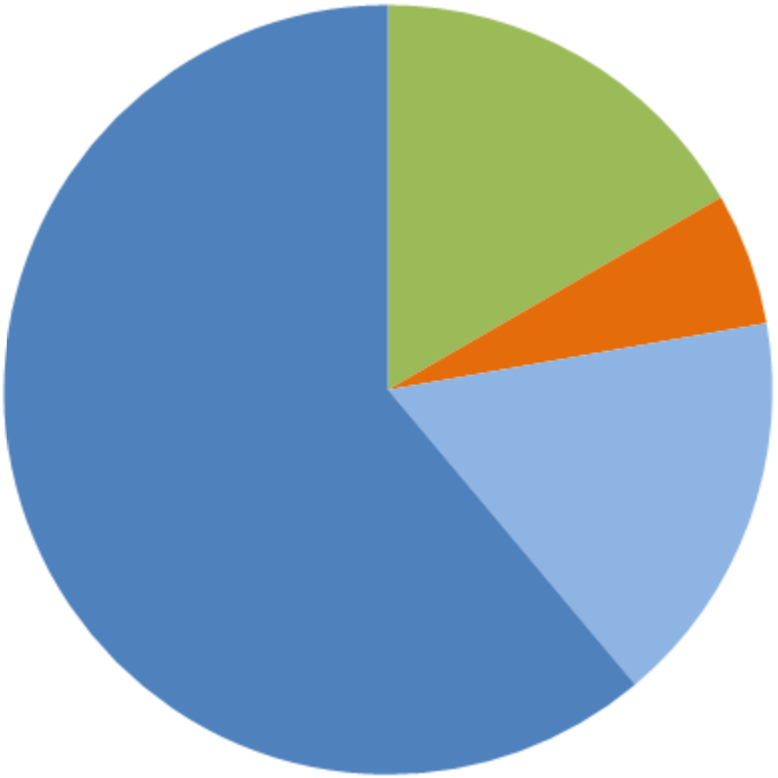
- 107 NMEs: approved in 2012 – 2014
- 18 NMEs: "teratogenic potential" per product label

Method-cont.

- Were Clinical DDI studies with HCs conducted ?
  - Study results & before Phase 3 studies ?
  - *In vitro* data: NME with CYP enzyme induction potential
- Was HC use allowed in Phase 3 trials?
  - Decision-making based on clinical DDI data?
- Are DDI findings reflected in the product labels?

Results: Clinical DDI Studies with HC

Of 18 NMEs with Teratogenic Potential



4 NMEs: Clinical DDI Studies Done

- 3: not inducer (in vitro): HC ↔
- 1: CYP3A4 induction (in vitro): HC↑

14 NMEs: Clinical DDI Studies **Not** Done

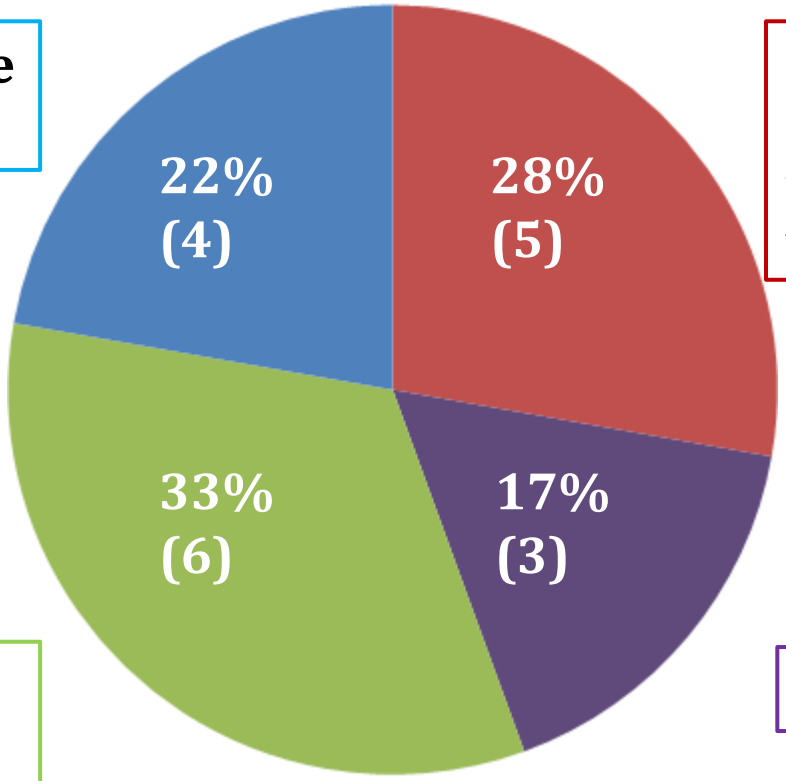
- 3 NMEs: CYP3A4 induction (in vitro)

4 clinical DDI studies were done **after** Phase 3 studies

Results: HC Use in the Phase 3 Studies

No DDI data available when Phase 3 studies were conducted

No Contraceptive Inform.



HC can be used alone: e.g. oral contraceptives transdermal patch or vaginal ring, etc.

HC + a barrier method

HC not permitted

Results: Label on DDI results & Contraception

- Reporting DDI results in the label: 3 out of 4 studies
- Teratogenic risk along with supporting data are stated in labels
- Instruction on Contraception
  - General Information: 50% (9/18):

    Require efficient contraception due to teratogenic risk
  - Specific Information on whether HC is a reliable method: 33% (6/18)
  - No Information on contraception: 17% (3/18)

Case Example 1: Teriflunomide

- **Indication**: Treatment of multiple sclerosis
- ***In vitro* data**: CYP3A4 inducer
- **Clinical DDI study with CYP3A4 probe**: midazolam ↑ 27%
- **Clinical DDI study with HC**: HC ↑ by 41-54%

Data source:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails

Case Example 2: Dabrafenib

- **Indication:** treatment of cancer
- **In vitro data**: induction potential
- **Clinical DDI study with HC**: not conducted
- **Clinical DDI with CYP3A4 probe**: 74% reduction in midazolam

Data source:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#Apphist

Summary

Based on 18 NMEs with teratogenic potential

- Conducting clinical DDI studies with HC has not been a common practice
- Clinical trials (Phase 3 trials):
  - Significant variability with regard to contraception practices
  - Allowing use of HC without evidence from DDI study
- Product Label :
  - DDI studies with HC are reflected in the label
  - Instructions on reliable contraception are variable

Take Home Messages

- Clinical DDI testing with HC is important to provide evidence-based guidance on reliable contraceptive method for FRP taking drugs with teratogenic potential

- Consistent practice to inform reliable contraceptive methods is needed to adequately protect women in clinical trials and after drug approvals.

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Teriflunomide

Table: Teriflunomide as a substrate, inhibitor or inducer of CYPs or other enzymes

CYPS	substrate	Inhibitor	Inducer*
1A2	X	X	X
2B6	X	X	Not evaluated
2C9	X	Yes	Yes
2C19	X	X	Co-induced
2C8	X	Yes	Co-induced
3A4	X	X	Yes
3A5	X	X	NA
2D6	X	X	NA

Of 4 NMEs with induction potential based on *in vitro* data

- HC Use in the Phase 3 Studies
  - HC use alone: 1/4
  - HC use was not permitted: 3/4
- Label Instruction on HC use
  - Specific instruction on whether HC cannot be used: 1/4
  - General information: 3/4