Drugs with Teratogenic Potential: Contraception Use and Labeling

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Outline

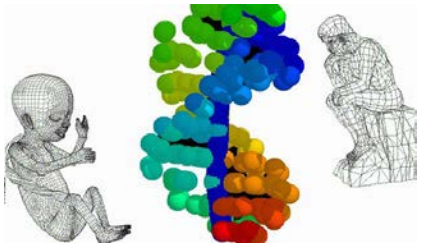
- Defining the drugs with teratogenic potential
- Considerations for Drug-Drug Interaction (DDI) studies
- Labeling

Teratogen

Any substance, agent, or process that interferes with normal prenatal development, causing the formation of developmental abnormalities of the embryo or fetus

All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy

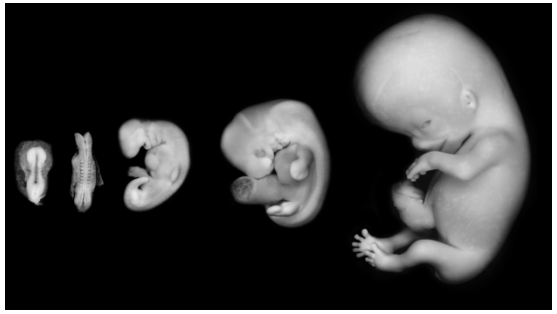
Paracelsus (1493-1541)



HAZARD Database

Scientific evidence of teratogenicity

- Non-clinical data
- Drug, drug class characteristics
- Impact of maternal disease or condition
- Human data
- Biological plausibility of the exposure



- Whether a drug is a teratogen depends on dose, route of administration, frequency and duration of exposure and timing of exposure during pregnancy

Evaluation of teratogenic risk in drug development

- Nonclinical (animal) toxicology studies
  - Designed to identify hazards, assess potential toxic effects and target organ systems and estimate the safe starting doses for clinical trials
  - Assess hazards that cannot be assessed in clinical trials, namely the potential for carcinogenicity and teratogenicity
- Specifically for the detection of teratogenicity
  - Reproductive and developmental toxicity studies
    - Fertility and Early Embryonic Development (one species)
    - Embryo/Fetal Development (two species)
    - Prenatal and Postnatal Development (one species)

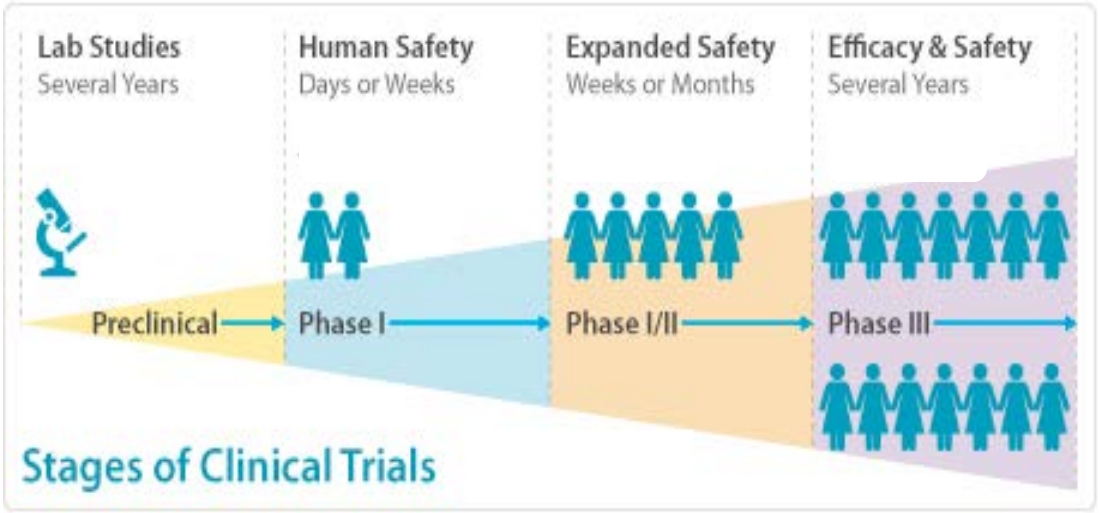
Conduct of Studies

- Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals [ICH M3(R2)]
  - "All female reproduction toxicity studies and the standard battery of genotoxicity studies **should be completed** before inclusion, in any clinical trial, of WOCBP [women of childbearing potential] **not using highly effective birth control** or whose pregnancy status is unknown**"**

Data from Nonclinical Studies

Safety Pharmacology
genetic toxicology,
in vitro DDI,
general toxicology
(short duration)

Carcinogenicity studies



General toxicity studies (increasing duration) Reproductive and developmental toxicity studies

Managing a drug with a teratogenic risk

- The goal is to prevent or minimize fetal exposure by
  - Use of contraception to prevent pregnancy
  - Use of pregnancy testing to
    - identify and prevent drug exposure prior to giving a drug
    - minimize drug exposure if pregnancy has occurred

Contraception Use

- Contraception use is an important risk management tool
- For products with teratogenic potential, recommendations for use of effective contraception are included in labeling
- Understanding whether hormonal contraceptive–drug interactions occur is important for making contraception recommendations

Regulatory Guidelines

- FDA Draft Guidance: Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations 2012

  "The evaluation of CYP enzyme induction should begin with studies of CYP1A2, CYP2B6, AND CYP3A in vitro…

  It should be noted that there may be mechanisms of induction that are presently unknown. Therefore, 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

- The same recommendations are found in the EMA Guideline on the investigation of drug interactions 2013

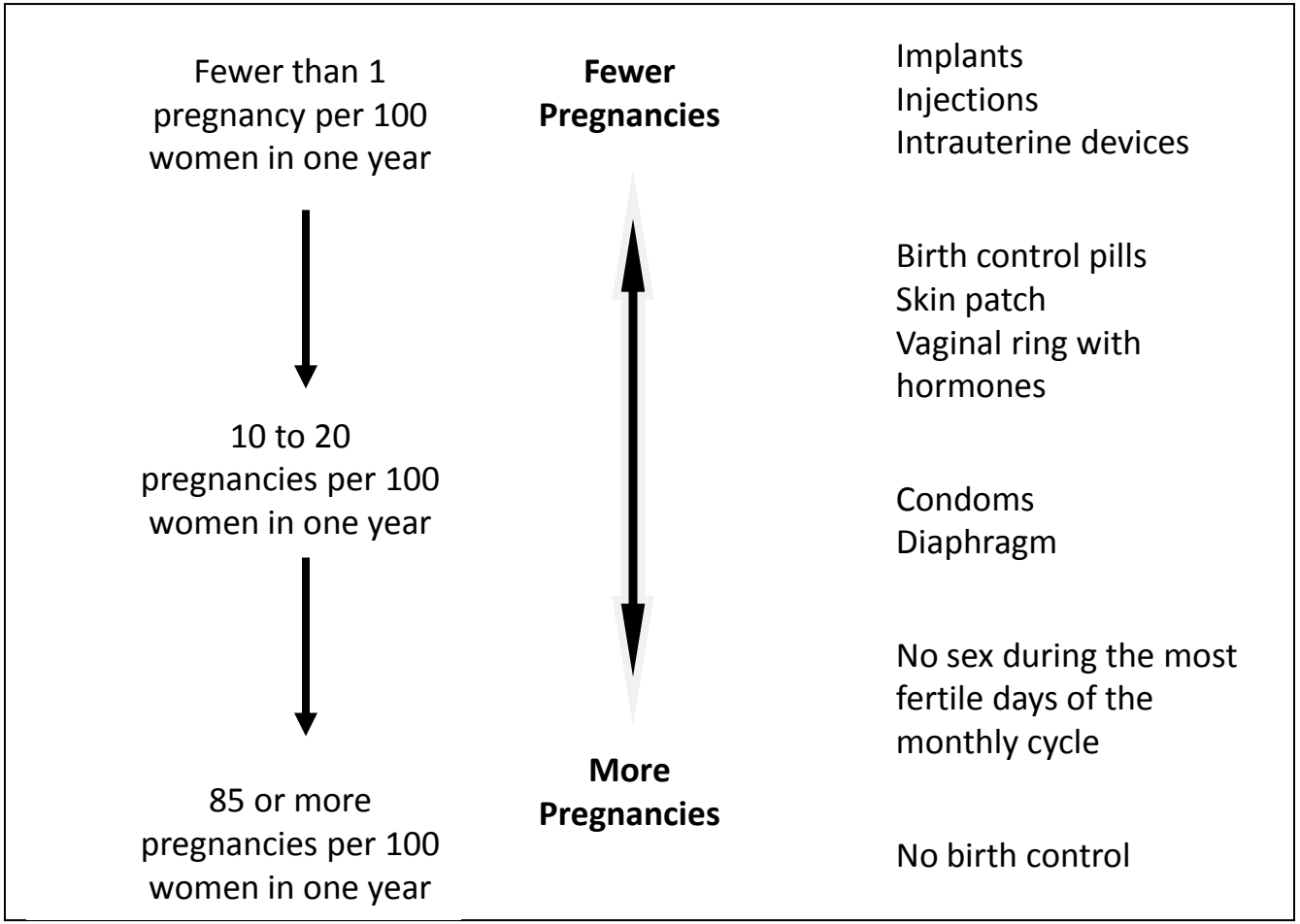
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf

Factors in the Decision Process: Contraception Effectiveness

- Contraception effectiveness depends on "the inherent efficacy of the method and on how consistently and correctly it is used"[1]
  - Typical use rate is lower than "perfect use" rate
- Factors that can affect inherent efficacy
  - Weight/ Body Mass Index (BMI)
  - **Drug-drug (contraceptive) interactions**
- Factors that can impact ability to comply with dose regimen
  - Self-administration vs. administered by healthcare provider
  - Need for daily vs. less frequent dosing
  - Psychosocial factors (age, educational level, etc.)
- Factors that can affect ability to tolerate a particular method
  - Bleeding profile or other side effects that may be method-specific

[1]Centers for Disease Control and Prevention, U.S. Selected Practice Recommendations for Contraceptive Use, 2013. MMWR 2013, 62: 1-61.

Effectiveness of Contraceptive Methods Based on Typical Use



Refer to the approved labeling for each contraceptive method for safety information. The combined use of two comparatively less effective methods does not necessarily equal one method with <1% failure rate. The phrase "no sex during the most fertile days of the monthly cycle" refers to fertility awareness programs.

Considerations for planning DDI

- What is the expected patient demographic?
  - Critically important when the expected patient population will include Females of Reproductive Potential (FRP)
- Were in vitro drug induction studies positive?
- Were there findings in the genotoxicity studies?
- Is the drug target known to be involved in normal embryonic development?
- Did the embryo fetal development study show adverse fetal effects at exposures that might be obtained in humans?

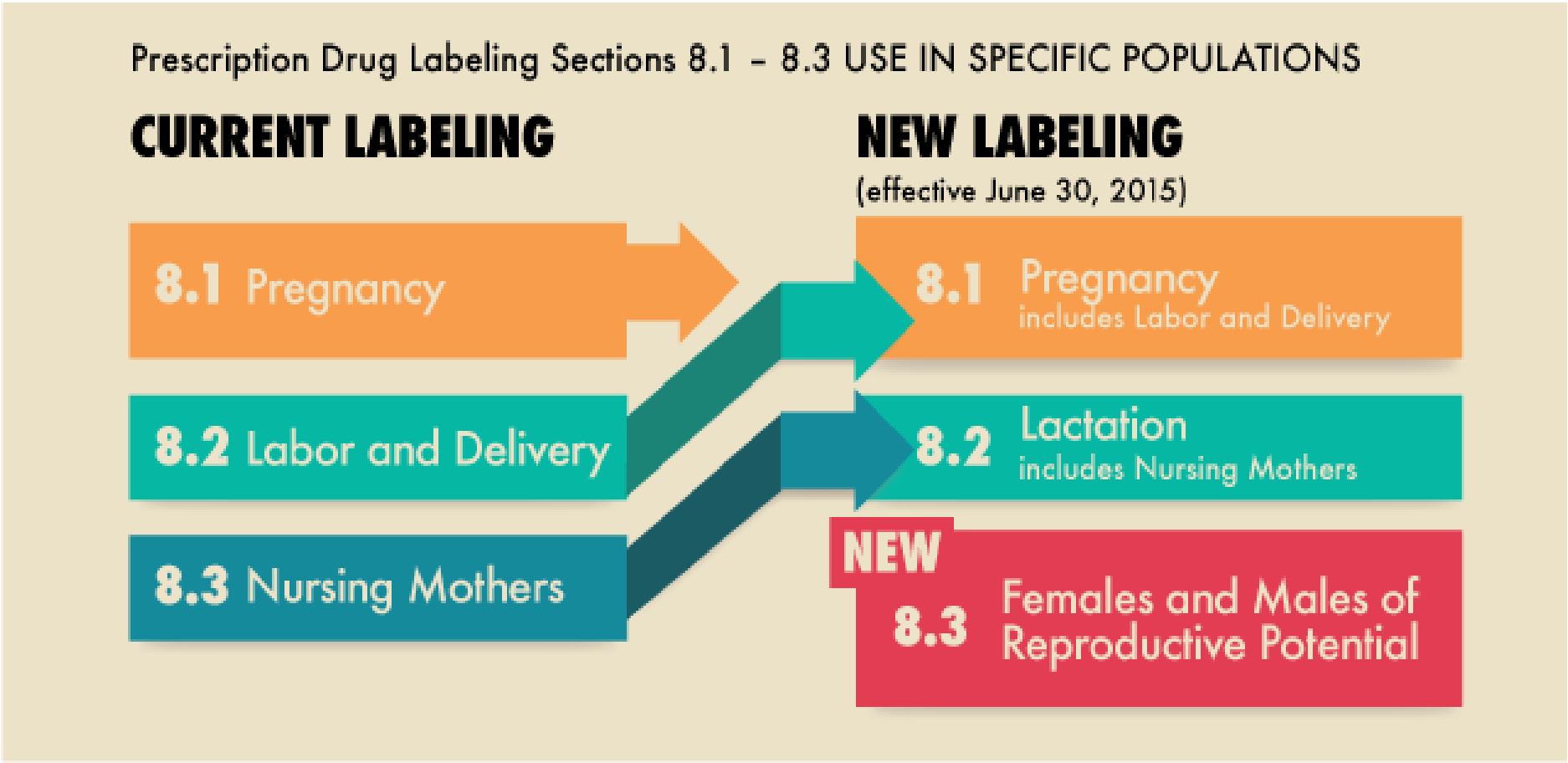
Plan DDI studies to develop appropriate contraception recommendations

there may be cases when this should be known before large numbers of FRP are exposed in clinical trials (Phase 3)

Pregnancy and Lactation Labeling Rule (PLLR)

- Took effect on June 30, 2015
- **ALL** prescription drugs are required to remove pregnancy letter categories over the next 3-5 years
- Prescription drugs approved on or after June 30, 2001 must revise content and format of the Pregnancy and Lactation sections of labeling
  - Pregnancy letter categories are replaced with an integrated Risk Summary

Comparison of Current Labeling with PLLR



Intent of PLLR

- Provide the prescriber with relevant information for critical decision-making when treating pregnant or lactating women
- More complete assessment of the known risks based on the available data
- Considerations of medical/disease factors
- Animal data put in context of human exposure
- Human data added when available
- Explicitly states when no data are available

PLLR – Changes to Labeling

8. USE IN SPECIAL POPULATIONS

8.1 Pregnancy	8.2 Lactation	8.3 Females and Males of Reproductive Potential
Pregnancy Registry Risk Summary* Clinical Considerations Data	Risk Summary* Clinical Considerations Data	Pregnancy Testing Contraception Infertility

*Required heading

See draft guidance: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

Contraception Recommendations for Labeling

- Recommendations located in Section 8 - Use in Special Populations
  - Under sub-section *8.3 Females and Males of Reproductive Potential*
  - Cross references to other sections as required (e.g., Contraindications, Warnings & Precautions, Drug Interactions, Clinical Pharmacology)

8.3 Females and Males of Reproductive Potential

Based on its mech … to a pregnant wor…

Pregnancy Testin…

Female patie…

Contraception

Females: Advise f… during treatment … patients that TRA… alternative effecti… *Precautions (5.x),*

Infertility

Females: Decreased fertility and ovarian toxicity were observed in female rats treated with DRUGNAME. Advise female patients of reproductive potential …

Males: Effects on spermatogenesis have been observed in animals treated with DRUGNAME. Advise male patients of the potential risk…

Contraception

Females:

Advise female patients of reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose of TRADENAME.

Advise patients that TRADENAME can reduce the effectiveness of oral contraceptives and to use alternative effective contraception during treatment with TRADENAME *[see Warnings and Precautions (5.x), Drug Interactions (7.x), Clinical Pharmacology (12.x)]*

Summary

- Nonclinical studies (reproductive and developmental toxicity studies) conducted in the course of drug development provide the data to estimate teratogenic potential.
- Clinical DDI studies for hormonal contraceptives should be conducted for drugs with known or suspected teratogenic potential
- Recommendations for contraceptive methods in large scale clinical trials and subsequently, for the approved product labeling should be informed from outcomes from hormonal contraceptive DDI studies
- When contraception recommendations are included in labeling, they are located in subsection 8.3 Females and Males of Reproductive Potential
  - Include impact on hormonal contraceptives when appropriate


Thank you
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