Labels without Categories: Writing Risk Summaries

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Objectives

- Provide brief overviews:
  - Of the "high level" purposes of the Risk Summaries
  - Of the types of information required by the Pregnancy and Lactation Labeling Rule (PLLR) for Risk Summary sections of 8.1
- Later in the workshop, we will consider specifics in drafting risk summaries under several scenarios
  - When a drug is newly registered, and there are only animal data available
  - When there are situations in which the maternal condition to be treated has implications for successful pregnancy outcomes
  - When human data become available
- A brief nod toward the types of expertise that must come together to the table to write successful Risk Summaries

What are Risk Summaries Intended to Convey?

In succinct format, for use by prescribers:

- 8.1: "A summary of the risks of using a drug during pregnancy"
  - "…based on data from all relevant sources (human, animal, and/or pharmacologic), that describe, for the drug, the risk of adverse developmental outcomes"
- 8.2: "A summary of the risks of using a drug during lactation"
  - When drugs are contraindicated during lactation
  - When drugs are not systemically absorbed (and therefore not excreted in breast milk)
  - A risk/benefit statement regarding the use of the drug while breastfeeding

Agency Thinking That Led to Creation of Risk Summaries

- Categories were:
  - Confusing
  - Did not accurately and consistently communicate differences in degrees of fetal risk
  - Concern that, while clinicians relied heavily on categories, [categories] were often misinterpreted and misused
    - Prescribing decisions made on category, in the absence of understanding the underlying information
  - Agency conviction that "narrative structure" best format to capture/convey potential risks of drug exposure during pregnancy

Elements of a Risk Summary: 8.1

- The Risk Summary is a set of conclusions regarding the impact of drug use on human pregnancy outcome
- Arrived at from weight of evidence assessment of all available data:
  - Human (when available)
  - Animal (traditional ICH S5 studies, as well as literature information regarding genetically modified animals)
  - Knowledge of the drug's mechanism of action

Elements of a Risk Summary: 8.1 (cont'd)

As per Federal Register:

- Risk Summary must address whether the drug is is systemically absorbed in humans
  - If yes: state background risk for malformations and miscarriages in the general population, "as well as certain other information".
  - If this information is available for the population(s) for which the drug is labeled (i.e. disease state or indicated condition), this must be included.
  - Background risk for specific malformations if reports of specific types - e.g. neural tube defects - are observed
- When human data establish presence of adverse developmental outcome(s), expectation is that risk summary convey specific developmental outcomes; incidence; and effects of dose, duration of exposure and gestational timing of exposure.
  - Adverse developmental outcomes defined as developmental mortality, dysmorphogenesis, alterations to growth or functional deficits, as per classic notions of developmental toxicity
- If no/insufficient human data, must be stated

Elements of a Risk Summary: 8.1 (cont'd)

- Risk statements must include a cross-reference to additional details in the "Data" subheading of "Pregnancy"
- If drug is contraindicated in pregnancy, must be stated here (and carried through to contraindications section in the Highlights of Prescribing Information at the beginning of the label)
- When animal data are available, labeling must summarize and describe potential for adverse effect in humans.
  - This must included the numbers and types of species affected; timing of drug exposure in pregnancy; animal pregnancy outcomes; and margins at which outcomes were observed, based on human exposure equivalents (preferably AUC).
- Risk summary based on pharmacology : when a drug has a well-understood MOA that may result in drug-associated adverse developmental outcomes, the Risk Summary must explain the MOA and potential associated risks

Building a Weight-of-Evidence Case

- Weight-of-Evidence (WoE) must start with the individual data (whether human, animal, MOA)
- Risk Summaries, then, are the *last* parts of the Pregnancy Section to be written
  - Require inductive reasoning: *
    - make many observations,
    - discern a pattern,
    - make a generalization
    - Infer an explanation
- In the next 2 days, we will construct Risk Summaries based on increasing availability of data
  - Mimics the situation at the time of registration, as well as when human information begins to emerge

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When Only Animal Data are Available

- Key points for interpretation include:
  - Biological plausibility
    - MOA, timing of exposure
  - Potential for windows of sensitivity (or lack of same)
  - Strength of signal
  - Existence of cross species concordance
  - MARGINS

Role for Genetically Modified Animals?

- Perhaps
  - May confirm what is observed in ICH S5/S6 study
  - When there are contradictory findings, however, a well-designed animal study with the clinical candidate should trump the genetically-modified candidate
    - Receptor occupancy, on-off rates, biologic redundancy may alter the developmental profile observed in knock-outs, in particular

Writing a Risk Summary from Animal Data

- Animal studies:
  - Look beyond the malformations: significant embryo-lethality is a problem
    - When 70% of embryos are resorbed, and half the remaining embryos are malformed, the big picture is not served by emphasizing the malformations
    - Late fetal death is relatively rare in animal studies – when it is observed, it can signal a concern
    - Look across animal studies - is there evidence of developmental mortality in fertility study? in PPND?

Writing a Risk Summary from Animal Data (cont'd)

- What message do you want to convey? Be as clear and concise as possible: Craft the *strongest statement* you can make that is valid, while still encapsulating what is known
  - If there is little concern, say so: Our drug is neither embryo-lethal nor teratogenic in rats and rabbits at systemic exposures that approximate 430-fold (rat) or 152-fold (rabbit) the AUC associated with the RHD.
    - Skeletal variations do not belong in a Risk Summary: these are common, of no lasting consequence for viability and quality of life, and often reverse with postnatal growth.
  - If there is significant concern, say so: Our drug is embryo-lethal and teratogenic in rats / rabbits at systemic exposures that are equal to or less than the AUC associated with the RHD.
  - If you are unsure, say that too: Our drug did not produce developmental toxicity in rats or rabbits at margins of 4-fold or 2-fold, respectively. However, craniofacial malformations were observed at the next dose tested in rats at 25-fold the human exposure

The Risk Summary Is Intended to Evolve with Time and the Emergence of New Data

- At registration, human data sources likely non-existent
  - For drugs that are not First in Class, perhaps information regarding Forerunner experience is available to inform assessment based on mechanism of Action
  - Risk summary for lactation is likely only to include animal data at the time of registration
- Later, depending on level of initial concern, perhaps pregnancy registry information available
  - In the absence of randomized clinical trials, the prospective pregnancy registry is the gold standard for data
    - Costly to administer, not generally set up in the absence of significant concern, or knowledge that drug likely to be needed in treatment of pregnant women

Who Needs to be at the Table when Writing Risk Summaries?

- Initially:
  - the DART Subject Matter Expert
  - Clinicians with experience in treating pregnant women with the disease indicated
- In time, pharmacovigilance
- Always: legal

Questions?