Guidance for Industry
Reproductive and
Developmental Toxicities—
Integrating Study Results to
Assess Concerns

AGAH Workshop Reproductive Toxicology
October 2012
History of the guideline

• The basic guideline was first issued as a Draft in October 2001 and a number of established scientists from the reproductive toxicology field were asked to evaluate it.

• DIA/FDA workshop held 2002 to discuss draft guideline
  – This was a practical evaluation using real data to assess the consistency of the findings.

• The final guideline was issued in September 2011
  – No further draft version was issued in between

• The basic principles of the new and old guideline are the same so it’s worth revisiting the original to see the evolution.

• Note that the respective EMA guidance has first been published in 2005 (draft) and was issued in 2009
Basic principles

• “This guidance describes an approach to estimating possible human developmental or reproductive risks associated with drug or biological product exposure when a nonclinical finding of toxicity has been identified, but definitive human data are unavailable”.

• This is intended for use at the time of an NDA and is designed to give a consistent approach to the review of Repro studies by the CDER.

• Involves the integration of different types of nonclinical data: reproductive; general toxicology; toxico- and pharmaco-kinetics (including ADME).

• This approach should be used when there is a toxicity finding and to focus on the likelihood that the drug will increase the risk of adverse human developmental or reproductive outcomes.
Basic principles cont’d

- Will be relevant to both drug and biological products, although some factors may not apply to biologics due to the availability of some data for factors considered in this guidance.

- Firstly a complete set of the expected general toxicology, reproductive and developmental toxicology and pharmacokinetic studies should be evaluated.

- This includes assessing the drug’s ability to produce positive findings in relevant animal studies (e.g. doses high enough?).

- The evaluation should also compare animal and human pharmacodynamic effects, metabolism and disposition, pharmacologic and toxic effects at drug exposures in animal studies in relation to the highest proposed dose in humans.
Original title:
Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities
(Integrative Assessment Tool = the "Wedge").

- Issued as “Reviewer Guidance” in October 2001
- i.e. to be used by FDA reviewers, not industry
- Focused on the likelihood a drug would increase the risk of adverse human developmental or reproductive effects.
- Did not consider the nature of the adverse response (e.g. severity, reversibility or reparability).
- Did not consider the clinical implications of the response.
Original Proposal (2001)

- **Overall Decision Tree** *(Figure A)*
  To evaluate availability and relevance of studies and presence or absence of a signal for each of 7 classes of reproductive toxicity

- **Decision Tree for Toxicities with No Signal** *(Figure B)*
  Evaluates the adequacy of the test system, species, dose and exposure, class alert, related signals

- **Integration Tool for Toxicities with a Positive Signal** *(Figure C)*
  Each class is scored based on six factors. For each factor, there is a determination of increased (+1), decreased (-1), or no change (0) in the level of concern.
FIGURE A. OVERALL DECISION TREE FOR EVALUATION OF REPRODUCTIVE/DEVELOPMENTAL TOXICITIES

1. AVAILABILITY OF STUDIES?
   - YES
   - NO
     - INFORMATION IS NOT AVAILABLE TO ASSESS RISK

2. RELEVANCE OF STUDIES (TEST SYSTEM AND ROUTE)
   - YES
   - NO
     - “UNKNOWN” OR “NOT EVALUABLE” RISK
     - DEFINE NON-RELEVANCE OF TEST SYSTEM OR STUDY
       (DO NOT USE FIGURE C)

3. PRESENCE OF A SIGNAL FOR AN ENDPOINT?
   - YES
     - “POSITIVE EFFECT OBSERVED”
       USE FIGURE C FOR INTEGRATION OF DATA FOR ENDPOINTS WITH POSITIVE RESULTS
   - NO
     - “NO OBSERVED EFFECT”
     USE FIGURE B FOR INTEGRATION OF DATA FOR ENDPOINTS WITH NO SIGNAL
FIGURE B. DECISION TREE FOR REPRODUCTIVE/DEVELOPMENTAL TOXICITIES WITH NO SIGNAL

NO SIGNAL

1. ADEQUACY OF MODEL
   NO
   "UNKNOWN RISK" OR "POSSIBLE RISK BASED ON RELATED DRUG"
   INADEQUATE INFORMATION EXISTS TO ASSESS RISK TO HUMAN REPRODUCTION, SINCE ... THE TEST SYSTEM OR TEST CONDUCT WERE DEEMED LACKING (DESCRIBE SITUATION) OR, THE COMPOUND WAS SUBJECT TO A CLASS ALERT (DESCRIBE SITUATION AND INCLUDE CLASS INFORMATION).

2. ADEQUATE STUDY DOSES/EXPOSURE?
   NO
   "UNKNOWN RISK" OR "POSSIBLE RISK BASED ON RELATED DRUG"

   3. CLASS ALERT?
      YES
      "NO OBSERVED EFFECT ON ..."
      "NO OBSERVED EFFECT ON ..."

   4. ANY ENDPOINT POSITIVE IN RELATED REPRO/DEVEL. CATEGORY?
      NO
      "NO PREDICTED RISK"
Risk Assessment
Factors to Consider

Signal strength I
- Cross-species concordance
- Multiplicity of effects
- Adverse effects at different stages

Signal strength II
- Maternal toxicity
- Dose-response relationship
- Rare events

Pharmacodynamics
- Therapeutic index (TI)
- Biomarkers as a benchmark
- Similarity between pharmacologic and toxicologic mechanisms.
Concordance Between the Test Species and Humans
• Metabolic and drug disposition profiles
• General Toxicity Profiles
• Biomarker profiles

Relative Exposures
• Kinetic comparison
• Biomarkers as measure of relative exposure

Class Alerts
FIGURE C - INTEGRATION TOOL FOR REPRODUCTIVE OR DEVELOPMENTAL TOXICITIES WITH A POSITIVE SIGNAL

CLASSES OF TOXICITY OR SIGNALS

REPRODUCTIVE TOXICITY
1. Fertility
2. Parturition
3. Lactation

DEVELOPMENTAL TOXICITY
1. Mortality
2. Dysmorphogenesis
3. Alterations to growth
4. Functional toxicity

DATA INTEGRATION PROCESS

ANIMAL DATA - HUMAN DATA
## Integrative Assessment

<table>
<thead>
<tr>
<th>Classes of Toxicity or Signals</th>
<th>Signal Strength I</th>
<th>Signal Strength II</th>
<th>PD</th>
<th>ADME Tox</th>
<th>Exposure</th>
<th>Class Alerts</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>REPRODUCTIVE TOX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Fertility</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-6</td>
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<td>2. Parturition</td>
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<td>-1</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>-4</td>
</tr>
<tr>
<td>3. Lactation</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>-5</td>
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<tr>
<td>DEVELOPMENTAL TOX</td>
<td></td>
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<tr>
<td>1. Mortality</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>2. Dysmorphogenesis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
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<tr>
<td>3. Alterations to growth</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>4. Functional toxicity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>
Interpretation of Positive Findings

- The values for the six factors are summed to arrive at one of the following “Summary Risk Conclusions”:
  
  
<table>
<thead>
<tr>
<th>Value Range</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;+3</td>
<td>Predicted to increase risk</td>
</tr>
<tr>
<td>+2 to -2</td>
<td>May increase risk</td>
</tr>
<tr>
<td>&lt;-3</td>
<td>Does not appear to increase risk</td>
</tr>
</tbody>
</table>

- May be included in the label.
There is no scientific basis for using an algorithm to replace nuanced judgement on a case-by-case basis. Assigning a value of -1, 0, or +1 to each factor and then adding these values does not make sense. Using a 3-point scale to characterize each factor dramatically decreases the information that is available to make subsequent decisions.

Moreover, the scientific value of the carefully considered weight-of-evidence approach proposed for each factor in the primary data analysis is debased by application of a process that assumes the equivalence of factors in any single class. The factors are not of equal importance, and their relative significance is likely to vary greatly from case to case. In some instances, one of them may trump all of the others.
Comments from PhRMA (2002)

• Focused on consistency and clarity of understanding of how to use. For example, greater clarity needed around how to identify a signal and what exactly constitutes a signal.

• “The Technical Group strongly prefers that the end result of the IAM not be a numerical ranking, but a summary narrative of evaluation that leads to a summary risk statement in labeling.”

• Suggested wording examples for Summary Risk Conclusions with and without a positive signal.
Risk Assessment
Final guidance - 2011
Guidance issued September 2011

To be used by Industry, no longer for Reviewers

Guidance for Industry
Reminder

- For assessing nonclinical reproductive and developmental toxicity data involving the integration of other nonclinical information: general toxicity, TK and PK information including ADME data.

- Approach used when there is a toxicity finding and focuses on assessing the likelihood that a drug will increase the risk of adverse human developmental or reproductive outcomes.

- Relevant to both drug and biological products.

- *Clinical information* on drug’s potential should be evaluated separately and can supersede any nonclinical findings.
Data Needed for Integration and Assessment

- A complete set of the expected general, reproductive and developmental toxicology, and pharmacokinetic studies.

- Full assessment of the drug’s ability to produce a positive finding in relevant animal studies (e.g., were doses high enough to induce toxicity of some kind?)

- Compare animal and human PD effects, animal/human ADME, pharmacologic and toxic effects and relative drug exposures (animal/human).
  - Safety ratios (relation of exposures in animals compared to those at highest proposed dose in humans)

- In the case of incomplete information, the product should still be evaluated to the extent possible according to the scientific principles and considerations described in this document.
Types of Repro and Developmental Toxicity Evaluated

Classes of reproductive toxicity include:
- male fertility
- female fertility
- parturition
- lactation

Classes of developmental toxicity include:
- mortality
- dysmorphogenesis (structural abnormalities)
- alterations to growth
- functional impairment
The Integration and Assessment Process
**Figure A: Overall decision tree for evaluation of reproductive/developmental toxicities**

- **Availability of Studies**
  - Were studies performed to assess the risk of that type of toxicity in humans, and are the detailed study results available for comprehensive evaluation?

- **Relevance of Studies**
  - Do the studies provide information relevant to assessing the risk of that type of toxicity for the proposed human use?

- **Presence or Absence of a Signal**
  - “Was there a positive signal (suggesting toxicity)?”
  - If no signal was seen, the evaluation process should continue per Section B (Figure B).
  - A *positive signal* is a biologically meaningful difference in dosed animals compared to concurrent or historical controls. If a positive signal was seen, the evaluation process should continue per Section C (Figure C)
**Figure A. Overall Decision Tree for Evaluation of Reproductive/Developmental Toxicities**

1. **Availability of studies?**
   - **NO**
     - Unknown or not evaluable risk
     - Information is not available to assess risk
   - **YES**

2. **Relevance of studies (test system and route)?**
   - **NO**
     - Unknown or not evaluable risk
     - Define non-relevance of test system or study
     - Do not use **Figure C**
   - **YES**

3. **Presence of a signal for an endpoint?**
   - **NO**
     - Use **Figure B** for integration of data for endpoints with no signal
   - **YES**

Positive effect observed
Use **Figure C** for integration of data for endpoints with positive results
Availability of studies

• 1\textsuperscript{st} question asked
  – „Were studies performed to assess the risk of that type of toxicity in humans, and are the detailed study results available for comprehensive evaluation?“

• Risk to humans is considered \textit{unknown or not evaluable}.
  – Example of wording: The risk of human [reproductive or developmental toxicity] with [Drug X] is unknown. There are no or inadequate data to evaluate its potential to cause human [reproductive or developmental toxicity].
Relevance of studies

• 2\textsuperscript{nd} question
  - "Do the studies provide information \textit{relevant} to assessing the risk of that type of toxicity for the proposed human use?"
  - Relevance to humans may be hampered by a number of factors including
    • Inappropriate study protocol
    • Non-relevant route of administration
  - Applicant must explain reasons and discuss all supporting information that bears on study relevance \textit{for example}
    • Study may have been relevant but design or conduct resulted in insufficient information to be useful

• Risk to humans is considered \textit{unknown} or \textit{not evaluable}
  - Example of wording: Animal data are insufficient to assess the risk of human [reproductive or developmental toxicity] with [Drug X].
Absence or presence of a signal

- Continue as per Figure B (absent) or Figure C (present)

- However remember the basic principle:
  - “This guidance describes an approach to estimating possible human developmental or reproductive risks associated with drug or biological product exposure when a nonclinical finding of toxicity has been identified, but definitive human data are unavailable”.
  - There is an element of inconsistency!

➢ The assessment will always be required, whether or not there is a finding
No Signal (Figure B)

• Four sets of questions should be considered during the evaluation of each type of reproductive or developmental toxicity for which there was no signal.
  
  – This implies that each type of signal should be assessed separately (!)

  – Q1: Model/Test Species Predictive Adequacy?
    • To what extent are the models or test species used likely to be predictive of human response?

  – Q2: Adequacy of Study Doses and Exposure?
    • Were adequate doses administered and were the drug exposures (AUC, Cmax) adequate relative to those expected in humans?

  – Q3: Class Alert?

  – Q4: Any signals for Related Types of Repro and Developmental Toxicity?
Figure B. Decision Tree for Endpoints with No Signal

No signal

1. Adequacy of model? NO

Unknown risk or possible risk, based on a related drug

Inadequate information exists to assess risk to human reproduction because—the test system or the test conduct was deemed lacking (describe situation)

or

The compound was subject to a class alert (describe situation) and include class information

2. Adequate study doses/exposure? NO

3. Class alert? YES

4. Any endpoint positive in related reproductive/developmental category? YES

No observed effect on ____

No predicted risk NO
Q1: Adequacy/predictivity of model?

- Test species pharmacologically relevant ("responder")?
- Toxicity profile in test species overall consistent with the human toxicity profile?
- DMPK profile in test species qualitatively similar to humans?
- Even if test system is of little relevance to humans, the applicant should consider questions 2-4
Q2: Adequacy of Study Doses and Exposures

a. Were adequate doses administered?
   - MTD, MFD, limit dose (see ICH S5R2 Note 7)
   - Caveat – MTD/MFD and limit doses are not consistently defined across a number of guidelines

b. Relevant drug exposures (based on AUC/Cmax or other appropriate systemic exposure metric) achieved in the test system?
   - Adequate = generally some multiple of human exposure
   - At least equivalent to human exposure
   - Greater relative exposure adds to credibility of negative finding

➢ If answer to either (a) or (b) is no
   - Studies may be inadequate to fully evaluate risk, but continue with Q3/4
Q3: Class Alerts

Class alerts should be based on adverse reproductive or developmental effects previously demonstrated in humans by

- closely related chemical entities or
- compounds with similar pharmacodynamic effects.

If there is a class alert for the drug based on

- a related chemical structure of parent or metabolite or
- related pharmacologic effect,

the class-specific information relevant to the type of toxicity reported to be negative should be included in the risk evaluation and discussion of the drug.
Q4: Signals for Related Types of Reproductive and Developmental Toxicity (1)

• “Consider whether or not there are findings for related reproductive and developmental toxicities”
  
  - A positive signal for one endpoint of toxicity may suggest some risk in humans for other toxicities in the same category for which there were no findings in animals. This may be a consequence of limitations of studies or cross-species differences in expression of effects.

• Most applicable to developmental toxicities
  
  - Examples:
    - No signal for fetal mortality but positive signal for alterations to growth or dysmorphogenesis in one (or more) animal species
      - “it may be inappropriate to conclude that there is no risk of fetal mortality for humans” (?!)
    - Hormonal mechanisms which could impact multiple aspects of the reproductive system
Reminder: developmental toxicity

- Mortality
- Dysmorphogenesis
- Functional impairment
- Alterations to growth
Q4: Signals for Related Types of Reproductive and Developmental Toxicity (2)

In the event of a positive signal for related endpoints, the evaluation should state that there was no observed effect on the type of toxicity being assessed, but positive signals were seen for related toxicities.
Q4: Signals for Related Types of Reproductive and Developmental Toxicity - Suggestions

Finding should probably be integrated in the overall evaluation i.e. adopting process C rather than B for a truly integrated risk assessment.

Remember: absence of evidence is not evidence of absence!

Note: Reproductive/developmental toxicities are considered to be threshold effects and may precipitate different phenotypic outcomes depending on stage of development, dose and species.

Example: Thalidomide
If there is no positive signal for any type of reproductive or developmental toxicity in adequate studies, the evaluation should state that there is no expected increase in risk for reproductive or developmental toxicity in humans, based on the results of animal studies.
Reproductive or Developmental Toxicity Endpoints with Positive Signal (Figure C)

1. Overview of integration
2. Factors
3. Summary/integration of positive findings
Figure C. Integration of Reproductive or Developmental Toxicities with a Positive Signal

**Signals**

**A. Reproductive toxicity**
1. Male fertility
2. Female fertility
3. Parturition
4. Lactation

**B. Developmental toxicity**
5. Developmental mortality
6. Dysmorphogenesis
7. Alterations to growth
8. Functional toxicity

**Animal Data**

**Factors that can increase or decrease concern (see text)**

- Cross-species concordance
- Multiplicity of effects
- Maternal/paternal toxicity
- Dose-response
- Rare event

**Data integration process**

- Predicted to increase human risk
- May increase human risk
- Does not appear to increase human risk

**Human Data**

- Increased risk
- Decreased risk
Process associated with evaluation of findings (Figure C)

1. Overview of integration

2. Factors

3. Summary/integration of positive findings
Overview of integration

- A positive nonclinical signal for any type of reproductive or developmental toxicity should be analyzed with respect to various factors that may affect the level of concern for adverse effects in humans.

- Since multiple factors contribute to the overall evaluation and conclusion, scientific judgment should be used to integrate all of the factors applicable to positive findings.

- The following factors may increase or decrease level of concern:
Overview of integration (2)

- List of factors to be considered
  1. Cross-species concordance of reproductive or developmental effects
  2. Multiplicity of effects
  3. Maternal/paternal toxicity
  4. Dose–response relationship
  5. Rare events
  6. Similarity between pharmacologic and toxicologic mechanisms
  7. Concordance between test species and humans: metabolic and general toxicity profiles
  8. Relative exposure
  9. Class alerts
Overview of integration (3)

• Example of factors increasing concern
  – Low relative exposure in animals
  – Presence of cross-species concordance
  – Absence of maternal toxicity
  – Similarity between pharmacologic and reproductive/developmental toxicologic mechanisms.

• Note: Mechanism often remain unknown, in particular for developmental toxicities!
Overview of integration (4)

- Examples of factors decreasing concern
  - High relative exposure in animals
  - Absence of cross-species concordance
  - Excessive maternal toxicity
  - Animal-specific mechanisms
    - Note: this is mostly impossible to demonstrate for developmental toxicities
Overview of integration (5)

- **Relative impact of factors**
  - Some can have greater impact than others
    - Exposures
  - Some may not be relevant
    - Biologics
    - Oncology products

- Applicant must discuss factors and how the overall conclusion was reached
Note: your signal for reproductive toxicology may have been identified in a general toxicity not reproductive toxicity study!
Process associated with evaluation of findings (Figure C)

1. Overview of integration
2. Factors
3. Summary/integration of positive findings
Q1: Cross-species concordance of reproductive or developmental effects?

- Generally, more convincing if there is a consistent signal across species

- **Caveat: not limited to same specific effect!**

- Different but related adverse effects in multiple species increase level of risk for categorically related endpoints in humans e.g.
  - Dysmorphogenesis in one species + embryofoetal mortality in another species
  - Effects on parturition in one species + effects on lactation in another species

- However: remember: PPND studies usually done in one species only!

- Ask questions:
  - Is a negative species appropriate?
  - Were the studies adequate?
Q2: Multiplicity of effects?

- Refers to multiple effects within one species
  - Can represent intraspecies concordance
  - Can reflect signal strength

- If positive signal at different stages of development
  - Generally greater concern

- If only observed for processes that are of limited concern to humans
  - Less concern

- Consider timing of the period of susceptibility to put into context!
Q3: Maternal/paternal toxicity?

• Not that easy!

• Positive signal observed only in the presence of frank maternal toxicity
  – May decrease concern, provided that the positive signal can reasonably be attributed to maternal toxicity i.e.
    • Causal relationship between parental toxicity and signal is established or biologically plausible
    • The expected paternal toxicity is not expected in humans
Q4: Dose-response relationship?

• **Increase of concern** when a positive signal is associated with any of the following
  1. increased **severity** of adverse effects with an increase in dose
  2. increased **incidence** of adverse effects with an increase in dose
  3. a **high incidence** of adverse effects **across all dosed groups**.

• Conversely, there is generally less (or decreased) concern when these indices of dose-response are absent
Q5: Rare events?

- Developmental toxicity studies lack statistical power to detect subtle increases in rare events
- Increased frequency = increased concern
- But: absence of rare events does not decrease concern!

- Note:
  Of particular concern in reproductive toxicity studies
  Sound background database of extreme importance!
Q6: Pharmacodynamics: similarity between pharmacologic and toxicologic mechanisms?

- Similarity between pharmacologic and reproductive/developmental toxicological mode of action (MoA) should be assessed

- Similar MoA in animals/humans?
  - Increased concern

- Species-specific MoA in animal model?
  - Decreased concern
  - Example: hypoprolactinemia in rats associated with pregnancy loss
Q7: Concordance between test species and humans: metabolic and general toxicity profiles?

• Q7 a: DMPK
  - Quantitative dissimilarities frequent
    • Should not be overemphasized
  - Qualitative similarity increases concern
  - High dissimilarity for metabolism and/or tissue distribution may decrease concern, however
    • If each species tested yields a positive signal
    • Then the toxicity is assumed to be attributable to the parent or a common metabolite = concern increased

• Q7 b: Toxicology
  - Higher similarity of general toxicity profiles increases concern
Q8: Relative exposures?

Scientifically plausible link between the exposure metric and the adverse reproductive or developmental effect?
- e.g. Cmax or AUC linked with adverse outcome?

Two measures to compare relative exposures
- Kinetic exposure
- Biomarker as measure of exposure

If so, then higher emphasis on exposures
Kinetic comparison of relative exposure

• Safety ratio (SR)
  - Exposure at **NOEL** (not NOAEL!) for reproductive/developmental toxicity in relation to human exposure at maximum recommended dose (MRHD)
  - Should be based on most relevant metric
    • Cmax, Cmin, AUC or body surface area-adjusted dose
  - Increased concern where SR
    $$\frac{[\text{exposure}]_{\text{NOEL animal}}}{[\text{exposure}]_{\text{MRHD human}}} < 10$$
  - Decreased concern where SR
    $$\frac{[\text{exposure}]_{\text{NOEL animal}}}{[\text{exposure}]_{\text{MRHD human}}} > 25$$
  - Doesn’t specify level of concern for SRs between 10 – 25 (“grey zone”)
  - Should consider both parent and metabolites!
  - Confirm appropriate metric in case of disparity between species
  - If metric does not reduce disparity, base on most sensitive species
Kinetic comparison of relative exposure (2)

- Guideline doesn’t specify whether SR calculations generally should refer to total or free drug concentrations

- However, where there is a level of disparity for NOEL exposures between species, the following should be considered:
  - Species differences in
    - Protein binding (free drug concentrations)
    - Receptor affinity (if related to positive signal)
    - Or site-specific drug concentrations

- In the absence of meaningful differences between the test species and humans compare based on total drug concentrations
Biomarkers as a measure of relative exposure

• “Purpose or relative exposure metric is...
  – ...to compare the dose causing reproductive or developmental toxicity in the test species to the therapeutic dose in humans, normalized to the doses causing a response common to both species”

• In practice
  a. \([\text{exposure}]_{\text{NOEL animal}} : \text{[exposure]}_{\text{biomarker response animal}} = \text{Ratio}_{\text{animal}}\)
  b. \([\text{exposure}]_{\text{MRHD human}} : \text{[exposure]}_{\text{biomarker response human}} = \text{Ratio}_{\text{human}}\)
  c. Divide (a)/(b)
  d. Similar to SRs, ratio of relative biomarker exposure (a)/(b):
     a. Increased concern for ratio (a)/(b) < 10
     b. Decreased concern for ratio (a)/(b) > 25
Biomarkers as a measure of relative exposure (2)

| Multiple species tested and relative biomarker exposure ratios can be computed | Level of concern to be based on integrated analysis from all adequately studied species |
| Non-concordant biomarker ratios between multiple species? | Consider relevance of biomarker before making assessment |
| No scientific rationale for disparity between species? | Biomarker as measure for exposure will be of questionable utility |
**Q9: Class Alerts?**

| Consideration of a class effect to be based on adverse reproductive or developmental effects previously demonstrated in humans by | • closely related chemical entities (parent or metabolite)  
• compounds with related pharmacologic effects. |
<table>
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<tbody>
<tr>
<td>If there is a “class alert” for the drug</td>
<td>• Then the concern is increased</td>
</tr>
</tbody>
</table>
| Decreased concern only where a class of compounds | • Although demonstrating adverse effects in animals  
• Was previously shown definitively to have no adverse effects on human reproduction or development |
Process associated with evaluation of findings (Figure C)

• Overview of integration

• Factors

• Summary/integration of positive findings
Summary/Integration of Positive Findings

• “When there is a positive finding in nonclinical studies for one or more endpoints of reproductive or developmental toxicity, there is a potential for increased human risk.

• Multiple considerations contribute to the overall evaluation of the nonclinical data and conclusions regarding human risk.

• These include factors that can modify the level of concern for human adverse effects determined from the nonclinical signal.

• Factors can increase or decrease concern, and some factors can carry greater weight than others.”
Summary/Integration of Positive Findings (2)

• "Positive signals should be evaluated to estimate the likelihood of increased reproductive or developmental risk for humans using the following general procedure:

  – In evaluating the level of increased risk, all relevant information should be considered, including nonclinical reproductive and general toxicology data and human and animal pharmacodynamic and pharmacokinetic data.

  – Factors that may affect the level of concern associated with a positive signal of reproductive or developmental toxicity should be assessed.

  – The analysis should take into account the quality and type of data under consideration."
Summary/Integration of Positive Findings (3)

• “A weight of evidence approach should then be applied to arrive at an overall conclusion for reproductive or developmental toxicity (Figure C). The following are examples of possible summary risk conclusions for the evaluation:

  - **Does Not Appear to Increase Risk**: The drug is not anticipated to increase the risk of adverse developmental (or reproductive) outcomes in humans when used in accordance with dosing information in the product label.

  - **May Increase Risk**: The drug may increase the risk of adverse developmental (or reproductive) outcomes in humans when used in accordance with the dosing information in the product label.

  - **Predicted to Increase Risk**: The drug is expected to increase the risk of adverse developmental (or reproductive) outcomes in humans when used in accordance with the dosing information in the product label.”
How is the outcome of the assessment currently reflected in (new US) drug labels?
Current Labelling (FDA)

- United States FDA Pharmaceutical Pregnancy Categories
  - Introduced in 1979
  - Under debate since years
  - **Pregnancy categories are still in use**
  - For exact definitions, please refer to ref. 6

- **Assessment not reflected in label at present (at least not visibly)**

- Other guidance refers back to pregnancy categories
  - Example: Nonclinical Safety Evaluation of Drug or Biologic Combinations (2006) (ref. 2)
Pregnancy categories (FDA) (Ref 6)

- Category A: Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.

- Category B: No evidence of risk in humans. Either animal studies show risk but human findings do not, or if no adequate human studies have been done, animal findings are negative.

- Category C: Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking. However, potential benefits may justify the potential risks.

- Category D: Positive evidence of risk. Investigational or post-marketing data show risk to the fetus. However, potential benefits may outweigh the potential risks. If needed in a life-threatening situation or serious disease, the drug may be acceptable if safer drugs cannot be used or are ineffective.

- Category X: Contraindicated in pregnancy. Studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk which clearly outweighs any possible benefit to the patient.
Consistency of pregnancy labelling across different therapeutic classes

- FDA poster publication, please refer to Ref. 4 for full information
- Objective: To evaluate consistency of pregnancy labelling across different therapeutic classes from the top 20 therapeutic classes
- Top-selling 22 (24) drugs taken from Drugs.com listing of the top 200 drugs of 2010
- Focus on teratogenicity and whether the drug was reported to cross the placental barrier
- Out of the 20 therapeutic classes surveyed, 9 (45%) were consistently labelled across class
- The majority was classified Pregnancy category C (60%)
EMA Guidance

• This guidance integrates non-clinical and clinical assessment

• It gives detailed information
  – On the assessment of effects both from a non-clinical and clinical perspective
  – And how the assessment will be reflected in the label

• Statistical basis for human data
  – Number of prospectively collected pregnancies to establish (absence of) signal

• However, not as detailed instructions as to how to discuss non-clinical data as in FDA guidance
  – Similar considerations as in FDA guidance

• Typical differences include
  – Level of maternal toxicity (minimal)
  – Reference is made to a NOAEL
References (in chronological order)

(1) Reviewer Guidance: Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities. Draft Guidance October 2001 (CDER)

(2) Guidance for Industry: Nonclinical Safety Evaluation of Drug or Biologic Combinations. Final March 2006 (CDER)


(4) Onyeka Otugo (1), Olabode Ogundare (1), Christopher Vaughan (1), Emmanuel Fadiran (1), Leyla Sahin (2): Consistency of Pregnancy Labeling Across Different Therapeutic Classes (2010) (1) Office of Women’s Health, (2) FDA Pediatric and Maternal Health Staff, Maternal Health Team, CDER, FDA, 10903 New Hampshire Avenue, Silver Spring, MD 20993 Poster publication

(5) Guidance for Industry: Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns. Final September 2011 (CDER)

(6) 21CFR201.57: Code of Federal Regulations (CFR), revised April 1, 2012 Sec. 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in 201.56(b)(1).
Back-up slides
Statins – example for labelling

- The statins were assigned category X based on human data and on the following argumentation: *Lipid lowering drugs offer no benefit during pregnancy because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy.*

- The statins are generally not associated with animal teratogenicity

- There is limited evidence for developmental toxicity from available human data

- Safety margins for example for Atorvastatin (Lipitor) are large
FDA guidance on drug combinations

- In general, EFD studies in one species unless specific risks are indicated for a particular trimester of pregnancy

- Generally not required if one of the (new/marketed) combination drugs is (likely to be) labelled category D or X

- See Reference 2 for full information