Guidance for Industry

Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmacology and Toxicology

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Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
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TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1] Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns

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I. INTRODUCTION

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. The guidance is intended for applicants of new drug applications (NDAs) and biologics licensing applications (BLAs). The recommendations included here will also help to ensure a consistent review of reproductive and developmental toxicity data among Center for Drug Evaluation and Research (CDER) review staff.

This guidance does not (1) give detailed advice about labeling or placement of toxicity information in product labeling (for information on labeling, see 21 CFR 201.57); or (2) discuss clinical data or the integration of nonclinical and clinical data.

FDA guidance documents, including this one, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance was developed in the Center for Drug Evaluation and Research at the Food and Drug Administration.

II. BACKGROUND

The approach presented here for assessing nonclinical reproductive and developmental toxicity data involves the integration and careful consideration of a variety of different types of nonclinical information: reproductive toxicology; general toxicology; and toxicokinetic and pharmacokinetic information, including absorption, distribution, metabolism, and elimination data. The approach is 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. The approach includes noting when studies were not conducted or when they were not performed using relevant model systems or at appropriate dose ranges.

The general principles described here (i.e., a comprehensive analysis of available data) will typically be relevant to both drug and biological products, although some factors may not apply to biological products, because data may not be available for all factors considered in this guidance (e.g., cross-species concordance, dose-response, metabolism, relative exposure (animal : human) of >25-fold). For some oncology products (e.g., cytotoxics), certain aspects of the guidance may not apply because patients may be dosed at the maximum tolerated dose (MTD).

Note: Available *clinical* information to evaluate a drug's potential to increase the risk of an adverse developmental or reproductive outcome in humans should be evaluated separately and, when definitive, can supersede any nonclinical findings.

A. Data Needed for Integration and Assessment

When determining what nonclinical data will be needed for integration and assessment, it is important to first evaluate a complete set of the expected general toxicology, reproductive and developmental toxicology, and pharmacokinetic studies.[2] The evaluation should include an assessment of the drug's ability to produce a positive finding in the relevant animal studies (e.g., whether doses used were high enough to induce toxicity of some kind). The evaluation should also compare animal and human pharmacodynamic effects, animal and human metabolism and disposition, animal and human pharmacologic and toxic effects, and drug exposures in animal studies in relation to the highest proposed dose in humans. The type and extent of available toxicology data may vary, depending on the product's biological actions, test systems available for studying the compound, and other factors. In some cases, the data will not include all desirable general toxicology, reproductive/developmental toxicology, and pharmacokinetic studies. Nevertheless, the product should be evaluated to the extent possible according to the scientific principles and considerations described in this document (see section III).

[2] See the following International Conference on Harmonisation (ICH) guidances for industry: *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*; *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*; *S5(R2) Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility*; and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*.

B. Types of Reproductive and Developmental Toxicity Evaluated

Reproductive and developmental toxicity can be manifested as a change in one or more specific endpoints. For the purposes of this document, there are two broad toxicity categories — reproductive and developmental — and, within those categories, eight classes of effects are considered (see Glossary).

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.

For a given drug, endpoints reflecting the full range of potential reproductive and developmental effects should ordinarily be assessed (for standard endpoints, see ICH S5(R2)). A positive signal of reproductive or developmental toxicity, whether in valid reproductive/developmental or other relevant nonclinical studies, should be evaluated to estimate the likelihood of increased reproductive or developmental risk for humans.

1. Reproductive Toxicities

Reproductive toxicity refers to structural and functional alterations that affect reproductive competence in sexually mature males and females. Reproductive toxicity includes effects on male fertility and female fertility, parturition, and lactation.

- Male Fertility

Male reproductive toxicity includes damage to the reproductive organs, alterations in endocrine regulation of gamete maturation and release, reduction in sperm count, alterations in sperm motility or morphology, aberrant mating behavior, altered ability to mate, alterations in endocrine function, or overall reduction in fertility.

- Female Fertility

Female reproductive toxicity includes damage to the reproductive organs, alterations in endocrine regulation of gamete maturation and release, aberrant mating behavior, altered ability to mate, or overall reduction in fertility. Diminished fertility in female animals is typically

detected by reductions in the fertility index, the number of implantation sites, time to mating, or fecundity.

- Parturition

Toxicities affecting labor and delivery in animals include abnormal or difficult delivery (dystocia) and changes in the onset or duration of parturition. Changes in the duration of parturition are frequently reported as mean time elapsed per pup, or total duration of parturition.

- Lactation

Drugs may alter the process of lactation in the nursing mother (e.g., the quality or quantity of milk), or may alter maternal behavior towards the nursing offspring.

2. Developmental Toxicities

Developmental toxicity refers to adverse effects on the developing organism that result from exposure prior to conception, during the prenatal period, or postnatally up to the time of sexual maturity. The four major manifestations of developmental toxicity are:

- mortality
- dysmorphogenesis (structural abnormalities)
- alterations to growth
- functional impairment

- Mortality

Mortality resulting from developmental toxicity may occur at any time from early conception to post-weaning (e.g., *embryo-fetal death* is a subset of mortality resulting from developmental toxicity). Thus, a positive signal may appear as:

- pre- or peri-implantation loss
- early or late resorption
- abortion
- stillbirth
- neonatal death
- peri-weaning loss

- Dysmorphogenesis (Structural abnormalities**)**

Dysmorphogenic effects are generally seen as malformations or variations of the skeleton or soft tissues of the offspring and are commonly referred to as *structural abnormalities*.

- Alterations in Growth

Alterations in growth are generally seen as growth retardation, although excessive growth or early maturation may also be considered alterations to growth. Body weight is the most common measurement for assessing growth rate. Crown-rump length and anogenital distance may also be measured. Sometimes it is not clear if an effect is a direct structural alteration or an inhibition of growth. For example, reduced ossification could be either. A distinction must be made upon review of all relevant data.

- Functional Impairment

Functional toxicities could include any persistent alteration of normal physiologic or biochemical function, but typically only developmental neurobehavioral effects and reproductive function are measured. Common assessments include:

- locomotor activity
- learning and memory
- reflex development
- time to sexual maturation
- mating behavior
- fertility

III. THE INTEGRATION AND ASSESSMENT PROCESS

Recommendations for wording in labeling should be based on the results of the integration and assessment process. The specific considerations leading to a risk conclusion should be provided. This information may later be helpful in discussions between FDA reviewers and applicants.

The complete data integration process is divided into three components as discussed below in Sections A through C and presented schematically in Figures A through C at the end of this document. Briefly, Figure A is applicable to all data sets, Figure B is applicable only to data sets without evidence of reproductive or developmental toxicity, and Figure C is applicable to data sets with positive indications of reproductive or developmental toxicity.

A. Overall Decision Tree (Figure A)

The decision process outlined in Figure A should be used for any of the endpoints of reproductive or developmental toxicity discussed in Section II.B. For a given drug, studies may have been conducted to evaluate potential effects on none, some, or all of the endpoints of reproductive and developmental toxicity. Where studies are available for any of the different endpoints, the outcome may be one or more positive signals, or no positive signal. It is recognized that, in practice, one study may address several endpoints of toxicity and a study may be considered adequate to evaluate all, some, or none of the endpoints of toxicity addressed. Figure A depicts the sequential decisions that should be made in evaluating the various situations

that may be encountered and the next steps that should be taken when there are evaluable studies with positive or negative findings.

1. Availability of Studies

In Figure A, the first question asked for each category or class of toxicity is: "Were studies performed to assess the risk of that type of toxicity in humans, and are the detailed study results available for comprehensive evaluation?" If no studies were conducted, or detailed study results are unavailable for comprehensive evaluation, the NDA or BLA review or applicant submission should explain that studies to assess the risk of that type of toxicity were not done, or are otherwise unavailable. In such circumstances, risk to humans is considered *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].

If studies were conducted and are available for comprehensive evaluation, the assessment process should continue with question 2.

2. Relevance of Studies

The next question asked for each category or class of toxicity is: "Do the studies provide information relevant to assessing the risk of that type of toxicity for the proposed human use?" If the studies were not relevant or were otherwise inappropriate (i.e., inappropriate test protocol, nonrelevant route of drug administration), the NDA or BLA review or applicant submission should explain why and should discuss all supporting information that bears on study relevance. For example, the studies might have been potentially relevant, but the study design or conduct may have resulted in insufficient information to be useful. If the study was not relevant, the risk to humans is considered *unknown* or *not evaluable*.

> Example of wording: Animal data are insufficient to assess the risk of human [reproductive or developmental toxicity] with [Drug X].

If the studies conducted were relevant to evaluating the risk of the particular type of toxicity in humans, the risk integration process should continue with question 3. Note that the processes in Figures B and C (see end of document) are intended to be used only when studies are considered adequate to assess the specified risk. They should not be used to evaluate findings (positive or negative) derived from inadequate studies.

3. Presence or Absence of a Signal

If relevant studies are available and the study conduct (including doses and exposure and route of administration) is appropriate for assessing the risk of toxicity in humans, the next question asked should be, “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).

If multiple studies are available to assess a particular type of reproductive or developmental toxicity (e.g., multiple studies would be expected for the evaluation of effects on embryonic development – ICH stage C), the process in Figure B should be used only if the results of all studies relevant to a particular aspect of reproductive or developmental toxicity were negative for that type of toxicity.

If any study (general toxicity, reproductive, or developmental toxicology study) had a positive signal for that aspect of reproductive or developmental toxicity, the process in Section C (Figure C) should be used.

B. No Signal (Figure B)

When there is no positive signal for an endpoint of reproductive or developmental toxicity, the risk assessment should be a step-wise process leading to a discussion in the NDA or BLA review or applicant submission of the applicability of the non-finding to humans. A graphic representation of this process is presented in Figure B.

The following four sets of questions should be considered during the evaluation of each type of reproductive or developmental toxicity for which there was no signal.

1. The Model/Test Species Predictive Adequacy

To what extent are the models or test species used likely to be predictive of human response? The questions below bear on determining a model's predictive adequacy. Affirmative answers to these questions would make the findings in that test system more credible in terms of human relevance.

Do the models or test species (or systems) demonstrate the intended pharmacodynamic effect(s) of the drug?

Do the models/test species (or systems) demonstrate an overall toxicity profile that is consistent with the human toxicity profile?

Do the models/test species (or systems) demonstrate pharmacokinetic (including ADME) profiles for the drug that are qualitatively similar to those in humans?

Negative answers to these questions may suggest that the response of the test species is of little relevance to humans, and the BLA or NDA review or applicant submission should explain why the animal study or studies conducted with the drug may not be fully adequate to evaluate the risk for the particular type of toxicity in humans (i.e., why the test may have low predictive value). Even if the test system is determined to be of limited relevance based on the above considerations, the review or applicant submission should consider the remaining questions (2–4

below) and describe any additional uncertainties associated with the nonclinical data and the relevance of the studies to humans.

2. Adequacy of Study Doses and Exposure

The following elements should also be considered in assessing the relevance to humans of the drug doses and exposure in the test system:

Were adequate doses (concentrations) of the drug administered to the test species or test systems (e.g., MTD or maximum feasible dose (MFD); see ICH-S5R2 Note 7 (3.1))? (This would usually not apply to biologics.)

Were the drug exposures (based on AUC, C_{max}, or other appropriate systemic exposure metric) achieved in the test species or test systems adequate relative to those expected in humans at the maximum recommended human dose (generally some multiple of the human exposure but at least equivalent to it)? A greater relative exposure adds to the credibility of a negative finding.

If the answer to either of these questions is no, the review or applicant submission should state that the animal studies conducted may be inadequate to fully evaluate the risk for the particular type of toxicity reported to be negative and should explain in detail why they may be inadequate. Even if the study doses and exposure are considered inadequate, the evaluation should proceed to the remaining sections (3–4 below), and any additional uncertainties should be described in the evaluation.

3. Class Alert

Is there a class alert? 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.

4. Signals for Related Types of Reproductive and Developmental Toxicity

The next step in evaluating the significance of a no-signal finding for a particular type of reproductive or developmental toxicity is to 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.

The issue of related toxicities is most applicable to developmental toxicities. For example, if there is no signal for fetal mortality, but a positive signal for alterations to growth or dysmorphogenesis in one (or more) animal species, it may be inappropriate to conclude there is no risk of fetal mortality for humans. Related toxicities may also be pertinent for reproductive

toxicities where a hormonal mechanism is identified that could impact multiple aspects of reproductive performance and is relevant to humans. If positive signals for related endpoints of toxicity were observed in the animal studies, 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. 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.

C. Reproductive or Developmental Toxicity Endpoints with Positive Signal (Figure C)

1. 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.

These factors, discussed in greater detail below, include the following.

- Cross-species concordance of reproductive or developmental effects
- Multiplicity of effects
- Maternal/paternal toxicity
- Dose–response relationship
- Rare events
- Pharmacodynamics: similarity between pharmacologic and toxicologic mechanisms
- Concordance between test species and humans: metabolic and general toxicity profiles
- Relative exposure
- Class alerts

These and other factors can either increase or decrease the level of concern. Examples of factors increasing concern when associated with a given positive signal include: low relative exposure in animals, presence of cross-species concordance, absence of maternal toxicity, and similarity between pharmacologic and reproductive/developmental toxicologic mechanisms. Conversely, concern may be decreased by: high relative exposure in animals, absence of cross-species concordance, excessive maternal toxicity, and animal-specific mechanisms. Case by case, some factors, such as relative exposure, can have a greater impact than others. Some of the factors may not apply to biologics or to products for oncology indications because the relevant data (e.g., from multiple species) may not exist or be expected (see ICH S6(R1)). The review or applicant submission should discuss the various factors and describe how the overall conclusion was reached.

The implicit assumption of the integrative assessment shown in Figure C is that the process begins with a positive signal that is evident in one or more of the examined species (either in a reproductive or developmental toxicology study or an effect on a reproductive tissue/system/behavior in a general toxicology study).

Note: Human data are considered separately from nonclinical findings, and human data may dramatically influence the overall assessment of human risk of reproductive or developmental toxicity, since definitive human data would supersede any nonclinical data.

2. Factors

- Cross-species concordance of reproductive or developmental effects

The observation of positive signals for the same or a related type of toxicity in more than one species is described as cross-species or interspecies concordance. In general, findings for which there is cross-species concordance are more convincing than findings in a single species; thus, there is increased concern for reproductive or developmental toxicity in humans when cross-species concordance of these effects is observed in nonclinical studies. In evaluating potential human risk for adverse reproductive or developmental outcomes, if there is cross-species concordance for a single type of adverse effect it may be reasonable to conclude that a similar effect is the most likely adverse event to be seen in humans treated with the drug. However, cross-species concordance is not limited to the observation of the same specific effect across species. If different but related adverse effects are seen in multiple test species (e.g., alterations to growth in one species and developmental mortality in another, or parturition effects in one species and lactation effects in the second), it is assumed that there is an increased level of risk for categorically related endpoints in humans.

Cross-species concordance is most likely to be identified for developmental endpoints examined in the organogenesis testing paradigm, in which multiple species are typically evaluated. However, alterations to endocrine function or gonadal histopathology (which may alter fertility) may be indirectly detected in subchronic and chronic toxicity studies in rodents and nonrodents. For alterations to parturition or lactation, it is often not possible to assess cross-species concordance because pre- and postnatal studies to assess these toxicity classes are usually done in only a single species. Although there may be less concern when a signal is detected in only one species, it is important to determine whether the negative species is an appropriate animal model and the studies were adequate in design, dosing, and implementation.

- Multiplicity of effects

Multiplicity of effects refers to the observation, in a single species or animal model, of two or more positive signals within one of the two general categories of toxicity (reproductive or developmental) or within one of the classes of reproductive or developmental toxicity. Evidence of multiple effects in an animal species is associated with increased concern for reproductive or developmental toxicity in humans, while an isolated finding is generally of less concern. The observation of positive signals in multiple classes of reproductive or developmental toxicity (e.g., increased malformation and embryo-fetal death) or of multiple signals for the same class of effects (e.g., motor and cognitive functional deficits) can represent intraspecies concordance or reflect signal strength by demonstrating effects in more than one setting or on more than one reproductive or developmental process. For example, developmental mortality can be manifested as early or late resorption, abortion, or stillbirth. If a positive signal in animals is observed at different stages of development, there is generally greater concern for adverse human

reproductive outcomes than if a positive signal is observed only during a single, discrete period. If the positive signal occurs only for processes that are of limited relevance to humans, there would be less concern for adverse human outcomes. In addition to its relevance to this evaluation process, it is also important to define the timing of the period of susceptibility for the observed positive signal to provide a context for the human risk.

- Maternal/paternal toxicity

In weighing a signal of toxicity, the relationship of adverse reproductive or developmental effects to maternal (and, for fertility studies, paternal) toxicity should be considered when assessing the level of concern. This assessment is relevant to all endpoints of reproductive and developmental toxicity. A positive signal occurring at doses that are not maternally toxic increases concern for human reproductive or developmental toxicity. If a positive signal is observed only in the presence of frank maternal toxicity, there may be decreased concern, provided that the positive signal can reasonably be attributed to maternal toxicity (i.e., a causal relationship between parental toxicity and the signal is established or biologically plausible,[3] and the observed parental toxicity is not expected in humans). When evaluating a positive signal in two or more species, assessment of the implications of maternal or paternal toxicity should be based on a composite analysis of the data from all adequately studied species. If any species is considered inappropriate for assessing the implications of maternal or paternal toxicity, the evaluation should be performed using the remaining available data.

- Dose-response relationship

Concern for human reproductive or developmental toxicity increases when a positive signal is characterized by 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, or (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.

- Rare events

Developmental toxicity studies usually lack the statistical power to detect subtle increases in rare events. Thus, an increased frequency of rare events in drug-exposed animals increases concern for reproductive or developmental toxicity in humans. The absence of an increased frequency of rare events, however, does not decrease concern.

- Pharmacodynamics: similarity between pharmacologic and toxicologic mechanisms

For drugs with a positive signal, the similarity between the pharmacologic and reproductive or developmental toxicologic modes of action should be assessed, to the extent that these are understood. If a positive signal is an extension or progression of, or related response to the drug's intended pharmacologic mode of action (e.g., delay of parturition by drugs known to suppress

[3] The attribution of adverse effects to maternal (or paternal) toxicity can be based on previously collected data demonstrating the relationship between the maternal/paternal and reproductive or developmental effects.

uterine smooth muscle contractility or hypotension in the offspring of dams treated during late gestation with a drug known to lower blood pressure), there is increased concern for reproductive or developmental toxicity in humans. There generally is less (or decreased) concern if the positive signal is attributed to an animal-specific pharmacological response, even though it may be an extension of the drug's pharmacologic effect (e.g., pregnancy loss in rats due to hyperprolactinemia).

- Concordance between test species and humans: metabolic and general toxicity profiles

The concordance between the metabolic and drug distribution profiles and general toxicity profiles in the test species and humans should be evaluated for drugs with a positive signal.

  – Metabolic and drug distribution profiles

  Drug distribution, elimination, and biotransformation (pathways and metabolites) in the test species and in humans should be compared. Quantitative differences in metabolic/drug distribution profiles between the test species and humans are often seen, may not have important implications, and should not be overemphasized. Reproductive and developmental toxicities in animals induced by compounds whose metabolic and distribution profiles are very similar in animals and humans increases concern for reproductive or developmental toxicity in humans.

  For compounds with highly dissimilar metabolic or tissue distribution profiles in animals and humans, there is generally less concern if the toxic effect seen in the test species can reasonably be attributed to a metabolite or tissue distribution profile not seen in humans. However, when there are significant differences in drug distribution or metabolic profiles between several species, yet each test species demonstrates a positive signal for a reproductive or developmental toxicity, the toxicity is assumed to be attributable to the parent drug or a common bio-transformed product and concern is increased.

  – General toxicity profiles

  If a drug's overall toxicity profile in one or more test species with a positive signal is similar to that in humans, there is increased concern for reproductive or developmental toxicity in humans. If the overall toxicity profiles are dissimilar, there is generally less (or decreased) concern. When general toxicology data are available for more than one species, the determination of the level of concern should be based on an assessment of each test species' ability to predict human adverse effects in response to the drug.

- Relative exposures

When considering the relative exposure comparisons discussed below, more emphasis should be placed on a parameter within this factor when there is a scientifically plausible link between the exposure metric and the adverse reproductive or developmental effect. For example, when a correlation between peak plasma concentration and a developmental effect has been

demonstrated for a particular drug, Cmax would be considered the most relevant exposure metric for making animal to human comparisons for that endpoint.

– Kinetic comparison of relative exposure

Comparison of systemic drug exposure at the No Observed Effect Level (NOEL) for the reproductive or developmental toxicity in the test species to that in humans at the maximum recommended dose is a critical determination. This comparison should be based on the most relevant metric (e.g., AUC, Cmax, Cmin, body surface area-adjusted dose). In general, there is increased concern for reproductive or developmental toxicity in humans for relative exposure ratios (animal: human) that are <10 and decreased concern for exposure ratios >25. When applicable, the relative exposure ratio should consider both the parent compound and its metabolites. For example, it is appropriate to combine parent and metabolite when both are pharmacologically active and the activity is known to relate to the reproductive or developmental toxicity. When there are exposure data for multiple test species, the NOEL exposure for each should be compared to human exposure at the maximum recommended dose. If the exposure ratios are low (<10 fold) in multiple species with a positive signal, there is increased concern. If the exposure ratios are high (>25 fold), there is generally less (or decreased) concern. In the event that a significant difference in relative exposures is observed between multiple test species, the appropriateness of the metric (for example, AUC, Cmax) being used to define the interspecies exposure comparisons should be reassessed. If an alternative metric fails to reduce the disparity between species, the assessment of concern should be based on the lowest ratio (i.e., in the most sensitive species).

Relative interspecies exposure data should be evaluated in light of possible species differences in protein binding (free drug concentration), receptor affinity (if related to the positive signal) or site-specific drug concentrations. In the absence of meaningful differences between the test species and humans in these parameters, the interspecies comparisons should be based on total drug exposure.

– Biomarkers as a measure of relative exposure

The purpose of this 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, this is done by taking the exposure at the NOEL for the adverse reproductive or developmental effect and dividing by the exposure at which the biomarker response is seen in the test species. This is compared to the human therapeutic exposure divided by the exposure at which the biomarker response is seen in the human. The ratio calculated for animals is then divided by the ratio calculated for humans. When this ratio of relative biomarker exposure (animal: human) is < 10, there is generally increased concern for human reproductive or developmental toxicity. When this ratio is > 25, there is generally less concern.

When there are data to compute relative biomarker exposure ratios for multiple species, the level of concern assessment should be based on an integrated analysis of data from all adequately studied species. When there are non-concordant biomarker ratios between multiple test species, the relevance of the biomarker as expressed in the various species should be considered before making an assessment. If there is no scientific rationale for the disparity between species, the biomarker, as a measure of exposure, will be of questionable utility.

- Class Alerts

Consideration of a class associated effect should be based on prior human experience for a drug with closely related chemical structure (parent or metabolite) or related pharmacologic effect and with known reproductive or developmental outcomes in humans. There is increased concern for reproductive or developmental toxicity in humans when the drug is from a class of compounds known to produce adverse effects in humans and animals. There is decreased concern only in circumstances in which a class of compounds, although demonstrating adverse effects in animals, has previously been shown definitively to have no related adverse effects on human reproduction or development.

3. 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. 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.

- 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.

The factors discussed above are derived from a limited sample of pharmaceuticals for which the clinical outcomes are reasonably well defined and are not considered exhaustive. CDER believes that using the various factors to assess a drug's potential to increase the risk of adverse reproductive and developmental outcomes in humans will result in a more accurate as well as more unbiased and uniform evaluation. CDER also believes this approach will help identify specific areas in which additional information about a pharmaceutical would be useful in more fully defining risk and would enable specific analyses of areas of disagreement that influence the risk evaluation.

GLOSSARY

ADME – Absorption, distribution, metabolism, and elimination

Class Alert – A structurally adverse reproductive or developmental effect previously demonstrated in humans by related chemical entities or compounds with similar pharmacodynamic effects

Developmental Toxicity – Any adverse effect induced prior to attainment of adult life. It includes effects induced or manifested in the embryonic or fetal period and those induced or manifested postnatally. These are divided into four major manifestations or classes: mortality, dysmorphogenesis, alterations to growth, and functional toxicities.

Factor – For purposes of this guidance, a factor is one of the various considerations used to evaluate the level of concern for a positive signal of developmental or reproductive toxicity. The factors include (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) Pharmacodynamics: similarity between pharmacologic and toxicologic mechanisms; (7) Concordance between test species and humans: metabolic and general toxicity profiles; (8) Relative exposure; and (9) Class alerts. They are summarized in Figure C and are discussed in Section C.

Fertility – Reproductive competence

Lactation – The secretion of milk or the period of milk secretion

Malformation – A permanent alteration (abnormality) in which there is a morphologic defect of an organ or a larger region of the body, resulting from an abnormal developmental process. They generally occur at a low frequency in the control population and/or will adversely affect survival, growth, or development of functional competence

Maternal (Paternal) Toxicity – Toxicity to the mother (maternal) or the father (paternal) in a reproductive toxicology study, but not necessarily a toxicity to reproductive function

Parturition – Labor and delivery

Positive Signal – A treatment-related reproductive or developmental toxicity

Rare Event – An endpoint that occurs in less than 1 percent of the control animals in a study and in historical control animals

Reproductive Toxicity – Structural and/or functional alterations that may affect reproductive competence in sexually mature males and females. These may be manifested as impairment of fertility, parturition, or lactation.

Structural abnormalities – Includes malformations and variations

Toxicologic Effect – Any adverse effect of a therapeutic agent

Variation – An alteration that may occur at a relatively high frequency and/or represents a retardation in development, a transitory alteration, or a permanent alteration not believed to adversely affect survival, growth, development, or functional competence

FIGURES

Figure A. Overall Decision Tree for Evaluation of Reproductive/Developmental Toxicities

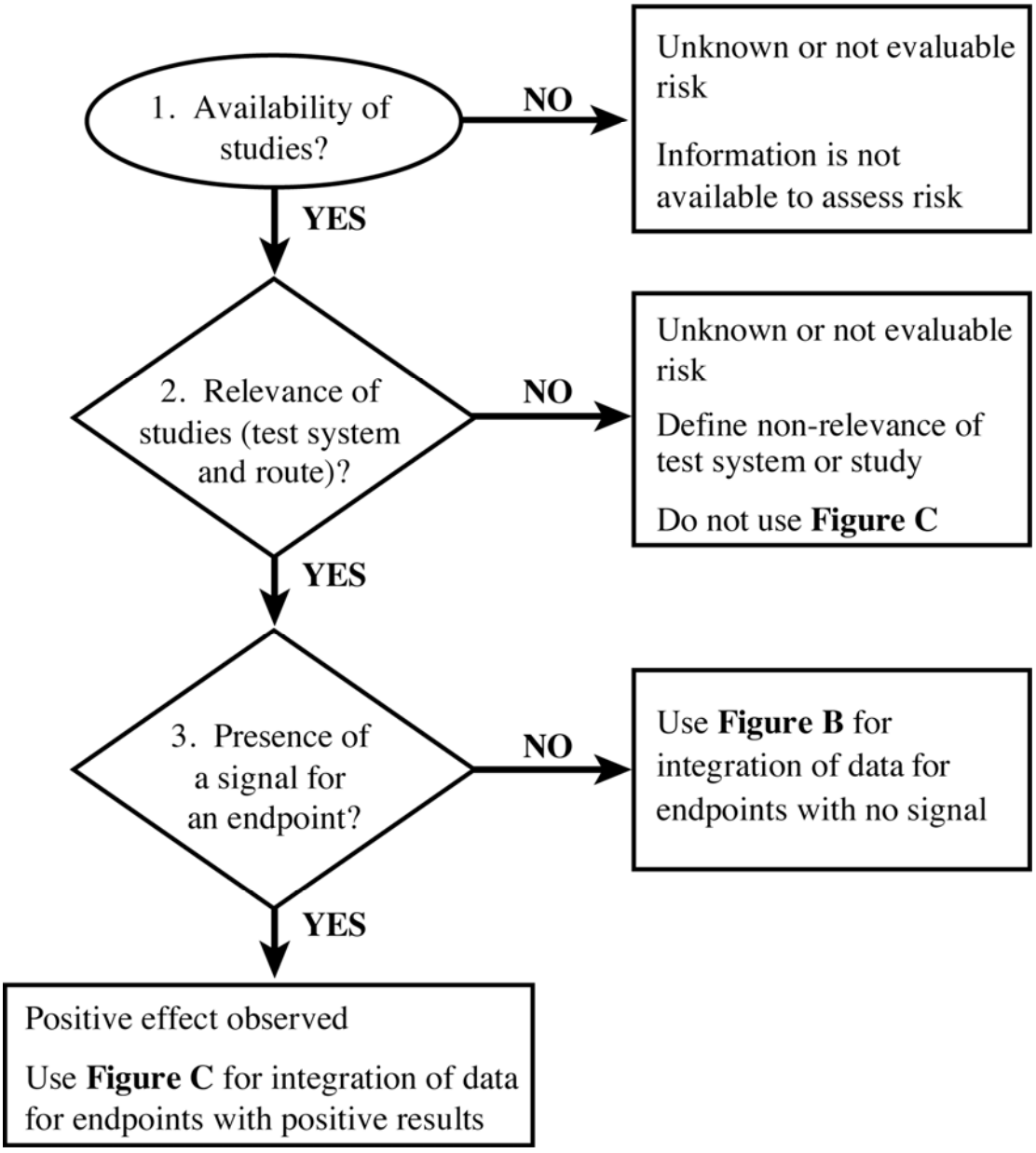

Figure B. Decision Tree for Endpoints with No Signal

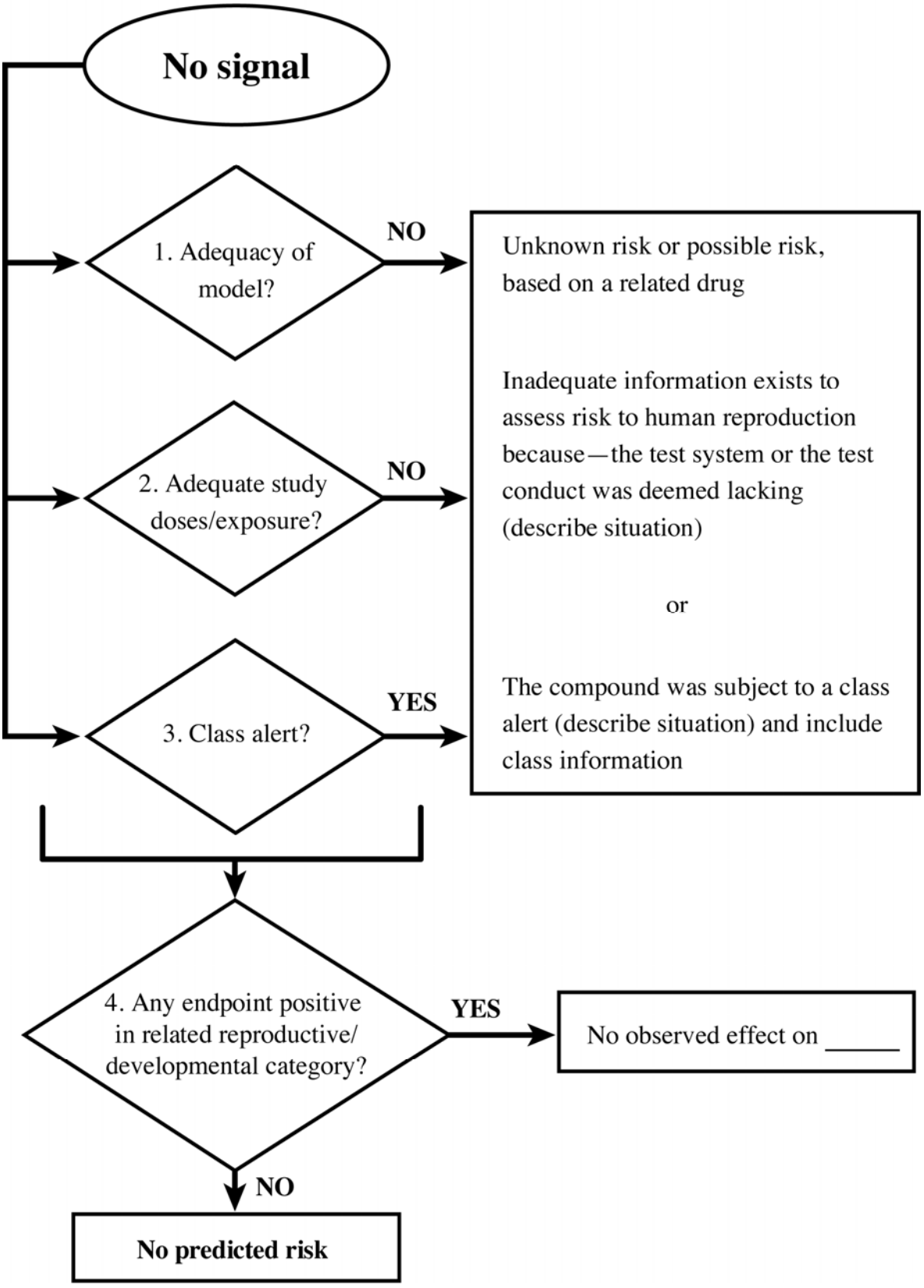

Figure C. Integration of Reproductive or Developmental Toxicities with a Positive Signal