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# Workshop 6.6

# Endocrine disruption and the USFDA's Center for Drug Evaluation and Research*

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*Abstract*: Drugs may have intended or unintended endocrine effects. Drug evaluation may include both in vitro and in vivo evaluations of toxicity and developmental/reproductive effects. After a signal is identified, human relevance is of utmost concern. An integration "tool" that formalizes a weight-of-evidence approach has been developed to assess concern about reproductive/developmental toxicity to humans. This approach can be used to assess concern about an endocrine disruption signal. A signal alone does not mean a concern for humans. An effect needs to have biologic relevance, and exposure thresholds for effects may exist. Risk/benefit for a particular drug is a clinical decision and may vary by the drug indication. Risk management for an identified concern could include wording in patient communications, tracking distribution or limited distribution, and patient or pregnancy registries.

## INTRODUCTION

Drugs may have intended or unintended endocrine effects. Several drug products have potent intended endocrine effects, such as oral contraceptives, selective estrogen receptor modulators, estrogen receptor antagonists, luteinizing hormone agonists, and some drugs with effects on the thyroid gland or with 5α-reductase inhibitory activity or aromatase inhibitory activity. Other drug products may have adverse effects on the thyroid gland, unintended luteinizing hormone agonist activity, or unintended inhibition of 5α-reductase or aromatase activity. The intended effects are the reason for developing particular drug products, whereas the unintended effects may only become apparent during drug development.

## IDENTIFICATION OF A HAZARD

Drug evaluations that might reveal endocrine effects include both in vitro and in vivo evaluations of toxicity and developmental/reproductive effects. Nonclinical in vitro evaluations of drugs could include receptor binding assays, transcriptional activation assays, gene expression assays, or enzyme inhibition assays. Specific in vivo endocrine evaluations could include uterotrophic assays for estrogenic activity and the Hershberger assay for androgenic activity. Other in vivo studies that could reveal endocrine effects include repeated dose toxicity studies that include clinical chemical analyses, organ weight measurements, histologic evaluation, and various reproductive and developmental toxicity studies. If an endocrine effect is suspected, additional endpoints evaluating reproductive performance or focused on

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specific aspects of the male and female reproductive systems can be added to standard studies to enhance the probability of detecting an effect. Carcinogenicity studies may reveal effects on the thyroid gland or on levels of luteinizing hormone or prolactin.

A positive endocrine finding in an in vitro nonclinical study must be carefully evaluated to determine its relevance to in vivo conditions. An in vitro effect without an in vivo adverse effect may not be considered to be a signal. Binding to a receptor or any other in vitro biologic activity does not necessarily translate into adverse effects for humans under clinical conditions of use. In vitro effects may depend on the tissue or species tested. A false-positive from an in vitro study may be detrimental to development of a drug product and may detract from a drug's therapeutic benefit. The value of in vitro studies may be greatest when they help clarify a mechanism of an observed in vivo effect.

## EVALUATION OF CONCERN FOR ADVERSE HUMAN ENDOCRINE EFFECTS, AN INTEGRATED ASSESSMENT

After an in vivo endocrine or reproductive developmental signal is identified, human relevance is of utmost concern. An integration "tool" that formalizes a weight-of-evidence approach has been developed in the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (USFDA), to assess concern about reproductive/developmental toxicity to humans. The draft document is described in the federal register and is available on the Center for Drug Evaluation, USFDA, Web site [1]. Ordinarily, the integration process would be based on an evaluation of a complete set of the expected general toxicology, reproductive toxicology, and pharmacokinetics studies. This evaluation would include an assessment of the ability of the drug to produce a positive finding in the relevant animal studies, or whether doses used were large enough to induce toxicity of some kind. The evaluation would 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. Three classes of reproductive toxicity are evaluated for degree of concern for human risk: fertility, parturition, and lactation. Four classes of developmental toxicity category are evaluated: mortality, dysmorphogenesis (structural alterations), alterations to growth, and functional toxicities. In this formalized approach to a weight-of-evidence evaluation, six factors are considered: signal strength part 1; signal strength part 2; pharmacodynamics; concordance between test species and humans; relative exposures in animals and humans; and class alerts in humans. Each factor has several elements. Signal strength part 1 includes cross-species concordance, multiplicity of effects, and adverse effects at different stages of development. Signal strength part 2 includes considerations of parental toxicity, the dose response, and rarity of the event. For each contributory element within a factor, the quality and type of data are considered. An assignment of increased (+1), decreased (–1), or no change (0) in the level of concern is made for each factor in an endpoint for an identified signal. The values for the factors are summed to arrive at an overall conclusion for an endpoint.

Sometimes, concern for an adverse endocrine effect can be estimated more simply by considering the biologic relevance for an effect, existence of a threshold for the effect, exposure in animals at which an effect occurred or did not occur, and availability of monitorable biomarkers in humans.

## RISK/BENEFIT OF ENDOCRINE EFFECTS OF DRUG PRODUCTS

For a drug product, risk is never considered in isolation from the benefit of the drug product. Risk/benefit for a particular drug product is a clinical decision and will vary with the drug indication. An endocrine effect could be desirable or undesirable. The more serious the indication, the greater the tolerance for adverse effects. Risk management for an identified concern could include monitoring patients, wording in patient communications regarding the drug product, tracking distribution or limited distribution of the drug product, and patient or pregnancy registries. Risk management programs are developed in cooperation with the drug sponsors. The Center for Drug Evaluation and Research (of the

USFDA), and the Center for Biologics Evaluation and Research (of the USFDA), are jointly working to develop final guidance documents that will address good risk assessment, risk management, and pharmacovigilance practices.

## REFERENCES

1. <www.fda.gov/cder/guidance/4625dft.pdf>.