Guidance for Industry

Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling

DRAFT GUIDANCE

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Guidance for Industry[1] Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling

I. INTRODUCTION

This guidance describes a basic framework for designing and conducting PK/PD studies in pregnant women. It provides recommendations to sponsors on how to assess the influence of pregnancy on the pharmacokinetics (PK), and where appropriate, the pharmacodynamics (PD) of drugs or biologic products.[2] Additionally, this guidance provides recommendations to primary investigators, clinical researchers, and clinical pharmacologists about issues to consider when designing and conducting PK studies in pregnant women.

The Agency recommends using this guidance in conjunction with other FDA and ICH guidances, and pharmacological and clinical literature, on the design, conduct, and interpretation of pharmacokinetic studies. Because the conduct of studies in pregnant women requires specialized knowledge in a variety of areas, investigators designing such studies are encouraged to obtain advice from experts in fields such as obstetrics, pediatrics, pharmacology, clinical pharmacology, pharmacometrics, statistics, and other applicable disciplines. Although this guidance provides recommendations on when PK studies in pregnant women are appropriate, it does not address ways to assess efficacy of a drug in pregnancy or how to assess whether the drug causes adverse pregnancy or neonatal outcomes.

[1] This guidance has been prepared by the PK in Pregnancy Working Group of the Pregnancy Labeling Task Force, Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] Throughout this document, the term *medical product* or *drug* means drug and biological products, including vaccines.

FDA's guidance documents, including this guidance, 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.

II. BACKGROUND

Ideally, pharmacologic agents would not be needed during pregnancy; however, some women enter pregnancy with medical conditions that require ongoing or episodic treatment (e.g., asthma, epilepsy, hypertension). During pregnancy, new medical problems can also develop, and old ones can be exacerbated (e.g., migraine headaches), requiring pharmacologic therapy. Studies have shown that most pregnant women do use either prescribed or over-the-counter medications during pregnancy (Bonati 1990, De Vigan 1999, Lacroix 2000, Mitchell 2001). Interviews of approximately 20,000 U.S. and Canadian women conducted over 25 years reported a mean of 2.3 medications used during pregnancy, excluding vitamins and minerals (Mitchell 2001). Of the women interviewed, 28 percent reported using more than four medications during pregnancy, and medication use increased with maternal age. In addition, the mean number of medications taken, in successive 5-year intervals, progressively increased from 2.7 to 4.4, indicating secular patterns of medication use by pregnant women. A comparison of therapeutic drug use during pregnancy in Europe showed that 64 percent of women used at least one drug during pregnancy (De Vigan 1999), while in France, pregnant women were prescribed an average of five drugs during the first trimester (Lacroix 2000).

Generally, the safety and efficacy of a drug are established for a particular dosage regimen or range of dosage regimens in late phase (Phase 3) clinical trials involving relatively typical representatives from the target patient population. Pregnant women are actively excluded from these trials, and, if pregnancy does occur, the usual procedure is to discontinue treatment and drop the patient from the study. Consequently, at the time of a drug's initial marketing, except for products developed to treat conditions specific to pregnancy (e.g., oxytocics, cervical ripening agents), there are seldom human data on the appropriate dosage and frequency of administration during pregnancy. Even after years of marketing, data in product labels regarding PK and dose adjustments during pregnancy rarely provide more information for appropriate prescribing in pregnancy than was available at the time of initial marketing.

The few data to address appropriate dosage and frequency of administration in pregnancy are not usually supported by a full understanding of the alterations of the PK of the drug in pregnancy. For example, the majority of published PK studies of anti-infective drug products during pregnancy were conducted at the time of abortion or delivery (usually via cesarean section) and were done to determine the transplacental passage of drug. In the absence of data, the usual adult dose is typically prescribed for pregnant women. Because of the physiologic changes inherent in pregnancy, the result can be substantial under dosing, or, in some cases, excessive dosing.

Extrapolation of PK data from studies performed in nonpregnant adults fails to take into account the impact of the many physiologic changes that occur during pregnancy. Most of the physiologic changes manifest during the first trimester and peak during the second trimester of pregnancy. Physiologic changes are not fixed throughout pregnancy but rather reflect a continuum of change as pregnancy progresses, with return to baseline at various rates in the postpartum period. The physiologic changes have the potential to alter the PK and/or PD of drugs. Some of these changes include:

- Changes in total body weight and body fat composition.
- Delayed gastric emptying and prolonged gastrointestinal transit time.
- Increase in extra cellular fluid and total body water.
- Increased cardiac output, increased stroke volume, and elevated maternal heart rate.
- Decreased albumin concentration with reduced protein binding.
- Increased blood flow to the various organs (e.g., kidneys, uterus).
- Increased glomerular filtration rate.
- Changed hepatic enzyme activity, including phase I CYP450 metabolic pathways (e.g., increased CYP2D6 activity), xanthine oxidase, and phase II metabolic pathways (e.g., N-acetyltransferase).

A significant amount of pharmacologic research has been conducted to improve the quality and quantity of data available for other altered physiologic states (e.g., in patients with renal and hepatic disease) and for other patient subpopulations (e.g., pediatric patients).[3] The need for PK/PD studies in pregnancy is no less than for these populations, nor is the need for the development of therapeutic treatments for pregnant women.

III. DECIDING WHETHER TO CONDUCT A PHARMACOKINETIC STUDY IN PREGNANT WOMEN

Ethical issues are important when considering studying drugs in pregnant women. Given the large number of pregnant women who need prescription medicines to maintain their health, some have argued that it is unethical *not* to obtain dosing information in this subpopulation (Faden 2000). Others recommend that only pregnant women who need a drug for therapeutic reasons be included in clinical studies, citing that drug studies cannot be done in "normal pregnant volunteers" (Stika 2001).

[3] Guidance for Industry *Pharmacokinetics in Patients with Impaired Renal Function,* http://www.fda.gov/cder/guidance/1449fnl.pdf, issued May 1998. Guidance for Industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling,* http://www.fda.gov/cder/guidance/3625fnl.pdf, issued May 2003. Draft Guidance for Industry *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products,* http://www.fda.gov/cder/guidance/1970dft.pdf, issued November 1998. Draft guidances, when finalized, will represent the Agency's current thinking on these issues.

All studies in pregnant women must conform to all applicable regulations, including human subject protection.[4] The Agency recommends that all studies in pregnant women have Institutional Review Board (IRB) review and informed consent for all study participants.

Pregnant women may be involved in PK studies if the following conditions are met (45 CFR Subpart B 46.204):

- Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses; and
- The risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

The definition of minimal risk is broad. The fetal risk is considered minimal when the estimated risk to the fetus is no more than that from established procedures routinely used in an uncomplicated pregnancy or in a pregnancy with complications comparable to those being studied.[5] Although PK studies in pregnancy can be considered in Phase 3 development programs depending on anticipated use in pregnancy and the results of reproductive toxicity studies, the FDA anticipates that most PK studies in pregnant women will occur in the postmarketing period and will be conducted using pregnant women who have already been prescribed the drug as therapy by their own physician. An example of a minimal risk study would be one to determine PK/PD of an antihypertensive medication in pregnant women who are taking that medication to treat hypertension during pregnancy. The decision to use the antihypertensive medication is made by the patient and her physician independent of participation in the PK/PD study.

Information on human pregnancy experiences and exposures will emerge during the postmarketing phase for virtually all drug products. Sponsors are requested to explicitly address positive or negative experiences during pregnancy or lactation as one of the safety issues in the Overall Safety Evaluation section of the Periodic Safety Update Report.[6] This source of information is valuable in determining whether to conduct PK studies in pregnant women. Other important sources of information include publications concerning safety (e.g., reports that describe the use of the drug in pregnancy) or efficacy in pregnancy and information from medical specialty groups. These types of postmarketing exposure and safety data on drug products provide the basis for determining the need for PK assessment of a drug in pregnant women.

This guidance recommends that PK studies be conducted in pregnant women in any of the following situations:

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[4] 45 CFR 46, Protection of Human Subjects, http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm.

[5] Office of Human Research Protections, http://ohrp.osophs.dhhs.gov

[6] Guidance for Industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs,* http://www.fda.gov/cder/guidance/1351fnl.pdf, issued May 1997.

- The drug is known to be prescribed in or used by pregnant women, especially in the second and third trimesters.
- For a new drug or indication, if there is anticipated or actual use of the drug in pregnancy.
- Use is expected to be rare, but the consequences of uninformed dosages are great (e.g., narrow therapeutic range drugs, cancer chemotherapy). Drugs of this type can normally be studied in pregnant patients.
- Pregnancy is likely to alter significantly the PK of a drug (e.g., renally excreted drug) and any of the above apply.

PK studies in pregnant women are not recommended if the drug is not used in pregnant women or the drug has known or highly suspect fetal risk.

For approved products, consider whether a study in pregnant women must be conducted under the investigational new drug (IND) regulations (21 CFR 312.2). If there is a concern for significantly increasing the risk (or decreasing the acceptability of the risks) in a patient population (i.e., the mother or fetus), an IND would be needed (21 CFR 312.2(b)(iii)). Also, according to the IND regulations, if a different route of administration or dosage level is used, an IND would be needed.

IV. STUDY DESIGN

Study design considerations are important when conducting a study in pregnant women to determine if the PK and/or PD are altered enough to require an adjustment from the established dosage. Ideally, PK studies in pregnancy would be done pre-pregnancy (for baseline comparison) and during all three trimesters, especially for chronically administered drugs. Given the constraints of a study design that enrolls women prior to pregnancy, an alternative can be to determine PK/PD in the second and third trimesters, with the baseline assessment for comparison to the pregnant state done in the postpartum period. The Agency recommends care be taken to select the most appropriate postpartum time for PK/PD determination, if known. Cardiovascular and renal changes do not return to the pre-pregnancy state until 3 months postpartum. Optimally, postpartum PK/PD assessments for comparative purposes to PK/PD in pregnancy would be done when the woman is neither pregnant nor lactating.

The PK and/or PD study can also be nested within a larger clinical study on safety, efficacy, and outcomes of interest (e.g., Prevost et al. performed a study on the PK of nifedipine on a small subset of patients who were participating in a larger clinical study to assess treatment for pregnancy-induced hypertension (Prevost 1992)).

A. Longitudinal Design

For drugs that are administered chronically or given for several treatment cycles during pregnancy, a longitudinal study design is most clinically meaningful. This allows for intensive PK studies in pregnant women conducted serially so that each woman serves as her own control,

avoiding the common criticism that PK/PD studies in pregnant women are flawed because of the comparison group employed (Reynolds 1991; Little 1999). Such a study would focus on comparing each pregnant woman enrolled at one trimester of pregnancy to the same patient at a different trimester as well as during the postpartum period. We recommend that the rationale for which trimesters are chosen be stated clearly in the study protocol. This longitudinal design minimizes interindividual variability across gestational ages; however, intraindividual variability would be taken into account when determining the sample size. It is important that the analytical plan take into consideration the repeat measures characteristics of a longitudinal design.

Because physiologic changes are continuous throughout pregnancy, and abrupt changes do not necessarily coincide with each trimester shift, the Agency recommends that investigators consider narrowing the time of sampling from trimester to a *window* of time during each trimester. For example, 4-week *windows* can be selected for second trimester (e.g., 24-28 weeks) and third trimester assessments (e.g., 34-38 weeks).

The Agency recommends that each woman serve as her own control and have PK/PD determinations performed at different trimesters and in the postpartum period. For certain drugs that are given acutely (e.g., single dose or short course of therapy) it can be difficult to implement a longitudinal design using the same subjects throughout and after pregnancy. For example, in certain circumstances drug therapy may no longer be medically essential in the postpartum period. In these situations, a multi-arm study can be designed to compare different pregnant subjects at different trimesters and in the postpartum period.

B. Population PK Design

A population PK approach with nonlinear mixed effects modeling techniques can be used as an alternate way to enroll pregnant women in PK studies and minimize the number of blood draws and PD assessments. The population PK approach can assess the impact on the PK of a drug on various covariates, such as maternal characteristics (e.g., age, gravity, parity, race, weeks or trimester of gestation), concomitant medications, and underlying medical conditions. For example, a measure of pregnancy status such as weeks gestation can be one of the covariates, making it possible to model the relationship between gestational age of pregnancy and PK parameters such as the apparent clearance of the drug (CL/F).

In principle, a population PK study design and analysis might detect PK differences large enough to warrant dosage adjustment if the study has enough pregnant and nonpregnant women enrolled with sufficient representation of second and third trimesters (with a continuum of gestational ages from 13 to 40 weeks). Typically, each patient is only sparsely sampled to obtain plasma drug concentration data and/or PD data. Due to the intrinsic characteristics of a population PK study, the controls for this study design can differ from other study designs and can potentially include matched healthy nonpregnant female volunteers. To ensure the ability to determine the inter-occasion variability and prevent a parallel group trial design, a cohort of study subjects would have data collected from all trimesters and the postpartum period. Considering the number of subjects in the study and the key objective of the study, efforts can be made to reduce the number of influential covariates such as concomitant medication.

Some investigators have proposed conducting a population PK study as a preliminary step and to subsequently conduct a standard intensive PK/PD study if the population PK study suggests changes between the pregnant and nonpregnant women (Stika 2000). For further information about the population PK approach, see the Guidance for Industry *Population Pharmacokinetics*.[7]

V. OTHER DESIGN CONSIDERATIONS

A. Study Participants

Study participants should be representative of a typical patient population for the drug to be studied including race, ethnicity, and trimester of pregnancy. Factors with significant potential to affect the PK of a drug to be studied (e.g., age, weight, diet, smoking, concomitant medications, ethnicity, renal function, other medical conditions) can be considered depending on the pharmacologic properties of the drug. The FDA recommends that uniform diagnostic measures be applied to all pregnant women to ensure similarity of diagnosis for the treatment being given and to reduce disease-specific variability in PK. The FDA recommends that measures used for dating the pregnancy be stated clearly in the study protocol and consistently applied throughout the study. Inclusion and exclusion criteria can be tailored to the study.

For drugs that are metabolized by enzymes known to exhibit genetic polymorphism (e.g., CYP2D6 or CYP2C19), the FDA recommends that the investigator consider the metabolic status of the enrolled subjects when analyzing the results of the study. Genotype has been shown to have an effect on pregnancy-related changes in metabolism (Wadelius 1997).

B. Postpartum Assessments

Physiology changes rapidly at delivery but can take from weeks to months to return to the pre-pregnancy state. The Agency recommends that drugs used only during the peripartum period (e.g., labor and delivery) be studied only at that time. In the peripartum period, PK and receptor sensitivity related to PD can change, so PK/PD studies for drugs used in the peripartum period are important.

A woman's own postpartum PK/PD assessments can serve as a control or comparator for the pregnant state. For women to whom drugs are administered chronically and for whom a pregnancy on the medication of interest is planned, the pre-pregnancy PK/PD assessment can serve as the comparison. For drugs used throughout pregnancy and the postpartum period, PK studies can be performed during the postpartum period to serve as the comparator or control group. Postpartum assessments can potentially be done longitudinally (e.g., at 2, 4, 6, and 8 weeks postpartum) to determine the time course for PK changes to return to the nonpregnant state. Some pregnancy-related medical conditions rapidly improve after delivery such that

[7] Guidance for Industry *Population Pharmacokinetics,* http://www.fda.gov/cder/guidance/1852fnl.pdf, issued February 1999.

pharmacologic therapy is no longer needed in the postpartum period (e.g., some cases of pregnancy-induced hypertension or gestational diabetes). In this scenario women can participate in a single-dose PK/PD study in the postpartum period. If a drug possesses linear kinetics, the single-dose PK data can be extrapolated to the multiple-dose steady state kinetics and then compared with steady state kinetics obtained during pregnancy when the drug was administered chronically.

If subjects are breast-feeding during the postpartum portion of the study, the FDA recommends that the study incorporate appropriate safety precautions concerning drug excretion into breast milk and the effects of the drug on the breast-fed infant. The study design should take into account data concerning the pediatric pharmacology and adverse effects of the drug. A lactation study might be performed in conjunction with postpartum sampling.

C. Sample Size

The objective and design of a study are determining factors in deciding adequate sample size. The number of subjects enrolled in a study should be sufficient to detect PK differences large enough to warrant dosage adjustments. Sample size considerations include PK and PD variability for the drug being studied, the study design (i.e., single-dose versus multiple-dose), and the physiologic changes inherent in pregnancy. For a population PK approach,[8] sparse sampling with a larger number of subjects that span the gestational time periods of interest is encouraged.

As a practical matter, it is prudent that the final number of subjects enrolled be in excess of that originally determined by standard sample size calculations to take into account withdrawal of subjects from the study. Even if data for a subject are missing for one trimester, the Agency suggests that the subject be retained in the study for the postpartum assessments.

D. Drug Administration

In single-dose studies, the same dose can usually be administered to all women in the study. Lower or less frequent doses can be considered to minimize fetal risk in pregnant women who volunteer to take the medication for study purposes, even if it is expected to pose minimal risk at standard doses. The dosage regimen can be adjusted based on the best available pre-study estimates of the PK of the drug and its active metabolites and what is known about drug elimination. A concentration-controlled study design or a dosage adjustment based on the patient's response are alternative methods to consider. For example, the study might be conducted to achieve a specific target concentration using therapeutic drug monitoring procedures. When studying pregnant patients who need the study drug, the dose can be modified, either increased or decreased as pregnancy progresses, to achieve the appropriate response (e.g., lowering of blood pressure, or to decrease adverse events such as hypotensive episodes with antihypertensive therapy).

[8] Guidance for Industry *Population Pharmacokinetics,* http://www.fda.gov/cder/guidance/1852fnl.pdf, issued February 1999.

E. Sample Collection and Analysis

The Agency recommends that plasma or whole blood samples and urine samples be analyzed for the parent drug and any metabolites with known or suspected activity, therapeutic or adverse. It is recommended that the frequency and duration of plasma sampling and urine collection be sufficient to estimate accurately the relevant PK parameters for the parent drug and its active metabolites (see Section VI, Data Analysis).

Plasma protein binding, like renal function, is often altered in pregnancy.[9] For example, albumin and alpha-1-acid glycoprotein levels are reduced in pregnancy, consequently the protein binding of drugs can be affected. With systemically active drugs and metabolites, the unbound concentrations are generally believed to determine the rate and extent of delivery to the sites of action. For drugs and metabolites with a relatively low extent of plasma protein binding (e.g., the extent of binding is less than 80 percent), alterations in binding due to pregnancy are small in relative terms. In such cases, description and analysis of the PK in terms of total concentrations would be sufficient. For drugs where the extent of protein binding is greater than 80 percent, primarily to albumin, it is recommended that the PK be described and analyzed with respect to the unbound concentrations of the drug and active metabolites. Although unbound concentrations should be measured in each plasma sample, if the binding is concentration-independent and unaffected by metabolites or other time-varying factors, the fraction unbound can be determined using a limited number of samples or even a single sample from each patient during each trimester. The unbound concentration in each sample should then be estimated by multiplying the total concentration by the fraction unbound for the individual patient.

F. Studies with No Intended Therapeutic Benefit

It is possible to study drugs that have no intended direct therapeutic benefit to the pregnant woman provided that the risk to the fetus is minimal (45 CFR 46). For example, probe substrates can be used to investigate drug metabolism (e.g., cytochrome P-450 activity) or drug transporter status (e.g., p-glycoprotein). Data from these studies offer generalizable information to other pregnant women but do not offer direct therapeutic benefit to study participants. The Agency encourages sponsors or investigators to explore additional safeguards for human subject protection for this type of study. To minimize exposure to a nontherapeutic drug, each pregnant woman can be exposed to the drug once during pregnancy and in the postpartum period employing a nonlongitudinal design (e.g., one cohort of women sampled in second trimester and postpartum and another cohort of women sampled in third trimester and postpartum). Examples of additional safeguards include administering only products with a long or known record of safety in pregnancy, administering products using only a single dose of the drug, using lower doses of the drug, decreasing the number of drugs (probe substrates) used in any study subject, and limiting study participants to pregnant women only in second or third trimester.

[9] Guidance for Industry *Pharmacokinetics in Patients with Impaired Renal Function,* http://www.fda.gov/cder/guidance/1449fnl.pdf, issued May 1998.

G. Pharmacodynamic Assessments

PK studies are usually enhanced by including PD assessments as part of the study. The Agency encourages sponsors to discuss the selection of the PD endpoints with the appropriate FDA review staff. Endpoints would be based on the pharmacological characteristics of the drug and metabolites (e.g., the behavior of other drugs in the same pharmacological class), and include consideration of relevant biomarkers.[10] Fetal PD endpoints can warrant study as well (e.g., fetal heart rate and rhythm response to maternal administration of an antiarrhythmic drug).

VI. DATA ANALYSIS

The primary intent of the data analysis is to assess whether dosage adjustment is needed for pregnant patients, and, if so, to develop dosing recommendations for such patients based on gestational age or trimester. The analysis, specifically modeling and dosing recommendations, will depend on the study design characteristics. The categorization of pregnancy status, either as nominal (e.g., trimester) or continuous (e.g., week of gestation) data will direct the type of analysis performed. The Agency encourages giving special analytical considerations to longitudinal study designs and the baseline (e.g., postpartum) comparisons. The data analysis typically consists of the following steps:

- Estimation of PK parameters
- Development of dosing recommendations

A. Parameter Estimation

The Agency recommends that total and unbound plasma concentration data (and urinary excretion data if collected) be used to estimate PK parameters of the parent drug and metabolite(s). Standard PK parameters of a drug include the area under the plasma concentration curve (AUC), peak concentration (C_{max}), plasma clearance (CL_T) or apparent oral clearance (CL/F), renal clearance (CL_R), apparent volume of distribution (V_Z/F or V_{ss}/F), and terminal half-life ($t_{1/2}$). It is recommended that PK parameters be expressed in terms of total and unbound concentrations and when applicable (e.g., oral and renal clearance, expressed in terms of body weight, L/hr/kg). For drugs and metabolites with a relatively low extent of plasma protein binding (e.g., extent of binding less than 80 percent), description and analysis of the PK in terms of total concentrations can be sufficient. Noncompartmental and/or compartmental modeling approaches to parameter estimation can be employed.

[10] Guidance for Industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*, http://www.fda.gov/cder/guidance/5341fnl.pdf, issued May 2003.

B. Development of Dosing Recommendations

Specific dosing recommendations should be constructed based on study results. Typically the dose should be adjusted to produce a comparable range of unbound plasma concentrations of drug or active metabolites in both controls and pregnant patients. Simulations are encouraged as a means to identify doses and dosing intervals that achieve that goal for pregnant patients at different trimesters or gestational ages.

One approach might be for the sponsor to recommend, prior to the conduct of the studies, specific *no effect* boundaries for the ratio of a PK measurement from pregnant patients and controls, such as (AUCu,pregnant/AUCu,control) or (Dpregnant/Dcontrol). If the 90 percent confidence interval for the ratio of PK measurements falls within these boundaries, the sponsor might claim *no effect* of pregnancy on PK, and it would be reasonable to conclude that no dosage adjustment is needed for pregnancy. The sponsor might determine *no effect* boundaries from population or individual PK/PD relationships, dose-finding studies and/or dose-response studies which are conducted as part of drug development.

Another approach might be for the sponsor to assume *no effect* boundaries of 80-125 percent for C_{max} and AUC without further justification, recognizing that the small sample sizes in pregnancy studies coupled with high intersubject variability can preclude meeting the 80-125 percent *no effect* boundaries.

For some drugs, pregnancy may not alter PK sufficiently to warrant dosage adjustment. A sponsor might make this claim by providing an analysis of the study data to show that the PK measurements most relevant to therapeutic outcome in pregnant patients are similar or equivalent to those in the comparator group.

VII. LABELING

The Agency recommends that labeling reflect the data from PK/PD studies in pregnancy and, if known, dosing recommendations during pregnancy. The labeling would reflect the data pertaining to the effect of pregnancy on the PK and PD obtained from studies conducted. If no studies were conducted, the Agency recommends that the labeling indicate that the impact of pregnancy was not studied. If the PK/PD is altered during pregnancy, the appropriate description of such and recommendations for dosing should be stated in labeling.

The various permutations of intrinsic drug characteristics and the effect of pregnancy on drug performance preclude precise specification of how such drugs would be labeled. The following comments offer general suggestions on labeling.

A. Clinical Pharmacology

1. Pharmacokinetics Subsection

It is recommended that this section include information pertinent to pregnancy such as:

- Disposition of parent drug and metabolites, if applicable
- Effects of pregnancy on protein binding of parent drug and metabolites, if applicable
- Effects of changes in urinary pH or other special situations (e.g., tubular secretion inhibited by probenecid)

2. Special Populations Subsection

It is recommended that this section recapitulate, in brief, the PK changes found in pregnancy and, if needed, dosing adjustments for pregnant patients. This information should be based on the studies performed as described in this guidance. Reference should be made to the PRECAUTIONS/PREGNANCY and the DOSAGE AND ADMINISTRATION sections. The following text provides examples of possible wording for these sections.

The simplest situation involves drugs for which pregnancy has little or no effect on PK:

> *The disposition of [Drug X] was studied in [number of] pregnant patients [in y trimester or from a through b weeks gestation]. Pregnancy has little or no influence on [Drug X] pharmacokinetics and no dosing adjustment is needed.*

This should be followed by a brief summary of the PK/PD data (e.g., mean, range).

Similarly, for drugs whose PK is influenced by pregnancy, the statement similar to the following can be modified as appropriate and in accordance with what is known about the drug (e.g., active or toxic metabolite) and from the studies performed in accordance with this guidance:

> *The disposition of [Drug X] was studied in [number of] pregnant patients [in y trimester or from a through b weeks gestation]. Elimination of the drug (and metabolite, if applicable) is significantly changed during pregnancy. Total body clearance of (unbound, if applicable) [Drug X]/metabolite was reduced/increased in pregnant patients compared to [healthy postpartum women, the same women prior to pregnancy or c weeks postpartum]. The terminal half-life of [Drug X]/metabolite is [prolonged/decreased] by Y-, and Z- fold in second and third trimesters, respectively. Protein binding of [Drug X]/metabolite [is/is not] affected by pregnancy. The [drug/metabolite accumulates/does not accumulate] in pregnant patients on chronic administration resulting in increased/decreased plasma levels of drug/metabolite. The pharmacologic response [is/is not] affected by pregnancy. The dosage/dosing interval should be [decreased/increased] in pregnant patients receiving [Drug X] (see DOSAGE AND ADMINISTRATION).*

B. Precautions/Pregnancy

In addition to standard labeling for use in pregnancy, including Pregnancy Category, a brief statement regarding PK/PD in pregnancy would be included in the PRECAUTIONS/PREGNANCY section with cross reference to DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY sections. If PK studies in pregnancy were not conducted, the Agency recommends that the labeling indicate that.

C. Dosage and Administration

As appropriate, the following information could be included:

- A statement describing the relationship between the drug's clearance and pregnancy
- A statement describing how the dose would be adjusted during pregnancy, for example:

  The dose of [Drug X] should be [increased/decreased by _____%] during pregnancy.

- A statement describing how the dose would be adjusted in the postpartum time period in nonlactating women, specifying the time period studied (e.g., 2 weeks postpartum)
- The dosing adjustment regimen can alternatively be represented in tabular format, for example:

Group	Dosage (mg)	Frequency
1st trimester	x	Every y hours
2nd trimester		
3rd trimester		
Postpartum (specify time)		
Standard adult dose		

- If no dose adjustment is necessary the following statement is suggested:

  The influence of pregnancy on [Drug X] pharmacokinetics is sufficiently small that no dosing adjustment is needed.

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