Guidance for Industry

Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Considerations, Content, and Format

DRAFT GUIDANCE

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For questions regarding this draft document contact the CDER Office of Clinical Pharmacology at 301-796-5008 or OCP@fda.hhs.gov, or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-7800.

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

August 2014
Labeling

Revision 1

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Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
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Food and Drug Administration
10903 New Hampshire Ave., WO71, Room 3128
Silver Spring, MD 20993
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Guidance for Industry[1]
Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Considerations, Content, and Format

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist applicants in preparing the CLINICAL PHARMACOLOGY section of product labeling to meet regulatory requirements (21 CFR 201.57(c)(13)) and ensure appropriate consistency in the format and content of this section for all prescription drug products approved by FDA.[2] The guidance provides recommendations to applicants submitting new drug applications (NDAs) (including applications submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(2)), abbreviated new drug applications (ANDAs), supplements to approved NDAs, biologics license applications (BLAs), and supplements to BLAs, who intend to prepare or amend the clinical pharmacology information in the labeling for human prescription drug or biological products. Not all of the information identified in this guidance for inclusion in the CLINICAL PHARMACOLOGY section of product labeling will be applicable for every drug; rather, the guidance provides a general framework and set of recommendations that should be adapted to specific drugs and their conditions of use. For clinical pharmacology information presented in other parts of labeling (see section III.B of this guidance), applicants should consult other relevant guidances for current perspectives on best labeling practices.

[1] This guidance has been prepared by the Office of Clinical Pharmacology, Office of Translational Sciences in cooperation with the Study Endpoints and Labeling Development Team, Office of New Drugs, in the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

[2] This guidance provides guidance on the CLINICAL PHARMACOLOGY section of the prescription drug labeling under the 2006 final rule that amended the requirements for the content and format of labeling for human prescription drug and biological products (commonly referred to as the Physician Labeling Rule (PLR)). See Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products (71 FR 3922).

This guidance is a revision of the draft guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* issued in February 2009. In its revised form, the guidance clarifies what information should be included in section 12 CLINICAL PHARMACOLOGY and outlines the use of subsections, headings, and subheadings to provide organization to this section. The revised guidance also discusses incorporation of clinical recommendations that are based on clinical pharmacology findings for other sections of the labeling and emphasizes the importance of providing variability measures related to pharmacokinetic (PK) parameters and clinical pharmacology study results. For the purposes of this revised draft guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

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

Optimal pharmacotherapy is driven by an understanding of a drug product's clinical pharmacology and the clinical context in which the drug will be used. Important clinical pharmacology attributes to consider in therapeutic decision making include, but are not limited to, drug mechanism of action, pharmacodynamic (PD) effects (e.g., on target/pathway, and off target/pathway), and PK properties in a variety of settings and specific populations.

Clinical pharmacology information collected throughout a drug product's life can contribute to the product's labeling. Specifically, we consider what clinical pharmacology information can be directly translated to patient care management and provide specific recommendations that should be included in relevant sections of the labeling. Examples of specific recommendations include strategies for dose selection, therapeutic individualization, and adverse reaction risk minimization. In these cases, supportive information (i.e., the clinical pharmacology basis for the specific recommendation) is generally expected to be concise to enable unambiguous application to patient care. Occasionally, depending on the complexity of the patient care recommendations, it can be appropriate to include expanded versions of this supportive information in the labeling. The reason for including this information is to provide sufficient detail for the health care provider to determine the relevance of the information for a given patient or clinical scenario; this information is typically included in the CLINICAL PHARMACOLOGY section of product labeling and is the main focus of this guidance.

III. GENERAL PRINCIPLES FOR THE CLINICAL PHARMACOLOGY SECTION

A. Content and Organization

The CLINICAL PHARMACOLOGY section appears under *Full Prescribing Information* in the labeling. Information in this section should be presented in a way that is understandable to practitioners who may not have specific expertise in clinical pharmacology. This section should generally include information on both positive and pertinent negative findings that are informative for clinical use of the drug product. The information presented must not be inaccurate, false, misleading, or promotional (21 CFR 201.56(a)(2)) and subjective wording (e.g., "fast" or "rapidly") should be avoided.

Specific content and format requirements for the CLINICAL PHARMACOLOGY section of the labeling are described in § 201.57(c)(13)(i):

> This section must contain information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling.

The CLINICAL PHARMACOLOGY section of the labeling consists of the following subsections:[3]

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

In addition, the following standard subsections should be used when appropriate:

12.4 Microbiology[4]
12.5 Pharmacogenomics[5]

These subsection numbers should not be used for other subsections (i.e., the numbers 12.4 and 12.5 are reserved for the *Microbiology* and *Pharmacogenomics* subsections, respectively).

Occasionally, the addition of subsections beyond 12.5 can be appropriate to convey important clinical pharmacology findings that do not fit within the scope of subsections 12.1 through 12.5. The additional subsections should be given identifying numbers beginning with 12.6. The title of the subsection should reflect the contents of the subsection. An example of an additional

[3] 21 CFR 201.57(c)(13)(i).

[4] See FDA draft guidance for industry *Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation*, which states that as provided for in the final rule Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, the microbiology portion of the labeling can be added as subsection 12.4 (citing 71 FR 3922 and 21 CFR parts 201, 314, and 601).

[5] See FDA guidance for industry *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling.*

subsection is "*12.6 Therapeutic Drug Monitoring.*" Therapeutic drug monitoring can be based on exposure measures or PD responses. If therapeutic drug monitoring is important for safe and effective use of the drug and is part of the therapeutic management of the patient, information that provides the basis for therapeutic drug monitoring should be described in a separate subsection. The use of therapeutic drug monitoring for individualization of dosing should be included in the DOSAGE AND ADMINISTRATION section.

Within each subsection, headings can be used to separate individual topics. Subheadings can be used to separate topics under headings. The use of headings and subheadings will help organize the information. We recommend using a consistent approach to distinguish headings and subheadings (e.g., italics are used for headings, while underlining is used for subheadings). See section IV.C of this guidance for examples.

B. Cross-Referencing of Clinical Pharmacology Information

Detailed information on clinical pharmacology topics is included in the CLINICAL PHARMACOLOGY section, while other sections of labeling contain summary information and clinical recommendations that may be related to clinical pharmacology information. Other FDA guidances provide additional instruction as to what specific information should be included in relevant sections of labeling.[6]

Cross-referencing should be used in accordance with the FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR and Format Requirements* when specific clinical pharmacology information appears in multiple sections of labeling.

Clinical recommendations based on PK or PD data should not be included in the CLINICAL PHARMACOLOGY section. Instead, a cross-reference should be made to the appropriate sections/subsections that include this information (e.g., INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, and OVERDOSAGE). If there are findings that do not warrant clinical recommendations or where the clinical implications of the findings are not known, there should be no cross-reference to another section of labeling. However, if positive findings are discussed in the CLINICAL PHARMACOLOGY section and a cross-reference to another section is not included, then additional information about the lack of clinical relevance of the information should be included (e.g., there is no clinical significance or the clinical significance of the findings is unknown). Repetition of detailed information in multiple sections should be avoided.

[6] The guidances referenced in this document are available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance page.

IV. INFORMATION TO BE INCLUDED IN EACH SUBSECTION

The pharmacologic and pharmacokinetic attributes of parent drug and metabolites that contribute to the overall efficacy or toxicity of a product in a meaningful way should be included in the CLINICAL PHARMACOLOGY section of labeling. If the drug is a racemate, a brief description of the racemic mixture followed by information about the clinical pharmacology of each enantiomer should be included in the appropriate subsection(s) if both are active and have different types of activity or different pharmacokinetics. Intended or unintended effects due to additives (adjuvants, excipients, or preservatives) present in the product should also be included in this section.

The subsections in the CLINICAL PHARMACOLOGY section can include quantitative information that is the result of specific clinical pharmacology studies, population analyses, other modeling approaches, or simulations. The summary of the data based on these analyses are included in this section while the corresponding clinical recommendations are included in other relevant sections of labeling.

A. Subsection 12.1 Mechanism of Action

This subsection should summarize what is known about the drug's established mechanism(s) of action (MOA) (§ 201.57(c)(13)(i)(A)). The MOA should be discussed at various levels, including the cellular, receptor, or membrane level, the physiologic system level (target organ), and the whole body level, depending on what is known. Target selectivity should be described when data suggest that target selectivity might be related to toxicity or effectiveness. Speculative claims of untested MOAs and unsupported suggestions of therapeutic advantages based on MOA must be avoided (§ 201.56(a)(2)). If different MOAs are the bases of response in different indications, the MOA should be summarized for each indication. If the mechanism of action for the desired effects is not known, a statement about the lack of information should be included. Information from animals and in vitro studies can be included where helpful and clearly relevant to the human response. Although rarely needed, a brief description of disease pathophysiology may facilitate an understanding of the drug's pharmacology and its impact on that process, especially if the drug is intended to modulate the effects of an underlying molecular aberration.

If the drug product is an antimicrobial agent, the antimicrobial MOA should be described in subsection *12.4 Microbiology*, rather than in subsection *12.1 Mechanism of Action.* The subsection *12.1 Mechanism of Action* should include a statement in the following form:

"*X* is an anti- (e.g., bacterial, viral, as appropriate*)* drug *[see Clinical Pharmacology (12.4)]*."

B. Subsection 12.2 Pharmacodynamics

This subsection must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's beneficial effect or related to adverse effects or toxicity (§ 201.57(c)(13)(i)(B)). This subsection should include a description of the drug's or its metabolites' effect on relevant PD biomarkers and their parameters. The

relevance of the PD biomarker is a function of how mechanistically related the biomarker is to the drug's clinical effect or toxicity.

If data exist and are pertinent to drug use, the following information should be summarized for the parent and active metabolites:

- Principal PD effect(s)
- Time of onset of the PD effect and time of peak PD effect
- Whether or not the PD effect is reversible
- Time to stable PD effect and whether this time is related to the attainment of steady state blood concentrations or reflects hysteresis (i.e., a delay between attainment of effective plasma concentration and drug effect)
- Duration of the PD effect after drug withdrawal and potential for rebound effect
- Differential PD effects in subpopulations
- Whether the PD effects are dose- or exposure-dependent and the nature of the dose-response or exposure-response relationship

Additional information relevant to the *Pharmacodynamics* subsection might include:

- Undesired PD effects with cross-reference to clinically important descriptions in sections such as CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, or USE IN SPECIFIC POPULATIONS, where appropriate.
- PD effects demonstrated outside the approved dosage range may be included for a complete understanding of the exposure-response relationship. However, dosing regimens not included in the DOSAGE AND ADMINISTRATION section must not be implied or suggested in the CLINICAL PHARMACOLOGY section (§ 201.57(c)(3)(ii)).
- Impact of anti-product antibody formation on pharmacodynamics of a biologic product.

Because the evaluation of drug effects on the QT interval is common, the *Pharmacodynamics* subsection should typically include the heading "Cardiac Electrophysiology." A drug's effect on the QT interval should be included under this heading, including the dose(s) studied or exposure range observed and any dose or exposure-response relationships identified. If there is no effect of the drug on the QT interval, this should be stated under this heading, and if the information is not known, a statement to this effect should be included under this heading. For example, if a thorough QT trial is negative, the following statement is recommended: "At a dose X times the maximum recommended dose, Drug Y does not prolong the QT interval to any clinically relevant extent."

C. Subsection 12.3 Pharmacokinetics

This subsection should begin with a brief introduction that describes the general, clinically significant PK properties of the parent drug and its active metabolites, and any unique drug product characteristics. For example, PK linearity/non-linearity or a drug's biopharmaceutics characteristics (e.g., modified release, orally disintegrating tablet) should be included in this introduction. The introduction also should include information such as time to steady state,

accumulation ratio following multiple dosing, metabolite-to-parent exposure ratios, and changes in pharmacokinetics over time. Information regarding the impact of anti-product antibody formation on the pharmacokinetics of a biologic product also should be included in this introduction.

Available PK measures and parameters (e.g., maximum plasma concentration (C_{max}), area under the plasma drug concentration time curve (AUC), clearance, volume of distribution, half-life) should be included in this subsection and can be used to provide context for the optimization of drug administration. Information on intra- and inter-subject variability, if known, should also be included. Whether or not the drug is subject to polymorphic enzymes or transporters that affect absorption, distribution, metabolism, or excretion should be stated under the respective headings with appropriate detail in subsection *12.5 Pharmacogenomics*.

Although bioequivalence or relative bioavailability may be a factor in the approvability of an application (e.g., 505(b)(2) applications), the term "bioequivalence" or the comparative PK data generally should not be included in the labeling. Instead, the applicant should include relevant PK measures and parameters that are important for the safe and effective use of the product. In certain cases, it may be clinically relevant to convey differences in concentration profiles (e.g., a comparison of the plasma concentration versus time profiles of a modified-release formulation and an immediate-release drug product).

Following the presentation of this general information, the *Pharmacokinetics* subsection should include the following headings: *Absorption, Distribution, Elimination, Specific Populations,* and *Drug Interaction Studies*, if applicable. These headings should be included in the order presented below. If a heading is not applicable, it should be omitted. Subheadings can be added under the headings as appropriate.

1. Absorption

This heading should include information related to the extent (i.e., absolute and/or relative bioavailability) and rate (e.g., time to maximum concentration (T_{max})) of absorption. Other factors related to absorption should be described, such as:

- The presence, location (liver and/or intestine), and extent of first pass effect, or other mechanisms affecting bioavailability (e.g., chemical degradation, intestinal metabolic enzymes, or transporters)
- A description of the absorption kinetics (i.e., linear or nonlinear) over the range of clinical doses
- Differential absorption of isomers in a racemate, if both enantiomers are active
- Extent and sources of variability of absorption within and between individuals, if known
- Clinical relevance of disease-related changes in absorption (e.g., due to fast or slow gastrointestinal transit time, short bowel syndrome)

The effect of food on the absorption of the drug product should be described. A description of the food(s) or meal(s) used with respect to total calories and composition (fat, carbohydrate, and protein content) should be stated. Specific study results, such as the effect of food on important

PK parameters should be included. If studies are conducted to assess the effect of the timing of meals on absorption, those study results should be included.

The effect of food substances that influence transporters and/or intestinal metabolic enzymes that ultimately affect absorption (e.g., grapefruit juice) should be included under the *Absorption* heading. However, the impact of drugs that affect absorption (e.g., acid reducing agents) should be included under the *Drug Interaction Studies* heading.

Specific instructions on how a drug product is to be administered relative to the ingestion of food or a food substance should be included in DOSAGE AND ADMINISTRATION. Other sections of labeling, such as WARNINGS AND PRECAUTIONS, should also be modified as appropriate, depending on the nature of the effect. Please refer to FDA guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies*.

2. Distribution

The drug's volume of distribution should be included under this heading. The reported value should be compared to physiologic volumes and the relevance of the volume of distribution for clinical use of the drug should be described. Other study results related to a drug's systemic distribution should be described here (e.g., distribution into blood components, tissue, central nervous system, or human milk). A drug's protein binding should be described in this section. The role of transporters in the distribution of the drug should be described if relevant (e.g., the importance of transporters for a drug's penetration across the blood-brain barrier). Details of a study that characterizes the distribution of the drug into human milk can be included under this heading; however, the summary and clinical implications of the results should be included in subsection 8.3 *Nursing mothers.* Any dosing recommendations resulting from PK findings for nursing mothers should be included in the DOSAGE AND ADMINISTRATION section.

3. Elimination

The *Elimination* heading should include an introductory paragraph followed by two subheadings: Metabolism and Excretion. The introductory paragraph should include the values of the drug's total body clearance with information related to relevant contributions to total clearance; for example, the percent of total clearance attributable to renal and non-renal clearance pathways. The drug's half-life should be stated here. The half-life value reported should usually be the half-life based on the time to reach steady state (i.e., the effective half-life). If a long terminal half-life is important from a safety or effectiveness standpoint, the long half-life should be stated here and any management strategies related to the long terminal half-life should be described in other appropriate sections of the labeling (e.g., WARNINGS AND PRECAUTIONS).

The Metabolism subheading should include a description of the in vitro and in vivo biotransformation pathways, including the contribution of specific enzymes and identification of major metabolites. The source of this information comes from in vitro and/or in vivo studies. Metabolic pathways that have been ruled out should also be stated. A description of a metabolite's activity, if relevant, should be included, including its contribution to activity in relation to the parent drug.

The Excretion subheading should include the modes and extent of parent and metabolite excretion from the body, as defined by chemical measures or radiolabel (mass balance) studies. Mechanisms involved in the excretory process should be included. For example, if a drug undergoes renal excretion, the mechanism of renal excretion should be described (e.g., glomerular filtration, active secretion, or reabsorption). If transporters involved in the excretion process have been identified, their contribution should be included.

4. Specific Populations

This heading includes results of studies or analyses that evaluate the potential for pharmacokinetic differences in subpopulations defined by age, sex, race/ethnicity, renal function, hepatic function, and pregnancy. We recommend that the following subheadings be used for consistency: Age, Sex, Race/Ethnicity, Renal Impairment, Hepatic Impairment, and Pregnancy. For clarity, details of studies and analyses should be included under these subheadings identifying the focus of the study or analysis. A subheading should be included only if the specific population was assessed. Brevity is encouraged. It is appropriate to simply list the specific population studies in which there were no changes (e.g., "The pharmacokinetics of X were not altered in subjects with renal impairment or hepatic impairment") instead of stating the same conclusion under separate headings. Explicit dosing modifications or subpopulation-specific therapeutic management (e.g., monitoring) should be included in the sections DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, and USE IN SPECIFIC POPULATIONS, and other sections as appropriate. PD differences observed in specific populations should be included in subsection *12.2 Pharmacodynamics* with appropriate subheadings included to identify the specific population.

Preferred subheadings and recommendations are as follows:

Age: Geriatric Population: Descriptions and results of studies/analyses conducted in subjects 65 years of age and older should be presented here. Results should be compared to those obtained in younger adult populations where possible. Analyses related to age can be included with age as a categorical variable or as a continuous variable. In some cases, it may be relevant to use age breakpoints other than 65 years. For example, if exposures are found to be much higher in patients older than 80, it would be appropriate to use 80 years of age as a breakpoint to describe the results. If appropriate, ranges of ages could also be included to describe the results.

Age: Pediatric Population: Pediatric PK information should appear under this subheading for approved pediatric indications; however, pediatric PK information should appear under subsection *8.4 Pediatric Use* when safety and effectiveness have not been established in the relavent pediatric population. Descriptions and results of studies/analyses to evaluate pharmacokinetics in pediatric patients from birth to less than 17 years of age should be presented here. PK exposure measures or parameter values should be summarized based on appropriate pediatric age groups. For example, PK parameter values can be described as a function of age or maturity that reflects ontogenic development. See FDA draft guidance for industry and review

staff *Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling*.[7]

Sex: Descriptions and results of studies/analyses conducted to identify pharmacokinetic differences between male and female subjects should be presented here. If differences between male and female subjects have been identified, the differences should be included under this subheading.

Race/Ethnicity: Descriptions and results of studies/analyses conducted to identify differences in pharmacokinetics among race/ethnicity groups should be presented here. If differences have been identified among races/ethnicity, these differences should be described here.

Renal Impairment: PK results in subjects with varying degrees of renal impairment should be presented relative to the pharmacokinetics of the drug in subjects with normal renal function. The definitions of the categories of renal function should be included. Changes in both the parent drug and relevant metabolites should be reported. The effect of hemodialysis, continuous renal replacement therapies, and chronic peritoneal dialysis in clearing the parent drug and metabolites from the body is described under this subheading, if known. Relevant extracorporeal means of removing the drug from the body should also be included in the OVERDOSAGE section of the labeling. The results can be presented as a function of the renal function categories or by using a renal function measurement as a continuous variable. See FDA draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*.

Hepatic Impairment: PK results in subjects with varying degrees of hepatic impairment should be presented relative to the pharmacokinetics of the drug in subjects with normal hepatic function. The categories of hepatic function should be defined and included. Changes in both the parent drug and relevant metabolites should be reported. See FDA guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.

Pregnancy: Although studies conducted to evaluate the PK of a drug during pregnancy are not common, descriptions and results of any studies conducted should be reported here. The pharmacokinetics should be described as a function of trimester or gestational age, and any immediate postpartum effects on drug exposure should be reported. See FDA draft guidance for industry *Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling.* Clinical management recommendations should be included in subsection *8.1 Pregnancy*.

5. Drug Interaction Studies

[7] When final, draft guidances referenced in this document will represent the FDA's current thinking on the guidance topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Both positive and pertinent negative results from in vitro or in vivo studies conducted to evaluate drug interactions should be included under this heading. Specific practical instructions for preventing and managing clinically significant drug interactions should be provided in the DRUG INTERACTIONS section of labeling. Other sections of labeling, e.g., CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS, may include information regarding drug interactions.

A list of studied drugs with no interaction could be included in one sentence that conveys the knowledge that no interactions were observed without the need for extensive elaboration. When a drug interaction study results in no PK changes but does have an important impact on pharmacodynamics, subsection *12.2 Pharmacodynamics* should be cross-referenced and the PD results should be included there.

Please refer to the FDA draft guidance for industry *Drug Interaction Studies — Study Design, Data Analysis, and Labeling Recommendations* for detailed recommendations on the information that should be included under this heading, how to describe the results of positive drug interaction studies, and when it is important to cross-reference other sections of the labeling.

D. Subsection 12.4 Microbiology

The *Microbiology* subsection includes information relevant to the microbiology characteristics of the drug. Refer to the FDA draft guidance for industry *Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation* for information to be included in subsection 12.4.

Pharmacodynamic information of antimicrobials should not be included in subsection *12.4 Microbiology*, but instead it should be included in subsection *12.2 Pharmacodynamics*. In addition, exposure-response relationships and relevant exposure relationships that are pertinent to the antimicrobial action of the drug, including impact on growth and resistance, should be included in subsection *12.2 Pharmacodynamics* (§ 201.57(c)(13)(i)(B)) using identifying subheadings (e.g., Exposure-Response, Exposure–MIC Relationships, etc.).

E. Subsection 12.5 Pharmacogenomics

See the FDA guidance for industry *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling.*

V. PRESENTATION OF INFORMATION

A. Central Tendency and Variation

Appropriate presentation of PK and PD data is critical to enable interpretation and translation of this information to individual patients and patient subgroups. Calculation and comparison of some central tendency measure (e.g., mean exposure) between two specific populations (e.g., with and without hepatic impairment) is often the basis of dose modification recommendations in

labeling. Additionally, therapeutic individualization and personalized medicine increasingly call for consideration of response variability (i.e., variability in observed measurements).

The distribution of PK and PD observations should be considered in determining the most appropriate approach to reporting central tendency and variation in labeling. The reasons for skewed distributions of PK or PD data may have important therapeutic implications and should be evaluated for inclusion in labeling. The following are examples of scenarios that should be evaluated for potential inclusion in labeling:

- Presence of PK or PD outliers (especially if relevant to response or adverse reactions)
- Bimodal (or multimodal) distribution of observations (which could represent more than one elimination process or polymorphic metabolism)
- Skewness due to evaluation of only a subset of data (e.g., because out-of-range, near zero, or other criteria were applied to create a subset of the original data)

The way information is presented can vary depending on what important attributes of the distribution should be conveyed. The following are context-specific examples of clinically useful presentations of data distributions:

- A histogram when knowledge of the frequency of observations across the entire range of results is important
- The number and/or percentage of subjects with exposures above a certain value in situations where high exposures are related to safety concerns (or when therapeutic failure is a concern, the number/percentage of subjects with exposures below a certain value)
- Minimum and maximum values when knowledge of the extremes is important

PK and PD values typically should be reported as mean (arithmetic or geometric) or median with the most informative measure of dispersion (e.g., standard deviation, coefficient of variation expressed as a percent, interquartile range). The presentation will depend on the distribution of the data, whether or not the data have been normalized, and/or which parameter is being reported (e.g., use of median may be more appropriate than mean for T_{max}). The choice of how to best present measures of central tendency and variability in labeling for a given drug should be informed by the utility of the information in providing a context for making clinical decisions.

B. Presentation Format

Information in the CLINICAL PHARMACOLOGY section of labeling is both qualitative and quantitative and can be presented in subsections as text, tables, and/or figures. The approach that best ensures clarity and understanding should be used. Tables can be useful if it is important to highlight specific values or other data. Figures may be useful to show trends and presence or absence of specific phenomena, especially when absolute data values are not critical to interpretation (e.g., for some drug interactions), or to explain relationships between independent and dependent variables and time-related phenomena (e.g., exposure-response relationships, concentration-time profiles, PD endpoint dynamics). These are just examples. Tables and figures should be self-explanatory, clearly labeled, nonrepetitive, and consistently formatted. Text should generally not repeat the content of tables and figures.