Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

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)

December 2016
Labeling

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Contains Nonbinding Recommendations

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Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA offices responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants in preparing the CLINICAL PHARMACOLOGY section of prescription drug labeling (henceforth referred to as labeling) to meet regulatory requirements and ensure appropriate consistency in the format and content of this section for all prescription drugs approved by FDA.[2,3] 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 drugs. Not all of the information identified in this guidance for inclusion in the CLINICAL PHARMACOLOGY section of 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

[1] This guidance has been prepared by the Office of Clinical Pharmacology, Office of Translational Sciences in cooperation with the 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 document provides guidance on the CLINICAL PHARMACOLOGY section of prescription drug labeling (21 CFR 201.57(c)(13)) 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, January 24, 2006).

[3] This guidance applies to drugs, including biological products that are regulated as drugs. For the purposes of this guidance, "drug product" or "drug" will be used to refer to human prescription drug and biological products that are regulated as drugs.

guidance), applicants should consult other relevant guidances for current perspectives on best labeling practices.[4]

In general, FDA's guidance documents 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'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, pharmacodynamics (PD) (e.g., both on-target and off-target pathways), and pharmacokinetics (PK) in a variety of settings and specific populations.

Clinical pharmacology information collected throughout a drug's life cycle can contribute to clinical decision making and may be appropriate for inclusion in a drug's labeling. Specifically, we consider what clinical pharmacology information can be directly translated to prescribing decisions 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 minimization of adverse reaction risk. 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 is appropriate to include more detailed 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 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.[5] Information in this section should be presented in a way that is understandable to health care providers who may not have specific expertise in clinical pharmacology. This

[4] Additional labeling guidances are available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[5] 21 CFR 201.57(c)(13)

section should generally include information on pertinent positive findings and may include pertinent negative findings that are informative for the safe and effective use of the drug. The information presented must not be inaccurate, false, misleading, or promotional in tone;[6] and subjective wording (e.g., "fast" or "rapidly") should be avoided. Indications or uses must not be implied or suggested in this section if not included in the INDICATIONS AND USAGE section and dosing regimens must not be implied or suggested if not included in the DOSAGE AND ADMINISTRATION section.[7]

Specific content and format requirements for the CLINICAL PHARMACOLOGY section of the labeling are described in 21 CFR 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 must contain the following subsections:[8]

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 [9]
12.5 Pharmacogenomics[10]

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).

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[6] 21 CFR 201.56(a)(2).

[7] 21 CFR 201.57(c)(2)(iv and v) and (c)(3)(ii), respectively.

[8] 21 CFR 201.57(c)(13)(i).

[9] 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). When final, draft guidances referenced in this document will represent the FDA's current thinking on the guidance topic.

[10] See FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR and Format Requirements.*

Occasionally, the addition of subsections beyond 12.5 can be appropriate to convey important clinical pharmacology findings that are not included in subsections 12.1 through 12.5 because the information does not fit within the scope of these subsections, the information spans across multiple existing CLINICAL PHARMACOLOGY subsections, or is of sufficient breadth to affect readability of other key information within the section. The additional subsections should be given sequential identifying numbers beginning with 12.6. The title of the subsection should reflect the contents of the subsection.

Subsections may also include the use of headings and subheadings that will help organize the information; we recommend using a consistent approach to distinguish headings and subheadings within sections (e.g., underlining for headings and italics for subheadings). Headings and subheadings should not be assigned a numerical identifier with an additional decimal point (e.g., 12.2.1).

Units for all measures and parameters for clinical pharmacology related information should be consistent throughout the labeling.

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.[11]

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. Although the preferred presentation of cross-referencing in the Full Prescribing Information is to use the section heading followed by the numerical identifier (e.g. *[see Warnings and Precautions (5.1)]*), we recommend an exception when cross-referencing to subsection *12.4 Microbiology* (i.e., use the subsection heading rather than the section heading *[see Microbiology (12.4)]*) because the term "Microbiology" more accurately reflects the information presented under this subsection (see section IV.A of this guidance).

Detailed clinical recommendations based on PK or PD data should not be included in the CLINICAL PHARMACOLOGY section. In general, if there are PK or PD 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 an additional statement about the lack of clinical relevance of the information should be included (e.g., there is no clinical significance or the clinical

[11] 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.

significance of the findings is unknown). Repetition of detailed information in multiple sections should be avoided.

IV. INFORMATION TO BE INCLUDED IN EACH CLINICAL PHARMACOLOGY SUBSECTION

The pharmacologic and PK attributes of parent drug and metabolites that contribute to the overall efficacy or toxicity of a drug 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 PK. Intended or unintended effects due to additives (adjuvants, excipients, or preservatives) present in the drug formulation 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, or other modeling and simulation approaches (e.g., physiologically-based pharmacokinetic (PBPK) modeling).

When describing a dosage that is outside the approved recommended dosage range (e.g., exposure-response, dose proportionality, and absorption kinetics), the dosage should be expressed in terms of the highest and lowest recommended dosage (e.g., "50 milligrams (mg) (0.5 times the lowest approved recommended dosage) to 400 mg (2 times the highest approved recommended dosage)" assuming the approved recommended dosages are 100 mg and 200 mg).

A. Subsection 12.1 Mechanism of Action

This subsection must summarize what is known about the drug's established mechanism(s) of action (MOA).[12] The MOA must be discussed at various levels, including the cellular, receptor, or membrane level, tissue, the physiologic system level (target organ), and the whole body level, depending on what is known.[13] Target selectivity should be described when data suggest that target selectivity might be related to toxicity or effectiveness. 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.

The subsection should include the MOA for the approved indication(s) or uses of the drug or about clinically significant adverse reactions or other potential safety hazards associated with the drug. The MOA for indications or uses not included in the INDICATIONS AND USAGE section of the labeling must not be included.[14] Speculative claims of untested MOAs and

[12] 21 CFR 201.57(c)(13)(i)(A).
[13] *Id*.
[14] 21 CFR 201.57(c)(2)(iv and v).

unsupported suggestions of therapeutic advantages based on MOA may be false or misleading and, therefore, must be avoided.[15] If different MOAs are the bases of response in different approved indications, the MOA should be summarized for each approved indication. If the MOA to achieve the desired clinical effects is not known, a statement about the lack of this information must be included.[16]

If the drug 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 only a statement in the following form:

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

B. Subsection 12.2 Pharmacodynamics

This subsection must include a description of any biochemical or physiologic pharmacologic effect of the drug or active metabolites related to the drug's clinical effect or related to adverse effects or toxicity.[17] This subsection should include a description of the drug's or its metabolites' effect on relevant PD biomarkers or other relevant clinical measures. 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 drug and its 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. This information should be expanded to support actionable therapeutic drug monitoring information described in other sections of the labeling (e.g., the DOSAGE AND ADMINISTRATION section) where applicable. Therapeutic drug monitoring information may be presented under a separate heading under this subsection if the breadth of information necessitates it to enhance clarity and readability of the information.

[15] 21 CFR 201.56(a)(2).

[16] 21 CFR 201.57(c)(13)(i)(A).

[17] 21 CFR 201.57(c)(13)(i)(B).

- Information supporting the clinical impact of anti-product antibody formation on PD without a clinically significant change in PK. If both PK and PD are affected by anti-product antibody formation, information supporting the clinical impact of anti-product antibody formation will be included in subsection *12.3 Pharmacokinetics*. The clinical impact of anti-product antibody formation, however, is included in other sections of the labeling (e.g., ADVERSE REACTIONS, WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and BOXED WARNING sections).

A concise description of key study designs and results of drug interaction or specific population studies with a clinically significant impact on PD that is independent of PK changes should be included in this subsection. A list of relevant studied coadministered drugs assessed for drug interaction potential or specific populations assessed for potential factor effects without a clinically significant impact on meaningful PD measurements may be included in one or more summary sentences that convey the knowledge that clinically significant issues were not observed. If PK changes cause the effect on PD, this information should be described in the *12.3 Pharmacokinetics* subsection.

If there are no relevant PD data, or the PD effects are unknown, this subsection must contain a statement indicating this lack of information.[18]

Additional information relevant to the *12.2 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. If it informs prescribing decisions, it should include information on PD effects demonstrated outside the approved recommended dosage range for a complete understanding of the exposure-response relationship. For example, knowing that an adverse reaction is associated with concentrations higher than what is expected from the approved recommended dosage would be useful information for the health care provider.

Nonclinical animal PD information should generally be included in subsection *13.2 Animal Toxicology and/or Pharmacology*. However, nonclinical PD data may be included in subsection *12.2 Pharmacodynamics* if it is necessary for the understanding of pharmacology data in humans.

Subsection *12.2 Pharmacodynamics* should typically include the heading "Cardiac Electrophysiology." A drug's effect on the QT interval should be described under this heading, and should include the dose(s) studied or exposure range observed as well as any dose or exposure-response relationships identified. If there are potential clinically significant risks associated with QT prolongation, these potential risks should be discussed in other sections of labeling (e.g., BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS sections).

If there is no effect of the drug on the QT interval, this should be stated under this "Cardiac

[18] 21 CFR 201.57(c)(13)(i)(B).

Electrophysiology" heading. For example, if a thorough QT trial is negative, the following statement is recommended: "At a dose X times the maximum approved recommended dose, Drug Y does not prolong the QT interval to any clinically relevant extent." [19] If the information is not known, the "Cardiac Electrophysiology" heading may be omitted.

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 relevant metabolites, and any unique drug characteristics. For example, this introduction may include PK linearity/nonlinearity over the range of studied doses and a drug's biopharmaceutics characteristics (e.g., modified release, orally disintegrating tablet). In addition, if the drug is classified as a prodrug then this designation should also be stated here. The introduction should also include clinically useful information on the expected exposure of the drug (e.g., the maximum plasma concentration (C_{max}), area under the plasma drug concentration over time curve (AUC)) at the approved recommended dosage, time to steady state, accumulation ratio following multiple dosing, and changes in PK over time.

Following the presentation of this general information, the *12.3 Pharmacokinetics* subsection should include the following headings (if applicable) in this order:

Absorption
Distribution
Elimination
Specific Populations
Drug Interaction Studies

If a heading is not applicable, it should be omitted. Headings or subheadings can be added as appropriate (e.g., *Anti-Product Antibody Formation Affecting PK)*. Information included in the brief introduction should not be repeated under the headings and subheadings. Alternative formats (e.g., tables and figures) may also be considered to present this information and the brief introduction information (see section V.B of this guidance).

Available PK measures and parameters (e.g., clearance, volume of distribution, half-life) should be included in this subsection to provide context for the optimization of drug administration. The use of general terms such as "systemic exposure" should be avoided unless they are qualified in the labeling (e.g., systemic exposure (i.e., AUC)). Information on intra- and intersubject variability, if known, should also be included if it is informative for clinical use of the drug. Whether or not the drug is subject to polymorphic enzymes or transporters that affect absorption, distribution, or elimination (e.g., metabolism, excretion) should be stated under the respective headings with appropriate detail in subsection *12.5 Pharmacogenomics* and a cross reference to, subsection *12.3 Pharmacokinetics*. If the drug is a transporter substrate, the specific transporter should be mentioned under the appropriate heading (e.g., Absorption, Distribution, or

[19] See FDA guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Proarrhythmic Drugs.*

Elimination) based on its location and roles. If the transport of a drug is subject to genetic variability, the information should be included under the relevant heading in the *12.3 Pharmacokinetics* subsection and cross-referenced to the fuller discussion in subsection *12.5 Pharmacogenomics*.

Although 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 drug. In certain cases, it may be clinically relevant to convey differences in concentration-time profiles (e.g., a comparison of the plasma concentration versus time profiles of modified-release and immediate-release formulations).

For fixed dose combination products that include previously approved individual components, only relevant information that forms the basis of a dosing decision from the individual component's approved labeling should be included in the labeling for the fixed dose combination. For example, if a fixed dose combination product cannot be administered to patients with renal impairment, the labeling should only include the data to support the recommendation to not administer the drug product to patients with renal impairment. General PK information relating to renal impairment should not be included for the individual component when it does not inform prescribing decisions for the fixed dose combination product.

1. Absorption

This heading is applicable to oral and other nonintravenous routes of administration and should include information related to the rate and extent of absorption. Other factors related to absorption should be described when applicable. Examples include:

- 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 studied doses
- 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, short bowel syndrome)
- Differences in absorption for different injection or application sites

The effect of food on the absorption of orally administered drugs should be described under a subheading called "Effect of Food" under the Absorption heading. 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 impact of drugs that affect

absorption (e.g., acid reducing agents) should be included under the Drug Interaction Studies heading within *12.3 Pharmacokinetics*.

Specific instructions on how a drug is to be administered relative to the ingestion of food or a food substance should be included in the DOSAGE AND ADMINISTRATION section. This information may also be included in other sections of labeling, such as WARNINGS AND PRECAUTIONS, as appropriate, depending on the nature of the effect.[20]

2. Distribution

The drug's volume of distribution should be included under this heading. Additional discussion should be included if the volume of distribution contributes to the understanding of the drug's activity or safety (e.g., a large volume of distribution contributes to a long terminal half-life that may need to be considered when stopping therapy). Other study results related to a drug's systemic distribution should be described here (e.g., distribution into blood components, tissue or central nervous system). A drug's protein binding should be described under this heading.

3. Elimination

The Elimination heading should include an introductory paragraph followed by two subheadings: Metabolism and Excretion. The introductory paragraph should include 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 nonrenal 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 noted 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). When a drug exhibits nonlinear elimination within the approved recommended dosage range, the dosage that is associated with the half-life should be included.

The Metabolism subheading should include a description of the biotransformation pathways, including the contribution of specific enzymes and identification of major metabolites. The source of this information (i.e., in vitro and/or in vivo studies) should be clearly stated. If there is uncertainty in the identification of the metabolic pathways, then pathways that have been ruled out should be identified.

A metabolite's activity, if relevant, should be described, including its metabolite-to-parent exposure ratio and contribution to activity in relation to the parent drug. For example, "Two active Drug X metabolites, metabolite Y and metabolite Z, that are equipotent to the parent were identified in plasma, and their AUCs represent 25% and 11% of the parent AUC, respectively."

The Excretion subheading should include the pathways and extent of parent and metabolite

[20] See FDA guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies*.

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 should include results of studies or analyses that evaluate the potential for PK 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 unless the specific population was not assessed: Geriatric Patients, Pediatric Patients, Male and Female Patients, Racial or Ethnic Groups, Patients with Renal Impairment, Patients with Hepatic Impairment, and Pregnant Women. Additional subheadings representing other specific populations (e.g., smokers, obese patients, or low-body weight patients) may be included if informative for clinical use of the drug. A description of the studies and the results should be included under these subheadings. Brevity is encouraged. Explicit dosage modifications or population-specific therapeutic management should be included in other sections as appropriate (e.g., DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, and USE IN SPECIFIC POPULATIONS)

Information regarding lactation, including PK, must be provided in the *8.2 Lactation* subsection of the USE IN SPECIFIC POPULATIONS section.[21]

If there were no clinically significant PK changes in specific populations or if there were no PK studies or analyses, consider including these populations in one or more summary sentences as needed instead of listing all of the subpopulations under different subheadings. For example:

> The pharmacokinetics of drug X were not altered in patients with mild renal impairment (i.e., estimated creatinine clearance (CLcr) by Cockcroft-Gault (C-G) equation: 60 to 89 mL/min), patients with any degree of hepatic impairment, or in geriatric patients. The impact of more severe renal impairment with or without hemodialysis on the pharmacokinetics of Drug X is unknown.

The lack of specific population information or PK change under this heading should not be repeated in the USE IN SPECIFIC POPULATIONS section. However, in certain circumstances, the lack of specific population information may be included in the USE IN SPECIFIC POPULATIONS section (e.g., there are clinical relevant differences in recommendations for use of the drug in patients with mild and moderate renal impairment compared to the indicated population, but patients with severe renal impairment have not been studied).

Preferred subheadings and recommendations are as follows:

[21] See 21 CFR 201.57(c)(9)(ii); see also FDA draft guidance for industry and review staff *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format.*

a. Geriatric Patients

Descriptions and results of PK studies and analyses conducted in subjects 65 years of age and older should be presented under this subheading. 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 years, 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.

b. Pediatric Patients

Pediatric PK information should appear under this subheading for approved pediatric indications and should include descriptions and results of studies and analyses to evaluate PK in pediatric patients from birth to less than 17 years of age. However, if applicable, pediatric PK information should appear under subsection *8.4 Pediatric Use* when safety and effectiveness have not been established in the relevant pediatric population.[22] 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.

c. Male and Female Patients

Descriptions and results of studies and analyses conducted to identify PK differences between male and female subjects should be presented under this subheading.

d. Racial or Ethnic Groups

Descriptions and results of studies and analyses conducted to identify differences in PK among race/ethnicity groups should be presented under this subheading.[23]

e. Patients with Renal Impairment

Descriptions and results of studies and analyses conducted to identify PK differences in subjects with varying degrees of renal impairment should be presented relative to the PK of the drug in subjects with normal renal function. The results can be presented as a function of the renal function categories or by using a renal function measurement as a continuous variable. The classification of renal function and how it was determined (e.g., C-G CLcr or modification of diet in renal disease (MDRD) estimated glomerular filtration rate (eGFR) equations) should be

[22] See FDA draft guidance for industry and review staff *Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling*.

[23] See FDA guidance for industry and Food and Drug Administration staff *Collection of Race and Ethnicity Data in Clinical Trials.*

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 should be described under this subheading, if known. Relevant extracorporeal means of removing the drug from the body should also be described with clinical management recommendations in the OVERDOSAGE section of the labeling.[24]

f. Patients with Hepatic Impairment

Descriptions and results of studies and analyses conducted to identify PK differences in subjects with varying degrees of hepatic impairment should be presented relative to the PK 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.[25]

g. Pregnant Women

Although studies conducted to evaluate the PK of a drug during pregnancy are not common, descriptions and results of any studies conducted and used to support risk statement(s) based on human data under the *Risk Summary* heading and *Dose Adjustments During Pregnancy and the Postpartum Period* subheading under the *Clinical Considerations* heading in subsection *8.1 Pregnancy* should be reported under this subheading. The PK, including known differences pertinent to pregnancy, should be described as a function of trimester or gestational age, and any immediate postpartum effects on drug exposure should be reported under this subheading.[26, 27] If there are PK data that support dosage adjustment(s) during pregnancy, a summary of this information must be provided in the *8.1 Pregnancy* subsection of the USE IN SPECIFIC POPULATIONS[28] section and the specific dosage adjustments must be provided in the DOSAGE AND ADMINISTRATION[29] section.

5. Drug Interaction Studies

[24] See FDA draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*.

[25] See FDA guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.*

[26] See the FDA draft guidance for industry *Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling*.

[27] See the FDA draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format.*

[28] 21 CFR 201.57(c)(9)(i)(C)(2).

[29] 21 CFR 201.57(c)(3)(i)(C).

Both positive and pertinent negative results from in vitro and/or in vivo studies conducted to evaluate drug interactions should be included under this heading.[30] Brevity is encouraged. A list of studied drugs with no clinically relevant interaction potential should be summarized in one or more sentences as needed to convey, without extensive elaboration, that no interactions were observed.

A concise description of clinically significant drug interactions in addition to specific actionable instructions for preventing and managing the drug interactions should be included in the DRUG INTERACTIONS section of labeling. The specific actionable instructions should not be repeated in the CLINICAL PHARMACOLOGY section. Other sections of labeling (e.g., DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, or SPECIFIC POPULATIONS[31]) may include information regarding drug interactions.

D. Subsection 12.4 Microbiology

The *12.4 Microbiology* subsection should include information relevant to the microbiology characteristics of the drug.[32]

The antimicrobial MOA should be described in the *12.4 Microbiology* subsection rather than in the *12.1 Mechanism of Action* subsection. Pharmacodynamic information of antimicrobials should not be included in the *12.4 Microbiology* subsection, but instead it should be included in the *12.2 Pharmacodynamics* subsection. 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 the *12.2 Pharmacodynamics* subsection using identifying headings (e.g., Exposure-Response, Exposure–Minimal Inhibitory Concentration (MIC) Relationships, etc.).

E. Subsection 12.5 Pharmacogenomics

If applicable, a *12.5 Pharmacogenomics* subsection should be included in the CLINICAL PHARMACOLOGY section of the labeling and should include clinically relevant data or information on the effect of genetic variations affecting drug therapy.[33]

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[30] See 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.

[31] When the results from a drug-hormonal contraceptive interaction study show the potential for altering the effectiveness of the contraceptive for a drug that also has a potential for adverse developmental outcomes, subsection *8.3 Females and Males of Reproductive Potential* should note the impact of this drug interaction on contraception effectiveness, and cross-reference to the DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections as appropriate.

[32] See the FDA draft guidance for industry *Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation* for information to be included in the *12.4 Microbiology* subsection.

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).

PK and PD values should be reported as mean (arithmetic or geometric) or median with a measure of dispersion (i.e., standard deviation and/or minimum and maximum values). 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 way information is presented can vary based on the attributes of the information that are important for clinical decisions. 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 when 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)
- A cumulative distribution function to quantify the fraction of the population affected for threshold values of interest

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)

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

[33] See the FDA guidance for industry *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* for information to be included.

best ensures clarity and understanding for the healthcare provider should be used. For example, general PK (e.g., linearity, accumulation, exposure parameters), absorption, distribution, and elimination information may be organized into a tabular format in lieu of text. In addition, 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). Tables and figures should be self-explanatory, clearly labeled, nonrepetitive, and consistently formatted. Text should generally not repeat the content of tables and figures. Headings or subheadings may be omitted if relevant information is presented in an organized table or figure.

VI. PROCEDURAL INFORMATION

Submission of a labeling supplement for an approved drug is not required to solely address a minor formatting change (e.g., modifying or re-ordering heading or subheading titles) referred to in this guidance document that is not a regulatory requirement or a safety issue. When such minor formatting changes are incorporated into labeling, they must be documented by the applicant in the next annual report.[34]

[34] 21 CFR 314.70(d)(2)(x).