

Guidance for Industry

Format and Content of Clinical Pharmacology Section of Human Prescription Drug Labeling

DRAFT GUIDANCE

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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)

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5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573
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I. INTRODUCTION AND BACKGROUND

This Guidance is intended to assist applicants in preparing the *Clinical Pharmacology* section of product labeling to meet the requirements of 21 CFR 201.57 and to facilitate communication about a sometimes complicated body of information. The guidance is also intended to assure consistency in clinical pharmacology labeling for all prescription drug products approved in the Center for Drug Evaluation and Research and the Center for Biologic Evaluation and Research. This guidance provides recommendations to applicants submitting New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), supplements to approved NDAs, 505(b)(2) supplements to ANDAs, and Biologics License Applications (BLAs) who intend to prepare or amend the *Clinical Pharmacology* section of the labeling for human prescription drug or biologics products. As stated in 21 CFR 201.56, the *Clinical Pharmacology* section of labeling is one of seventeen sections that are to appear in the Comprehensive Prescribing Information section of labeling: Boxed Warning, Indications and Usage, Dosage and Administration, How Supplied/Storage and Handling, Contraindications, Warnings/Precautions, Drug Interactions, Use in Specific Populations, Adverse Reaction, Drug Abuse and Dependence, Overdosage, Clinical Studies, Description, Clinical Pharmacology, Nonclinical Toxicology, References, and Patient Counseling Information. Specific content and format requirements for the *Clinical Pharmacology* section of the labeling are described in 21 CFR 201.57(c)(13) which states:

“(13) **12 Clinical Pharmacology**”: (i) Under this section, the labeling shall contain information relating to the human clinical pharmacology and actions of the drug. Information based on in-vitro data using human biomaterials (e.g., human liver slices) and/or pharmacologic animal models or preparations may be included if it is essential to

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On June 1, 1998, the President instructed all Federal agencies to ensure the use of plain language in all new documents. This guidance reflects Agency efforts to comply with the President’s plain language initiative.

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This guidance has been prepared by the Office of Clinical Pharmacology and Biopharmaceutics in consultation with the Office of Pharmaceutical Science, Office of Review Management, the Associate Center Director for Medical Policy, and the Clinical Pharmacology Section of the Medical Policy Coordinating Committee all within the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration and the Center for Biologics Evaluation and Research (CBER). Although this guidance does not create or confer any rights for or on any person and does not operate to bind the FDA or the industry, it does represent the agency’s current thinking on the subject. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

the description of the biochemical and/or physiological mode of action of the drug or drug-drug interactions, or is otherwise pertinent to human therapeutics. The section shall include the following subheadings and information:

- (A) "Mechanism of Action":
- (B) "Pharmacodynamics":
- (C) "Pharmacokinetics":
- (D) "Other Clinical Pharmacology Information":"

All of the specific information identified in this guidance for inclusion in the *Clinical Pharmacology* section of product labeling may not be applicable for every drug. Only information that will be useful to practitioners, that is, important to safe and effective use of the drug should be included the *Clinical Pharmacology* section of product labeling. The guidance thus provides a general framework and set of recommendations that should be adapted depending on the drug and its conditions of use. In general, the information included in the *Clinical Pharmacology* section should include both positive findings and those pertinent negatives. A lack of specific information should be noted only when that information is clinically pertinent. Additionally, the information should be presented in such a manner to be understandable to practitioners who may not be well versed in clinical pharmacology and pharmacokinetics. The information presented should not be speculative or promotional in any manner.

The term *drug* as used in this guidance refers to the active moiety(s) (parent, metabolites, isoforms, enantiomers, biologics entities) that lead to the intended therapeutic effect or a toxic effect. Active moieties are defined as those that contribute significantly to the efficacy or toxicity of the drug. In general, for purposes of this guidance, moieties that are thought to contribute 20% or more towards the overall efficacy or toxicity of a product should be considered active. In certain cases, where there are multiple moieties that contribute to activity to a small degree individually (i.e. <20%), but to a large degree collectively, such moieties can be considered to be active moieties. Information about the parent drug and other active moieties should be presented in the labeling. If the drug is a racemate, information about the clinical pharmacology of each enantiomer should be provided if both are active, but have different types of activity.

The specifics of the product need to be considered when applying this guidance. For example, with a vaccine used for active immunization, there is not an assay of the product or metabolite per se *in vivo*. Rather, the vaccine-induced immune response in the host, usually an antibody level or titer, is assessed at specific time points post immunization and will be used to determine the equivalence of PK/PD. Concepts such as compensatory mechanisms and the evaluation of drug levels in different body fluids and tissues (below) may not apply.

II. COMPREHENSIVE CLINICAL PHARMACOLOGY SECTION

A. Mechanism of Action

This section of the labeling should summarize what is known about the established mechanism(s) of action in humans, focusing on the desired effects of the drug. If a mechanism of any adverse effects is understood, that information should also be included. The mechanism(s) of action should be discussed at various levels, including the receptor or membrane level with a description of selectivity where important, the physiologic system level (target organ), and the whole body level (i.e., human) depending on what is known. Information from animals and *in-vitro* studies may be helpful. A brief description of disease pathophysiology may facilitate an understanding of the drug's action and its impact on that process. If the mechanism of action is not known, that should be indicated. Reasonably well-accepted mechanisms should be accurately described, and care should be taken to avoid speculative conclusions and claims that may be considered promotional as related to the impact of the drug or biologic on the disease process.

B. Pharmacodynamics

This section should include a description of the pharmacologic effects thought to be pertinent to the action of the drug, i.e., preventing, diagnosing, or treating disease, and/or causing adverse effects/events or toxicity. The section may include both pharmacologic endpoints such as inhibition of angiotensin II activity as well as surrogate or clinical endpoints such as blood pressure reduction and stroke rate. Details of clinical trials should be provided in the *Clinical Trials* section. Pertinent dose and/or concentration response relationship(s), the time course of action, and other information, such as tolerance, withdrawal effects, and pharmacodynamic differences between special populations should be presented. If information about PK/PD relationships are not demonstrated or are unknown, the labeling should so state. In such cases, the labeling should also indicate that it is not established whether reduction in dose or dosing interval may still provide efficacy with less adverse events.

The section should also describe pertinent negative and important pharmacologic effects other than the main desired effect.

If data exist, the following specific PD subjects should be discussed for the active moiety(s) (parent compound, metabolites, isoforms, and enantiomers if they differ in activity one from the other):

- C The principal PD effects of the drug at pertinent concentrations and locations such as receptors/membranes, organs, body tissues, with relevant information about how this relates to the clinical effect of the drug; receptor selectivity for pertinent receptors, as well as information pertaining to resistance and tolerance. Some of this information may appear in the *Mechanism of Action Section* of the labeling.
- C Information on the magnitude and duration of the principal clinically relevant PD effect(s), including any differences related to regimen or input rate; information

about the time to return to pretreatment PD activity (baseline), whether effects persist throughout the dosing interval, the time required to reach therapeutic effect, and whether this is related to the predominant PK half-life (half-life associated with the majority of AUC after single dose, or half-life associated with time to reach steady-state after multiple dosing)

- C The PK/PD relationships for peak effect and duration of effect; whether some or all of the effects are irreversible, and the presence of different PK/PD relationships for different effects
- C A therapeutic window, if one has been established, and the role of drug concentration monitoring for favorable or unfavorable effects. This information should be discussed further in the *Dosage and Administration* section of the labeling
- C Clinically significant PD effects not related to the desired effect that occur, e.g., sedation, or pertinent effects that do not occur, e.g., does not prolong QT interval. Information regarding undesired PD effects could also appear in the *Precautions/Warnings*, and/or *Adverse Reactions* sections of the labeling
- C Compensatory mechanisms, such as an increase in heart rate when blood pressure falls or the effect of an angiotensin II receptor antagonist on plasma renin levels, insofar as they may relate to the safety and efficacy of the compound. The dose/concentration effect relationship of such phenomena may also be pertinent
- C Patient characteristics such as disease severity, hormonal status, concomitant drugs, genetic or racial/ethnic factors, diurnal variation, menstrual cycle effects, environmental factors, and other known sources of variability in PD response
- C Modification of dose and dosing regimens in relation to therapeutic intent or toxic effects. Information on the magnitude, timing, initiation, and limitation of procedures to titrate a drug to an individual patient should be further discussed in the *Dosage and Administration* section of the Labeling
- C PD effects with excessive doses
- C Tolerance, rebound, abuse/dependence, and withdrawal effects related, for example, to up- or down-regulation of receptors if identified
- C Additional information for diagnostic imaging products, including quality of imaging versus dose and/or concentration, development of antibodies, onset of satisfactory imaging, time to maximum imaging quality, imaging duration time, and imaging characteristics. Any toxicologic effects or dose/concentration versus toxicity relationships with a diagnostic agent should be presented here and may be referenced to the *Clinical Studies*, *Dosage and Administration*, *Adverse*

Reactions, and/or Precautions/Warnings sections

C. Pharmacokinetics

The most important PK information related to clinical use for drugs or biologics with systemic absorption sufficient to elicit systemic efficacious or toxic effects should appear in this *Comprehensive Clinical Pharmacology* section. In general, study details other than identification of the population need not be provided. The reporting of coefficients of variation or standard errors of the mean is useful. The range may also be helpful for critical measures, principally clearance and half-life. In certain situations, PK study size may be pertinent. If PK information is lacking, this should be noted. In general, the focus should be on factors that explain and lead to altered critical measures such as maximum concentration (C_{\max}), minimum concentration (C_{\min}), area under the curve (AUC), half-life ($t_{1/2}$), and volumes of distribution (V_d).

More detailed, clinically pertinent information should be provided as follows:

1. **Absorption and Distribution** (or **Distribution** for intravenously administered entities)
 - C A brief statement about rate and extent of absorption for products that are absorbed (oral, intramuscular, subcutaneous, rectal, vaginally administered products, etc), presence and location (liver and/or intestine) of first pass effect, or other mechanisms of pre-systemic clearance such as the p-glycoprotein transport system or chemical decomposition
 - C Differential absorption of isomers in a racemate (for non-intravenously administered entities)
 - C Linear or nonlinear absorption kinetics at expected clinical doses (for non-intravenously administered entities)
 - C Sources of variability of absorption between and within individuals, if known and important (for non-intravenously administered entities)
 - C Effects or lack of effects of other drugs or biologics, food (including grapefruit juice), antacids, or chelating cations on absorption of orally administered entities
 - C Rate and extent of uptake by or transport to particular organs and multi-compartment behavior
 - C Passage across the blood brain barrier, placental transfer, and secretion into breast milk
 - C Plasma protein binding, erythrocyte binding, soluble factors, antibodies, and binding to cellular constituents
2. **Post-absorption Pharmacokinetics** (or **Post Administration Pharmacokinetics** for intravenously administered entities)
 - C Description of pharmacokinetic behavior including time to maximum concentration (t_{max}), $t_{1/2s}$, clearance, time to steady state, accumulation ratio, changes in PK over time, and important special population differences or interactions for parent, active metabolites, and separate enantiomers
3. **Metabolism and Excretion**
 - C Biotransformation pathways based on in vitro or in vivo findings,

including contribution of specific enzymes, with known or expected effects of inducers or inhibitors of the pathway

- C Metabolites formed, based on in vivo findings with quantitative data, if available
- C Interconversion and interaction of enantiomers or enantiomer specific pharmacokinetics
- C Known or potential alteration in metabolism by other drugs or specific substances (food, tobacco), with details listed in the *Drug Interactions* section
- C Variations in metabolism and effect on pharmacokinetics caused by factors such as age, gender, ethnic factors, polymorphic metabolism, concomitant pathology, e.g., renal or hepatic insufficiency, dietary factors, environmental, and other factors, including pertinent negatives
- C Mode(s) and extent of parent and metabolite(s) excretion from the body, including clearance measures of the excretory routes of elimination as defined by chemical measures or radiolabel (mass balance) studies
- C Mechanisms of the various excretory routes such as passive or active renal excretion, filtration, secretion, active reabsorption, and any other factors that may influence excretion, e.g., pH in renal excretion, azotemia, hepatic failure, enterohepatic circulation, or other drugs competing for the same excretory pathway
- C Variations in excretion and/or clearance other than metabolic-based as considered above caused by factors such as age, concomitant drugs, and concomitant pathology, e.g., renal or hepatic insufficiency
- C The effectiveness of chronic peritoneal dialysis or hemodialysis in clearing the parent and metabolites from the body

D. Other Clinical Pharmacology Information

Information may be presented that is not covered by the three required subsections but is helpful to optimal use and an understanding of the clinical pharmacology of the product. Information within this section should include information such as clinical pharmacology related drug interaction information and clinical pharmacology related specific population information which may not appear in the *Drug Interactions* or the *Specific Populations* sections of the labeling.

1. Special Populations

Clinically relevant changes in PK or PD parameters in special populations or the absence of differences if studied should be reported in this section. When recommendations are necessary, the information should be considered briefly in this section with a detailed presentation placed in the *Warnings/Precautions* and/or *Dosage and Administration* sections of the labeling.

Special populations and conditions that should be considered in this component of the labeling include:

- C Specific Disease Effects on PK and or PD
- C Renal Insufficiency
- C Hepatic Insufficiency
- C Age: elderly
- C Age: pediatric
- C Gender
- C Race and Ethnicity
- C Smoking
- C Alcohol intake
- C Overdose

2. Drug Interactions

Clinically relevant PK or PD drug-drug interactions that affect either the labeled drug or the other drug based on in vitro or in vivo studies should be presented in this section. Clinically relevant PK or PD drug-food interactions that affect the labeled drug should be presented in this section. Important negative results, e.g. differences between members of a drug class or failure of an in vivo study to support a possibility suggested by in vitro studies, should also be presented. When dosage adjustment or monitoring are necessary, these topics should be considered briefly in this section with a detailed presentation placed in the *Warnings/Precautions* and/or *Dosage and Administration* sections of the labeling.

Some specific topics for consideration for this component of the labeling include:

- C Metabolically based PK drug-drug , drug-food (e.g. grapefruit juice), and drug-substance (e.g. tobacco) interactions, e.g., induction or inhibition of enzyme systems
- C Non-metabolically based PK drug-drug and drug-food interactions, e.g., concomitant drug or food affecting GI transit, GI conditions (e.g. pH), binding to form non-absorbable complexes, or affecting renal secretion of a drug

C PD drug-drug interactions, e.g., interaction in receptor binding

3. Antibody Formation

Information regarding antibody formation and any resultant impact on the PK and PD of the product should be presented and discussed in this section

E. Pharmacokinetic and/or PK/PD Graphs

Graphs depicting PK performance and/or PK/PD relationships may be included if considered essential. The addition of variability indicators to these graphs will be helpful in their interpretation

