# Guidance for Industry

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

***DRAFT GUIDANCE***

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For questions regarding this draft document contact (CDER) Paul Hepp at 301-796-1538 or Lei Zhang at 301-796-1635; or (CBER) the Office of Communication, Outreach and Development at 301-827-1800 or 800-835-4709.

**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)**

**February 2009**
**Labeling**

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

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*Office of Communications, Division of Drug Information*
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*10903 New Hampshire Avenue*
*Building 51, Room 2201*
*Silver Spring, MD 20993-0002*
*(Tel) 301-796-3400*
*http://www.fda.gov/cder/guidance/index.htm*

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*Rockville, MD 20852-1448*
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# Guidance for Industry[1]

# Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products— 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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 the requirements of FDA regulations (21 CFR 201.57) and to facilitate communication about this sometimes complicated labeling information. This guidance is also intended to ensure consistency in clinical pharmacology labeling for all prescription drug products approved in CDER and CBER. 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* section of the labeling for human prescription drug or biological products. This guidance does not pertain to 21 CFR 201.57(c)(13)(ii) (*13.2 Clinical pharmacology*), which relates to the conditions for including in the labeling in vitro or animal test information that has not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use.

This guidance provides a general framework and set of recommendations that should be adapted to specific drugs and their conditions of use. 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. Only information that is important for safe and effective use of the drug should be included.

[1] This guidance has been prepared by the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research (CDER) in consultation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

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. CLINICAL PHARMACOLOGY SECTION

As stated in 21 CFR 201.56, the *Clinical Pharmacology* section of labeling is one of the sections that appear in the *Full Prescribing Information*. When clinical pharmacology information has important implications for safe and effective use, it will often appear in other sections of labeling such as *Drug Interactions, Warnings and Precautions*, *Dosage and Administration*, or *Contraindications*, and it could appear in the *Highlights of Prescribing Information*. Where specific clinical pharmacology information appears in multiple sections of labeling, cross-referencing should be used. To the extent possible, repetition of detailed information in multiple sections should be avoided.

Specific content and format requirements for the *Clinical Pharmacology* section of the labeling are described in § 201.57(c)(13)(i), which states the following:

> (13) *12 Clinical pharmacology*. (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. This section must include the following subsections:
>
> (A) *12.1 Mechanism of action. . . .*
>
> (B) *12.2 Pharmacodynamics. . . .*
>
> (C) *12.3 Pharmacokinetics. . . .*

Generally, the *Clinical Pharmacology* section should include information on both positive findings and pertinent negative findings. A lack of specific information should be noted only when the absence of that information is clinically pertinent. The information should be presented in a way that is understandable to practitioners who may not be well-versed in clinical pharmacology. The information presented must not be speculative or promotional in any manner (21 CFR 201.56(a)(2)). When appropriate, additional subheadings within the three subsections should be created to help organize the information. For example, a *Drug Interactions* subheading could be included in the *Pharmacokinetics* subsection where there is a large amount of drug interaction information that should be included in labeling.

Information about the parent drug, active metabolites, and enantiomers that lead to the intended therapeutic effects or unintended effects (e.g., toxicities) should be presented in the *Clinical Pharmacology* section of labeling. Intended or unintended effects due to additives (adjuvants, excipients, or preservatives) present in the product should also be included in this section of the labeling. Generally, for purposes of this guidance, parent drug or metabolites that are thought to contribute 20 percent or more of the overall efficacy or toxicity of a product should be considered of potential interest for discussion. In certain cases, however, multiple substances or

metabolites that contribute to activity to a small degree individually (i.e., less than 20 percent), may also be of interest. In some cases, analytical methodology may not be available to measure the parent drug or all active metabolites for certain products, so reporting their concentrations would not be possible. When this situation exists, it should be addressed in the 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 if both are active and have different types of activity or different pharmacokinetics.

### A. Mechanism of Action (How Therapeutic and Adverse Effects Occur)

This subsection of the labeling should summarize what is known about the established mechanism or mechanisms of action in humans, focusing on the desired and adverse effects of the drug. The mechanism of action should be discussed at various levels, including the cellular, receptor, or membrane level (with a description of selectivity where important), the physiologic system level (target organ), and the whole body level, depending on what is known. Only reasonably well-characterized mechanisms should be described, and care must be taken to avoid speculative and undocumented suggestions of therapeutic advantages (21 CFR 201.56(a)(2)). If the relationship of the drug's mechanism of action to the desired effects is unknown, this also should be stated. Information from animals and in vitro studies can be included where helpful and clearly relevant to the human response. Although not generally needed, a brief description of disease pathophysiology can sometimes facilitate an understanding of the drug's pharmacology and its impact on that process. Speculation on the mechanism of drug action must be avoided (21 CFR 201.56(a)(2)). Any relevant pharmacogenomic factors affecting drug action should be included as well as whether established serologic correlates can be used to infer vaccine-induced protection against an infectious agent.

### B. Pharmacodynamics[2]

For all of the topics discussed under *Pharmacodynamics*, there is particular interest in dose-response (D-R) and in pharmacokinetic/pharmacodynamic (PK/PD) (i.e., concentration-response) analyses. This subsection should include a description of all pharmacologic effects that are reasonably well-established as pertinent to the therapeutic action of the drug or to drug toxicity. The subsection can include effects on mechanistically important biomarkers, for example, biological product-induced antibodies or angiotensin II activity for an antihypertensive that acts via this pathway. For the pharmacodynamic effects described, and in addition to pertinent D-R and PK/PD information, this section should provide information about the time course of action and other information, such as tolerance, withdrawal effects, and differences in PD effects in specific populations. The subsection should also describe pertinent PD negatives (therapeutic and potentially toxic pharmacologic effects that might be expected of a member of a drug class, but that have not been observed). Examples of pertinent PD negatives would include

[2] For additional information on pharmacodynamics (PD), see also the CDER/CBER guidance for industry *Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications.* We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Page (http://www.fda.gov/cder/guidance/index.htm) or the CBER guidance Page (http:www.fda.gov/cber/guidelines/htm).

failure of a calcium channel blocker to increase heart rate or prolong the PR interval, or lack of antipyretic activity for a nonsteroidal anti-inflammatory drug (NSAID). An example of a pertinent negative for a potentially toxic drug effect for almost any drug would be a lack of effect on QTc. Similarly, a biological therapeutic product that does not produce the sort of autoantibodies observed with other mechanistically similar products would also be an example of pertinent PD negative. Important pharmacologic effects other than the main desired effect should be described. This subsection of the labeling should contain a summary of dose-response studies and the related exposure-response relationships for pharmacologic effects pertinent to effectiveness and safety (dose-response information for clinical effectiveness and safety endpoints would be in the *Clinical Studies, Warnings and Precautions, Adverse Reactions,* or other sections). Finally, this subsection should be used only to modify and provide further information pertinent to the demonstrated benefits of the drug; it must not be used to suggest additional claims of effectiveness (21 CFR 201.56(a)(2)).

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

- The principal PD effects of the drug; information regarding undesired PD effects could also appear in other sections of labeling such as the *Warnings and Precautions, Adverse Reactions*, or *Contraindications*. Potentially clinically important effects that have not been observed for a drug or biologic within a particular class (e.g., QT prolongation or induction of autoantibodies) should also be included.

- Receptor selectivity when there are data to suggest that receptor selectivity may be related to toxicity or effectiveness. Information on whether the PD effects are irreversible and information pertaining to resistance, tolerance, and phenotypic variability should be included.

- The magnitude and duration of the principal clinically relevant PD effects and how these effects relate to dose or changes in blood concentration, including any clinically important differences related to regimen, input rate, or titration regimen. Information should be included regarding the time to return to pretreatment PD activity (baseline) after the drug is discontinued, whether effects persist throughout the dosing interval, the time required to reach desired therapeutic effect and whether this time is related to the attainment of steady state blood levels or reflects hysteresis (i.e., a delay between attainment of effective plasma concentration and drug effect).

- If established and clinically useful, the therapeutic window (or range), or threshold concentrations for efficacy or toxicity, and the role of plasma drug concentration or other exposure measures (such as area under the curve (AUC)) in monitoring for favorable or unfavorable effects. This information should be discussed further in the *Dosage and Administration* section of the labeling.

- 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. The dose effect relationship of such phenomena may also be pertinent.

- Any differences in effect related to patient characteristics such as disease severity, hormonal status, concomitant drugs, age, gender, genetic or racial/ethnic factors, diurnal variation, menstrual cycle effects, environmental factors, and other known sources of variability.

- Whether it is useful to modify dose or dose interval by monitoring PD responses, favorable or unfavorable. Information on the magnitude, timing, initiation, and limitations of specific procedures to titrate a drug to individual patient needs should be further discussed in the *Dosage and Administration* section of labeling.

- PD effects of doses that may have been used in the clinical development program but that are greater than those ultimately approved for use, particularly when higher doses were associated with undesirable effects. This information might also appear in the *Clinical Studies*, *Adverse Reactions*, *Dosage and Administration*, and in some cases, the *Warnings and Precautions* sections of the labeling.

- Clinical results of doses that may have been used in the clinical development program but that are lower than those ultimately approved for use, particularly when the lower doses were associated with pharmacologic activity. This information might alternatively or also appear in the *Clinical Studies* section of the labeling.

- Tolerance, rebound, abuse or dependence, and withdrawal effects related to, for example, up- or down-regulation of receptors, if this information has been documented.

- Antibody formation and any resultant impact on the PD of the product. This information can be cross-referenced to other sections of the labeling, such as the *Clinical Studies*, *Dosage and Administration*, *Adverse Reactions*, and/or *Warnings and Precautions* sections.

- 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 and/or concentration versus toxicity relationships with a diagnostic agent should be discussed. This information can be cross-referenced to other sections of the labeling such as the *Clinical Studies*, *Dosage and Administration*, *Adverse Reactions*, and/or *Warnings and Precautions* sections.

- Additional information for photodynamic therapy products, including quality of therapy versus dose and/or concentration, development of antibodies, optimal time from dosage administration to light administration (laser or other source), optimal

wavelength and duration of light administration. Any toxicologic effects or dose and/or concentration versus toxicity relationships with a photodynamic therapy agent should be discussed. This information can be cross-referenced to other sections of the labeling such as the *Clinical Studies*, *Dosage and Administration*, *Adverse Reactions*, and/or *Warnings and Precautions* sections.

### C. Pharmacokinetics

The *Pharmacokinetics* subsection should provide information that is important and useful to prescribers for a drug or biological product that is delivered systemically directly (i.e., intravenously) or absorbed systemically by other routes of administration (e.g., oral, sublingual, inhaled, buccal, transdermal) to an extent that permits measurement of parent drug and/or active metabolites (both toxic and therapeutic metabolites). Information should be included in cases where absorption is unintended, minimal, or not necessary for therapeutic effect, but is nonetheless sufficient for measurement of a parent or active metabolite (e.g., topical, intravesicular, intravaginal, intrauterine). Generally, study details other than identification of the population (e.g., normal, with disease, age, gender), and in some cases subject numbers, need not be provided. The average values and overall variability (percentage coefficient of variation) for critical pharmacokinetic (PK) parameters should be included. In cases where intrasubject variability is known for pharmacokinetic parameters, it may be useful to report this information and contrast it to the overall variability (e.g., large variability between subjects, but little variability within subjects). The range of individual pharmacokinetic parameter values may be helpful, for example, principally for clearance and half-life, particularly for drugs with narrow therapeutic ratios. If important PK information is not available, this should be noted. Generally, the focus should be on factors that explain and lead to altered critical measures, such as those that change maximum concentration ($C_{max}$), minimum concentration ($C_{min}$), time to maximum concentration ($T_{max}$), AUC, half-life ($t_{1/2}$), clearance (CL), and volumes of distribution ($V_d$). In most of these cases, the direction and magnitude of the changes (e.g., changing of AUC or $C_{max}$) are of interest, not the actual values (of AUC or $C_{max}$). In contrast, actual values of $T_{max}$ or half-life are important. In some cases when the formulations are significantly different, information relative to the bioequivalence between the formulations of the marketed strengths and between clinically studied formulations and marketed formulations may be important. Subjective wording (e.g., fast, rapidly, or completely absorbed) must be avoided (21 CFR 201.56(a)(2)).

The *Pharmacokinetics* subsection should begin with a summary of the information that can influence treatment by the prescriber, and thus would be most useful in patient treatment. This information would usually include the extent and variability of bioavailability, the pertinent half-life, major routes of elimination, metabolic pathways, major interactions, population differences (such as polymorphic metabolism), and any significant nonlinearity or time effects (e.g., from induction or inhibition of the drug's metabolism). The summary should be followed by more detailed, clinically pertinent information as follows:

1. *Absorption and Distribution (or Distribution for Intravenously Administered Entities)*

- The extent (i.e., absolute and/or relative bioavailability) and rate (e.g., $T_{max}$ and $C_{max}$) of absorption. The presence, location (liver and/or intestine), and extent of first pass effect, or other mechanisms affecting bioavailability (e.g., chemical degradation), should be included.

- Whether absorption kinetics are linear or nonlinear over the range of clinical doses and concentrations.

- Time of maximum concentration ($T_{max}$).

- Differential absorption of isomers in a racemate, if both enantiomers are active.

- Estimated volume of distribution (e.g., volume of distribution steady state ($V_{dss}$), volume of distribution/bioavailability (VD/F)) and how this relates to known values of physiological volumes.

- Extent and sources of variability of absorption between and within individuals, to the extent this is understood. This includes differences in absorption seen in specific populations, differences in genetics, and factors influencing drug uptake (e.g., transporters or CYP (cytochrome P450 oxidase) enzymes). Clinically important information related to the differences should also appear in the *Use in Specific Populations* section.

- Known effects or lack of effects of other drug or biological products, herbal products, food (including grapefruit juice), antacids, or chelating cations on absorption of orally administered entities should be mentioned here, and if important, described in more detail in the *Drug Interactions* section.

- Rate and extent of uptake by or transport to particular organs and observed multicompartment behavior, to the extent known, but only if clinically relevant.

- Plasma protein, erythrocyte, soluble factors, antibodies, and cellular constituents binding.

- Passage across the blood brain barrier (placental transfer and secretion into breast milk) information should normally be placed in the *Use in Special Populations, Pregnancy and Nursing Mothers* section of the labeling.

*2. Metabolism and Excretion*

- Description of pharmacokinetic behavior, linear or nonlinear pharmacokinetics, and clinically relevant $t_{1/2}$ values. In some cases, it may be useful to describe the absorption, alpha (distribution) and beta (terminal) half lives, but the half-life value should usually be the half-life based on time to reach steady state (i.e., the effective half-life). If a long terminal half-life is important from a toxicity standpoint or from

an effectiveness standpoint (persistent effect because of peripheral binding), this should be stated and elaborated upon in other appropriate sections of the labeling (e.g., *Warnings and Precautions*). The *Pharmacokinetics* subsection should discuss the range of linearity or nonlinearity in relation to clinically relevant dosage regimens and drug concentrations. It should also include clearance values and percentage of total clearance that is renal and nonrenal, time to steady state, accumulation ratio following multiple dosing, any changes in PK over time, and a brief discussion of important specific population differences or interactions for parent, active metabolites, and separate active enantiomers. Details of specific population differences and interactions should be placed in the *Use in Specific Populations* and *Drug Interactions* sections.

- Biotransformation pathways based on in vitro and in vivo findings (including contribution of specific enzymes) and known or expected effects of inducers or inhibitors of the pathway. Any pathways or interactions that have been ruled out by in vitro data should be identified.

- Major active metabolites formed, based on in vivo findings with quantitative data, if available, for active metabolites.

- Brief description of known or potential alteration in metabolism by other drugs or specific substances (food, juices, tobacco, herbal products), with important interactions listed in the *Drug Interactions* section.

- Effects of the drug on metabolizing enzymes and transporters. Clinically important inhibition or induction information should also appear in the *Drug Interactions* section.

- Variations in metabolism and effect on pharmacokinetics caused by factors such as age, gender, ethnicity, polymorphic metabolism (i.e., genetic-based differences in activity (e.g., with the cytochrome P450 2D6 genetic variants)), concomitant pathology (e.g., renal or hepatic insufficiency), diet, environment, and other factors, including pertinent negatives (i.e., factors not causing variations in metabolism and effect on pharmacokinetics). Clinically important information related to such differences should also appear in the *Use in Specific Populations* section.

- Modes and extent of parent and metabolites excretion from the body, as defined by chemical measures or radiolabel (mass balance) studies.

- 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).

- Effects on excretion and/or clearance (other than the metabolic-based differences

considered previously) caused by factors such as age, concomitant drugs, and concomitant pathology (e.g., renal or hepatic insufficiency or impairment). Information related to any of these effects that are clinically important should also appear in the *Use in Specific Populations* section.

- The effectiveness of chronic peritoneal dialysis and hemodialysis in clearing the parent and metabolites from the body.

- Information regarding antibody formation and any resultant impact on the PK of the product. This information can be cross-referenced to other sections of labeling, such as the *Clinical Studies*, *Dosage and Administration*, *Adverse Reactions*, and/or *Warnings and Precautions* sections.

### D. Microbiology

For antimicrobial products, certain clinical pharmacology information that would ordinarily be included in the *Mechanism of Action* or *Pharmacodynamics* subsection should be consolidated under a subsection created specifically for microbiology information (i.e., *12.4 Microbiology*). This microbiology subsection should contain all information relevant to the microbiology characteristics of the drug (e.g., the mechanism of action, mechanism of resistance) and the pharmacodynamics as it relates to the effect of the drug on the microbe. For antimicrobial products, the microbiology information should appear as follows:

***12.1 Mechanism of Action*:** The following statement should appear in subsection *12.1 Mechanism of Action*: *"X* is an anti- (e.g., bacterial, viral, as appropriate*)* drug (see *12.4 Microbiology).*" Subsection *12.4 Microbiology* should include a description of the mechanism of action of the drug on the microbe. This information can be presented under subheadings (e.g., *Mechanism of Action*) within the *Microbiology* subsection to enhance labeling organization and readability.

***12.2 Pharmacodynamics*:** Human pharmacodynamic data, including information on concentration-response and toxicity, should remain in subsection *12.2 Pharmacodynamics*. If applicable, pharmacologic effects that are pertinent to the antimicrobial action of the drug, including important blood levels and impact on growth and resistance, should be contained in subsection *12.4 Microbiology*. This information can be presented under a subheading (e.g., *Pharmacodynamics*) within the *Microbiology* subsection.

***12.3 Pharmacokinetics*:** Pharmacokinetic information should remain in subsection 12.3.

All other microbiology information should be included in subsection *12.4 Microbiology*. Additional subheadings within the *Microbiology* subsection should be created as appropriate. For additional information on this topic, see the CDER guidance Page (http://www.fda.gov/cder/guidance/index.htm).

### E. Pharmacogenomics

When there is genetic information that would be useful to prescribers and that is more extensive than appropriate for the *Pharmacokinetics* or *Pharmacodynamics* subsection, a *Pharmacogenomics* subsection should be created to include the clinically relevant information on the effect of polymorphic variation in drug metabolizing enzymes, transporters, receptors, and other proteins on pharmacokinetics, pharmacodynamics, and/or clinical responses (both safety and efficacy). Pharmacogenomic information can include, but is not limited to, the following:

- Description of polymorphic enzymes (for example, genetic-based differences in enzyme activity such as reduced cytochrome P450 enzyme activity due to polymorphisms in a CYP gene).

- Subpopulation-based information on the prevalence or frequencies of alleles, genotypes, haplotypes, or other genomic markers.

- Positive and negative predictive values associated with the use of the genomic marker for safety and/or efficacy purposes.

- Clearance of the drug in relationship to the genotype.

- Pharmacogenomic studies performed that provide evidence of genetically based differences in drug metabolism.

- Changes in dose based on genotype.

- Other relevant information pertaining to genetic and genomic biomarkers associated with the safety and/or efficacy of the therapy.

When pharmacogenomic information has important implications for safe and effective use and the consequences of the genetic differences result in recommendations for restricted use, dosage adjustments, contraindications, or warnings, this information should be included in other sections of labeling as appropriate, such as the *Indications and Usage*, *Dosage and Administration*, *Boxed Warning*, *Contraindications*, *Warnings and Precautions*, and/or *Drug Interactions* sections and can be cross-referenced in the appropriate sections.

## F. Use of Pharmacokinetic, Dose-Response, and/or PK/PD Graphs and Tables

Graphs and/or tables depicting PK attributes, exposure- or dose-response relationships, and/or PK/PD relationships can be helpful in simplifying and/or clarifying the labeling and their use is encouraged. When graphs or tables are used, variability measures should be included.