Guidance for Industry and Review Staff

Target Product Profile — A Strategic Development Process Tool

DRAFT GUIDANCE

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For questions regarding this draft document contact Jeanne M. Delasko at 301-796-0900.

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

March 2007
Procedural

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TABLE OF CONTENTS

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I. INTRODUCTION

The purpose of this guidance is to provide sponsors and the review staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) with information regarding target product profiles (TPPs). A *TPP* is a format for a summary of a drug development program[2] described in terms of labeling concepts. A TPP can be prepared by a sponsor and then shared with the appropriate FDA review staff to facilitate communication regarding a particular drug development program. Submission of a TPP is voluntary.

This guidance describes the purpose of a TPP, its advantages, and its optimal use. It also provides guidance on how to complete a TPP and relates case studies that demonstrate a TPP's usefulness.

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. Although guidance documents do not legally bind FDA, review staff may depart from guidance documents only with appropriate justification and supervisory concurrence.

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drug* include both human drugs and therapeutic biological products unless otherwise noted.

II. BACKGROUND

In 1997, a Clinical Development Working Group composed of representatives from the FDA and pharmaceutical sponsors began discussions on ways to improve sponsor and FDA interactions in the drug development process. The working group recommended use of a template that provides a summary of drug labeling concepts to focus discussions and aid in the understanding between sponsors and the FDA. The name given to this template was the target product profile.

Experience with TPP-focused meetings with sponsors at the FDA has indicated that such documents can be useful (see Appendix A). An efficient dialogue between a sponsor and the FDA during the drug development process can minimize the risk of late-stage drug development failures, increase the probability that optimal safety and efficacy data are available in a timely manner, improve labeling content, and possibly decrease the total time involved with drug development.

III. DESCRIPTION AND BENEFITS OF A TPP

A. Purpose of a TPP

The purpose of a TPP is to provide a format for discussions between a sponsor and the FDA that can be used throughout the drug development process, from pre-investigational new drug application (pre-IND) or investigational new drug application (IND) phases of drug development through postmarketing programs to pursue new indications or other substantial changes in labeling. The TPP embodies the notion of *beginning with the goal in mind*. That is, the sponsor specifies the labeling concepts that are the goals of the drug development program, documents the specific studies intended to support the labeling concepts, and then uses the TPP to assist in a constructive dialogue with the FDA. The ideal version of what the sponsor would like to *claim in labeling* guides the design, conduct, and analysis of clinical trials to maximize the efficiency of the development program. Ideally, the final version of the TPP will be similar to the annotated draft labeling submitted with a new drug application (NDA) or biologics license application (BLA).

B. Attributes of a TPP

Ideally, the TPP provides a statement of the *overall intent* of the drug development program, and gives information about the drug *at a particular time* in development. Usually, the TPP is organized according to the key sections in the drug labeling and links drug development activities to specific concepts intended for inclusion in the drug labeling. The sponsor can draft and update pertinent sections of the template that are intended to support the specific statements in labeling. The sponsor can also use these updated versions of the TPP in preparation for discussions with FDA review staff to identify the most important development goals for the drug. The TPP is a *dynamic* summary that changes as knowledge of the drug increases. For optimal use, we recommend that the TPP be updated regularly to reflect new information about the drug and changes in the clinical development program.

Generally, the final TPP is shorter than the ultimate annotated draft labeling since it captures only a summary of the drug development activities and concepts. Early TPPs can be brief depending on the status of the sponsor's development process.

C. Advantages of a TPP

A well-organized TPP can save meeting time for discussion of issues by eliminating the need for a sponsor's introduction to the history of the drug development program. Sponsors can also use a TPP to streamline their interactions with FDA review staff by distinguishing TPP entries and sections that have been previously discussed from entries that are the current or future focus of a discussion. This process can eliminate the need to revisit the established entries, unless the development goals change or new scientific issues emerge. The use of a TPP is especially important at pre-new drug application (pre-NDA) and pre-biologics license application (pre-BLA) meetings, when it can help the review staff focus on a sponsor's goals and make sure previously discussed items have not changed when the sponsor submits an NDA or BLA. In a Briefing Document, a sponsor can use a TPP to quickly update new FDA or sponsor personnel who join the program.

A TPP enables a sponsor to pursue the desired outcome (i.e., approval and optimal labeling of a safe and effective drug) in the most efficient manner with respect to FDA interaction because all such interaction is focused on the explicitly stated goals of the development program.

The TPP is part of the proprietary IND file.

D. What a TPP is Not

Submission of a TPP is voluntary and is not required for granting an end-of-phase 2 (EOP2) or other meeting with sponsors.

A TPP does not represent an implicit or explicit obligation on the sponsor's part to pursue all stated goals. Providing a TPP summary does not constrain the sponsor to submit draft labeling in an NDA or BLA that is identical to the TPP.

The TPP does not represent a commitment or an obligation on the FDA's part to consider the resultant evidence as adequate to attain approval. FDA concordance with part or all of the TPP does not represent a commitment to approve the identical language in the final label.

E. Using a TPP as Part of a Briefing Document

Regulatory procedures and Agency recommendations introduced in recent years provide sponsors with standardized mechanisms to prepare sound drug development proposals, submit them to the FDA for review, and engage in a structured dialogue to reach an understanding of the FDA's thinking on various aspects of a drug development program. Specifically, regulations related to EOP2 meetings (21 CFR 312.47(b)), the guidance for industry *Formal Meetings With*

Sponsors and Applicants for PDUFA Products,[3] and the guidance for industry *Special Protocol Assessment* all contribute to fostering an environment that encourages proactive dialogue between sponsors and FDA review staff on drug development programs. FDA regulations and guidances such as those relating to drugs and biologics with a fast track designation,[4] drugs for severely debilitating or life-threatening diseases (21 CFR 312.82), and drugs and biologics pursuing accelerated approval (21 CFR part 314, subpart H) further recognize and reinforce structured, proactive dialogue. The TPP summary goes a step further in the recognition of the value of proactive dialogue. The TPP enhances a sponsor's effort in preparing a Briefing Document that will provide the basis for a constructive milestone meeting with review staff.

With respect to meetings between a sponsor and the review staff, the guidance for industry *Formal Meetings With Sponsors and Applicants for PDUFA Products* states the following key points:

- The sponsor should prepare and submit a *Briefing Document* (also referred to as an *information package*), including specific information on the sponsor's clinical development plan and specific questions from the sponsor posed to the review staff for feedback.

- The review staff will review and discuss the background information, as well as the sponsor's questions, in advance of the meeting.

- The meeting's dialogue will focus on the questions posed to the review staff, thereby providing constructive feedback.

A TPP can provide the structure to such a Briefing Document and help ensure the sponsor presents all relevant medical and scientific information in the context of the overall drug development goals.

The TPP itself can assist in the achievement and maintenance of constructive feedback and understanding between the FDA and sponsor, which is critical for successful drug development.

The FDA official meeting minutes should reflect when the sponsor submitted a TPP and the review staff and the sponsor discussed its contents. For the meetings, the TPP should be attached as an appendix to the official meeting minutes.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[4] See the guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review* (http://www.fda.gov/cder/guidance/index.htm).

IV. COMPLETING A TPP

A. Labeling Concepts

The TPP can include information from each discipline. Usually, the TPP briefly summarizes the specific studies (both planned and completed) that will supply the evidence for each conclusion that is a labeling concept. The TPP should be organized according to key sections in the drug's labeling. Typical key sections from which a sponsor can choose, depending on the nature of the meeting, include:

- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations
- Drug Abuse and Dependence
- Overdosage
- Description
- Clinical Pharmacology
- Nonclinical Toxicology
- Clinical Studies
- References
- How Supplied/Storage and Handling
- Patient Counseling Information

The Target Product Profile Template, shown in Appendix C, details the information (in *italics*) that we suggest sponsors include in each section.[5] In general, we recommend sponsors use the following steps to complete a TPP:

1. Sponsors should complete the appropriate sections (see Appendix B for an example of a completed section of a TPP) depending on the drug, stage of development, and the questions and issues they wish to discuss with the review staff. Sponsors can delete nonrelevant sections or add additional subsections. Each section contains the following areas:

    a. **Target.** This area should include labeling language sponsors hope to achieve based on the outcome of the indicated studies.

    b. **Annotations.** This area should include summary information regarding completed or planned studies to support the target. Sponsors should also include the protocol

[5] A clean copy of the Target Product Profile Template can be found at http://www.fda.gov/cder/regulatory/TPP/default.htm.

number, serial number, and submission date that will help guide discussion about the overall development program, the number of studies, and how sponsors will conduct the studies. Sponsors can include additional information about the studies, but they should avoid repeating detail contained elsewhere in the Briefing Document.

c. **Comments.** This area should include additional information that can aid communication and understanding (e.g., date of discussions with FDA review staff, progress toward target, key points during discussions, key issues for discussions, questions). Sponsors are encouraged to use this area to provide clarity.

To avoid revisiting portions of the TPP as the document evolves, sponsors should indicate items they have previously discussed with the review staff by a notation (e.g., *previously discussed on*) and a reference to the interaction with the review staff (e.g., *previously discussed on 05MAY2004, during EOP2 meeting*). Sponsors can include this notation in the Target, Annotations, or Comments area of the TPP, as applicable.

2. Sponsors should update the milestone box as needed. (The milestone box appears at the top of the TPP, regardless of the sections of the template completed.) Sponsors should indicate a version date each time they submit an updated template.

3. Sponsors should update the template at appropriate milestones. Sponsors can highlight new information. After implementation of the TPP, sponsors can continue to use the TPP to help with final labeling discussions related to both initial approvals and labeling supplements.

B. Proposed Promotional Claims

A TPP can assist in a constructive dialogue with FDA review staff regarding proposed promotional claims and/or presentations for use in product promotional materials and the documentation of specific studies intended to support these claims. The TPP can link drug development activities to specific concepts intended for proposed promotional claims.

In general, we recommend sponsors use the following steps to complete the Target, Annotations, and Comments areas of a TPP for proposed promotional claims:

1. **Target.** This area should prominently state **Proposed Promotional Claim(s)** and should include the proposed claims and/or presentations for use in the product's promotional materials.

2. **Annotations.** This area should include summary information regarding completed or planned studies to support the proposed promotional claims and/or presentations. Sponsors should include the protocol number, serial number, and submission date that will help guide discussion about the overall development program, the number of studies, and how sponsors will conduct the studies.

3. **Comments.** This area should include additional information about the studies that can aid in communication and understanding.

V. LINKAGES WITH OTHER INITIATIVES

The TPP initiative complements other initiatives in which the FDA and pharmaceutical sponsors are participating. The FDA is sponsoring the Critical Path Initiative following the March 16, 2004, release of the report entitled "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products."[6] In this report, the FDA suggests that there is a substantial opportunity to increase the pace of discovery and development of new medical products. The report stresses the need for new tools from discovery or the pre-IND phase through approval of the medical product. Since a TPP can facilitate constructive discussion and understanding between a sponsor and the FDA, the TPP represents a potential *critical path* tool.

VI. CONCLUSION

Both the FDA and sponsors have seen the advantages of using a TPP at meetings early in the drug development process. Use of a TPP can facilitate the efficiency of sponsor-FDA interactions and communications. A TPP helps focus a sponsor's drug development team and FDA review staff on the drug development goals in terms of drug labeling. If used properly, a TPP can help address issues early on in the drug development process thereby preventing late-stage drug development failures and decreasing the total time involved with drug development.

[6] http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

APPENDIX A: CASE STUDIES

A. Advantages of Using a TPP During Development of an Antibacterial Drug

From 1999-2001, the Division of Anti-Infective Drug Products (DAIDP) piloted the use of a TPP with a sponsor during phase 2 and phase 3 in the development program of an antibacterial drug. The drug product was a new molecular entity for which the sponsor was seeking multiple indications and for which the sponsor wished to develop three formulations simultaneously. This goal created additional challenges in the drug development process, but was considered by both parties to be a good test case for using a TPP. The DAIDP suggested holding a face-to-face meeting with the sponsor before the EOP2 meeting solely to discuss the TPP.

The TPP facilitated FDA-sponsor discussions regarding the development of the antimicrobial product and the appropriateness of targeted labeling statements resulting from the proposed development program. The TPP meeting helped to clarify for the sponsor the data currently thought to be supportive of its proposed indications. The proposed statements within the TPP were used to identify and discuss critical elements of the development program. The TPP meeting with the DAIDP was helpful in light of the evolving scientific and regulatory issues. These discussions gave the sponsor the opportunity to clearly delineate desired labeling concepts and ensured the FDA was satisfied that the proposed clinical development program could support labeling concepts that were proposed in the TPP.

Throughout product development, the TPP was updated as new information became available, with the sponsor seeking additional guidance from the DAIDP as the development plan progressed. Meeting minutes and advisory comments from the FDA referenced the current version of the TPP, promoting efficiency in written communication as well as in the meeting process. Throughout the phase 2 and phase 3 development processes, the TPP served as a valuable *anchor document* that provided historical context and enhanced the clarity of communication and understanding between the sponsor and the FDA.

Ultimately, the applications received priority review designation, and the sponsor and FDA review staff presented the data from the development program at an advisory committee meeting in the fifth month of the 6-month review cycle. Even though there were continued challenges in labeling negotiations, both the review staff and the sponsor agreed that the use of a TPP was integral to the successful first-cycle review and the approval of three new drug products for serious and life-threatening diseases.

The use of the TPP continued post-approval to guide discussions of new labeling claims for supplemental indications.

B. Advantages of Using a TPP During Development of a New Therapy for Osteoporosis

A sponsor's development team began preparing a Briefing Document for the EOP2 meeting with the Division of Metabolism and Endocrinology Products (DMEP) to discuss phase 3 registration

trials and how the sponsor might use the trial results to support important descriptions in labeling for the prescriber. The sponsor's development team considered including draft label language in the document to facilitate discussion with the review staff about the studies needed to achieve the sponsor's labeling concepts should the trial results be adequate to support approval. Since this was the development team's first experience with this meeting strategy, it looked for the best approach to this issue.

The development team became aware of the TPP template and proceeded to create a full TPP. However, the sponsor decided that including so much detail in the absence of final data might distract the review staff from the main goals of the meeting. Therefore, the sponsor submitted as an appendix to the Briefing Document only those label elements that related to the primary and secondary endpoints of the phase 3 trials under discussion. Using this abbreviated version of the TPP would allow all meeting attendees to focus on the sections of the label that required the greatest discussions. Before the meeting began, the sponsor modified the agenda based on the review staff's evaluation of the TPP by adding topics suggested by review staff comments and deleting sections where review staff agreed the planned studies were reasonable for the development of substantiating data for the labeling targets.

After the meeting, both FDA representatives and the development team attributed the efficiency of the meeting to the structure that the TPP provided to the discussion. Not only did the TPP highlight important discussion topics, but review staff also were able to easily identify the sponsor's goals for its development program. Both the sponsor and review staff agreed that the TPP enabled the review staff to provide focused feedback to the sponsor.

C. Disadvantages of Not Using a TPP for an EOP2 Meeting

In preparation for an EOP2 meeting with a sponsor, the review division consulted the Study Endpoints and Label Development Team, in the Office of New Drugs Immediate Office, who reviewed many volumes of briefing materials documenting the generation and validation of five new patient-reported measures. The drug under development represented a new class of treatment with no established diagnostic or disease severity assessments in standard medical practice. Therefore, it was critical to the sponsor to reach an agreement with the review staff about an adequate development plan to support product approval.

Without a TPP, the review staff could not identify the specific goal of the endpoint measurement in terms of the concept measured. Without a clear statement about the desired labeling claims, it is not possible to determine whether an endpoint is adequate to meet that goal. The FDA was in the position of attempting to discern the most likely scenarios and develop comments accordingly, rather than to develop comments according to clear goals provided by the sponsor.

During the meeting, the sponsor's representatives were able to state their measurement goals when asked about these issues. The sponsor did have a clear plan for incorporating the measures into the drug development program. If the review staff had been informed of these goals in advance, the sponsor could have had a more valuable discussion. Reviewer time and resources also would have been saved.

D. Disadvantages of Not Using a TPP Early in Development

A sponsor developed a new molecular entity whose therapeutic target was similar to several approved agents in a drug class. The sponsor noted in correspondence and in meetings with the review division that the product achieved its therapeutic effect via a novel mechanism of action on the target. The novel mechanism of action was used as a descriptor and the sponsor did not discuss its use as an endpoint for a clinical trial, as a surrogate marker of safety or efficacy, or as the basis for a statement of treatment benefit.

However, when the sponsor submitted an NDA, the sponsor prominently mentioned the novel mechanism of action in the drug label implying treatment benefit based upon this mechanism. The preclinical studies submitted as documentation did not provide adequate evidence to support this statement, and the data could not rule out the conventional mechanism of action shared by other drugs in the class. In addition, there were no clinical data available to link such a finding to clinical benefit. The review staff held several teleconferences with the sponsor to discuss this concern.

A TPP early in development would have given the review division an awareness of the intended claim. Review staff could have worked with the sponsor to agree upon the type of data and trial design needed to support the statement, as well as integrate the data collection into the existing development program. Lack of communication about the intended claim to the review division prevented review staff from providing prospective comments that might have aided the sponsor in collecting the appropriate data to support its labeling concepts. Using a TPP would have obviated the need for additional correspondence and meetings during the NDA review cycle and would have facilitated labeling negotiations.

398 **APPENDIX B:**
399 **SAMPLE SECTION OF A TPP**
400

401 # Target Product Profile: *Drug Name*
402

Milestone (meeting or submission)	Date	*TPP Submitted? Y/N	TPP Version Date	TPP Discussed? Y/N
Pre-IND	02FEB2005	N		N
IND Submission	17JAN2006	Y		Y
EOP1	09NOV2006	Y		Y
EOP2A	N/A			
EOP2/Pre-Phase 3	12DEC2007	Y		Y
Pre-NDA/BLA				
Other (specify)				

403 * The TPP can be submitted to the FDA as part of a Briefing Document or as a stand-alone document.
404

405 ## 1 Indications and Usage
406

Target	Annotations
Postmenopausal Osteoporosis *Drug name* is indicated for the treatment and prevention of osteoporosis in postmenopausal women. **Treatment of Osteoporosis:** In postmenopausal women with osteoporosis, *drug name* reduces the incidence of vertebral fractures and increases bone mineral density (BMD). **Prevention of Osteoporosis:** *Drug name* may be used in postmenopausal women at risk of developing osteoporosis and for whom the desired clinical outcome is to increase or maintain BMD and to reduce the risk of fractures.	Protocol-XXX-001: completed dose range finding study to support phase 3 registration trials Protocol-XXX-002 planned study: protocol not yet submitted Protocol-XXX-003: protocol to be submitted FEB 2008

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408

Comments:

The proposed biomarkers included in Protocol-XXX-02 and Protocol-XXX-03 are acceptable to the DMEP. Protocol XXX-003 will be submitted for special protocol assessment.

The sponsor intends to submit an NDA supported by a clinical pharmacology package (Section 3 and Appendix D of the Briefing Document) and data from the proposed 2-year osteoporosis prevention trial and the 3-year osteoporosis treatment trial (Section 2; Appendix A). Does the FDA agree that the proposed clinical pharmacology package and phase 3 registration trials are sufficient for registration of *drug name* for the proposed osteoporosis indications in postmenopausal women?

At the pre-IND meeting, the FDA stated that 3 years of fracture data were required to obtain an osteoporosis indication. Would the FDA consider an NDA submission if the analyses of the osteoporosis treatment trial data demonstrated robust vertebral fracture risk reduction at a 2-year interim analysis?

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411 **APPENDIX C:**
412 **TARGET PRODUCT PROFILE TEMPLATE**
413

414 # Target Product Profile: *Drug Name*
415

Milestone (meeting or submission)	Date	*TPP Submitted? Y/N	TPP Version Date	TPP Discussed? Y/N
Pre-IND				
IND Submission				
EOP1				
EOP2A				
EOP2/Pre-Phase 3				
Pre-NDA/BLA				
Other (specify)				

416 * The TPP can be submitted to the FDA as part of a Briefing Document or as a stand-alone document.
417
418

419 ## 1 Indications and Usage
420

Target	Annotations
• *A statement that the drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, OR* • *A statement that the drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, OR* • *A statement that the drug is indicated for the relief of symptoms associated with a disease or syndrome, OR* • *A statement that the drug is indicated for a particular indication only in conjunction with a primary mode of therapy*	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date* *When listing studies, consider:* • *The intent to develop evidence to support safety and efficacy in selected subgroups (i.e., limitations of use)* • *Tests needed for selection or monitoring of patients (i.e., susceptibility tests)* • *Whether safety considerations require the drug to be reserved for certain situations (i.e., in refractory patients)* • *Whether the drug is to be used on a chronic basis* • *What evidence will be developed to support comparator statements regarding safety or effectiveness*

421

Comments:

422
423

2 Dosage and Administration

Target	Annotations
For each indication, state the following: • *Route of administration* • *Recommended usual dose* • *Dose range shown to be safe and effective* • *Exposure (dose- or blood level-response relationship, if any)* • *Dosage intervals or titration schedule* • *Usual duration of treatment course when treatment is not chronic* • *Dosage adjustments (e.g., in specific genotypes, pediatric patients, geriatric patients, or patients with renal or hepatic disease)* • *Tests for guiding dosing (e.g., target plasma drug levels, therapeutic range, response biomarkers)*	*Summary information regarding completed or planned studies to support the safety and effectiveness of the proposed dosage and route of administration:* • *Protocol #, Serial #, Submission date*

Comments:

3 Dosage Forms and Strengths

Target	Annotations
Include information on the available dosage forms, including strength or potency of dosage form in metric system and a description of identifying characteristics of dosage forms	*Summary information regarding completed or planned studies to support the dosage forms and strengths:* • *Protocol #, Serial #, Submission date*

Comments:

4 Contraindications

Target	Annotations
List situations in which the drug might be contraindicated, including: • *Increased risk of harm because of age, sex, concomitant therapy, disease state* • *Adverse reactions which would limit use* • *Known, not theoretical, hazards*	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date* *Or, literature references describing contraindication for drug class.*

Comments:

5 Warnings and Precautions

Target	Annotations
Include a description of clinically significant adverse reactions and potential safety hazards and limitations of use because of safety considerations, as reasonable evidence of these issues is established or suspected during the drug development program. A causal relationship need not be demonstrated. *Include information regarding any special care to be exercised for safe use, including precautions that are not required under any other section of the label.* *Identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions.*	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date* *Or, literature references describing significant adverse reactions shared by the drug class of the new drug.*

Comments:

6 Adverse Reactions

Target	Annotations
Describe overall adverse reaction profile of the drug based on entire safety database. List adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. Within a listing, adverse reactions should be categorized by body system, severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions should be listed in decreasing order of frequency. *Include the studies in the development program that will address adverse reactions associated with a particular drug class.*	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date*

Comments:

7 Drug Interactions

Target	Annotations
Describe clinically significant interactions, either observed or predicted (i.e., other prescription drugs or over-the-counter drugs, class of drugs, or foods such as grapefruit juice or dietary supplements); practical advice on how to prevent drug-drug interactions; (description of results from studies conducted or observations from the integrated safety summary); drug-laboratory test interactions (known interference of drug with lab test outcome).	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date*

Comments:

8 Use in Specific Populations

Target	Annotations
Consider the following: • *Limitations, need for monitoring, specific hazards, differences in response, or other information pertinent to the population.*	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date* *If there are no plans to study the drug in a specific population, include rationale.*

Comments:

8.1 Pregnancy *(This subsection can be omitted if the drug is not absorbed systemically)**:***

- *Teratogenic effects: Pregnancy Categories: A, B, C, D, X*
- *Nonteratogenic effects: Other effects on reproduction, the fetus, or newborn.*

8.2 Labor and Delivery: *Use during labor or delivery, effects on mother, fetus, duration of labor, delivery, and effects on later growth of newborn.*

8.3 Nursing Mothers: *If the drug is absorbed systemically, information about excretion of drug in human milk and effects on the nursing infant. Describe pertinent adverse events in animal offspring or tumorigenicity potential if it is detected or suspected.*

8.4 Pediatric Use: *Statements relevant to the use of the drug product in the pediatric population (birth to 16 years of age). Cite any limitations, need for monitoring, specific hazards, differences in response, or other information pertinent to the pediatric population.*

8.5 Geriatric Use: *Statements relevant to the use of the drug product in the geriatric population (age 65 and older). Cite any limitations, need for monitoring, specific hazards, differences in response, or other information pertinent to the referenced population.*

8.6 Additional Subsections: *Use of drug in other specified populations (e.g., those with renal or hepatic impairment).*

9 Drug Abuse and Dependence

Target	Annotations
Include the following subsections, as appropriate for the drug:	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date*

Comments:

9.1 Controlled Substance: *Anticipated DEA schedule.*

9.2 Abuse: *Identify types of abuse and adverse reactions pertinent to them. Identify particularly susceptible patient populations.*

9.3 Dependence**:** *Discuss potential for dependence and describe the characteristic effects resulting from psychological or physical dependence.*

10 Overdosage

Target	Annotations
Provide specific information about: • *Signs, symptoms, and lab findings associated with an overdosage of the drug* • *Complications that can occur with overdose of the drug (e.g., organ toxicity)* • *Concentrations of the drug in biofluids associated with toxicity or death* • *The amount of the drug in a single overdose that is ordinarily associated with symptoms, and the amount of the drug in a single overdose that is likely to be life-threatening* • *Whether the drug is dialyzable* • *Recommended general treatment procedures*	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date* *Update with human data, if available.*

Comments:

11 Description

Target	Annotations
Include the proprietary name and established name, dosage form and route of administration, qualitative and quantitative ingredients, pharmacologic or therapeutic class, and any other important physical and chemical characteristics.	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date*

Comments:

12 Clinical Pharmacology

Target	Annotations
Include a concise factual summary of the clinical pharmacology and actions of the drug in humans. Data that describe the drug's pharmacologic activity can be included in this section, including biochemical or physiological mechanism of action, pharmacokinetic information, degree of absorption, pathway for biotransformation, percent dose unchanged, metabolites, rate of half-lives including elimination concentration in body fluids at therapeutic and toxic levels, degree of binding to plasma, degree of uptake by a particular organ or fetus, and passage across the blood-brain barrier. Include the following subsections:	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date* *If applicable, a subsection (e.g., 12.4 Microbiology) can be created under this section heading and all of the microbiology information for antimicrobial products consolidated into that subsection.*

Comments:

12.1 Mechanism of Action: *Summarize* ***established*** *mechanisms of action in humans at various levels (e.g., receptor membrane, tissue, organ, whole body). Do not include theorized mechanisms of action.*

12.2 Pharmacodynamics: *Include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical*

effect or those related to adverse effects or toxicity. Include data on exposure-response relationship and time course of pharmacodynamic response.

12.3 Pharmacokinetics: *Describe clinically significant pharmacokinetics of a drug or active metabolites (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Include results of pharmacokinetic studies that establish the absence of an effect, including pertinent human studies and in vitro data.*

13 Nonclinical Toxicology

Target	Annotations
Include the following subsections, as appropriate:	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date*

Comments:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:

- *Results of long-term carcinogenicity studies — species identified*
- *Mutagenesis results*
- *Reproduction study results*

13.2 Animal Toxicology and/or Pharmacology: *Ordinarily, significant animal data necessary for safe and effective use of the drug in humans should be included in other sections of the labeling, as appropriate. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this subsection can be used.*

14 Clinical Studies

Target	Annotations
Provide a description of studies that support statements about the efficacy or safety benefits. Consider including a description of supporting tables and graphs.	*Summary information about completed or planned studies regarding the intent to develop evidence to support benefits of treatment (i.e., safety or efficacy benefits of primary or secondary endpoints in the selected population):* • *Protocol #, Serial #, Submission date* • *Measurement instruments (e.g., patient-reported outcomes instrument) and references to supporting development and validation documentation* *Also consider including where the studies will be (or have been) run (i.e., geographical area).*

Comments:

15 References — *Can include when labeling must summarize or otherwise rely on recommendation by authoritative scientific body, or a standardized methodology, scale, or technique, because information is necessary for safe and effective use.*

16 How Supplied/Storage and Handling

Target	Annotations
Include information about the available dosage forms to which the labeling will apply and for which the manufacturer or distributor will be responsible. For example: • *Strength of the dosage form* • *Units in which the dosage form ordinarily is available* • *Information to facilitate identification of dosage forms* • *Special handling and storage conditions*	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date*

Comments:

17 Patient Counseling Information

Target	Annotations
Include information for prescribers to convey to patients to use the drug safely and effectively. For example: • *Precautions concerning driving* • *Concomitant use of other substances that may have harmful additive effects* • *Proper use and disposal of syringes and needles* • *Adverse reactions reasonably associated with use of the drug* • *Lab tests and monitoring required* *Indicate whether a Patient Package Insert or MedGuide are planned.*	*Summary information regarding completed or planned studies to support the target:* • *Protocol #, Serial #, Submission date*

Comments: