Targeted Product Information Template

New Drug X

The objective in preparing the Targeted Product Information (TPI) document is to develop a working package insert (PI) by including 1) what we know to be true today as statements which can be taken from completed reports (reference these statements with report numbers) **OR** 2) to indicate what studies have been planned to address each section of the label and/or to support specific claims desired. The TPI template below follows the format of the PI. If no data are available to support a statement, include a general statement to insert the topic with a reference to a protocol number. As studies are completed, appropriate summary statements, data and report numbers should replace the general statements and protocol numbers. The TPI should conform to the overall product development plan and bolster beginning the project with the end, the package insert, in mind.

The template below provides a recommended outline for a TPI with a description of suggested information (in *italics*) for each section. Because the template follows the general format of a proposed PI, the section numbers correspond to the subsections of 21 CFR 201.56 and 201.57 which describe the specific regulatory requirements for the content and format of labeling for human prescription drugs.

(a) Description
(b) Clinical Pharmacology
(c) Indications and Usage
(d) Contraindications
(e) Warnings
(f) Precautions
(g) Adverse Reactions
(h) Drug Abuse and Dependence
(i) Overdosage
(j) Dosage and Administration
(k) How Supplied
(l) Animal Pharmacology and/or Animal Toxicology (if necessary)
(m) Clinical Studies/References (if necessary)

(a) Description
This section should include the proprietary name and established name, dosage form and route of administration, qualitative and quantitative ingredients, pharmacologic class, and any other important physical and chemical characteristics.

Example:
NEW DRUG X tablets contain NEW DRUG X, a semi-synthetic antibiotic for oral administration.

Chemically, NEW DRUG X, is designated as (chemical name). Its molecular weight is ( ). The following is NEW DRUG X's chemical structure. (Reference)

NEW DRUG X (discuss chemical properties and provide reference).

NEW DRUG X tablets are (describe and list excipients).

(b) Clinical Pharmacology
Data demonstrating drug actions should be included in this section, including the drug's actions (animal/in vitro or humans), biochemical or physiological mode of action, PK information, degree of absorption, pathway for biotransformation, % 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 in fetus, and passage across the blood-brain barrier. PK data are restricted to that

which relates to clinical use of drug.

(1) Pharmacokinetics:

(2) Absorption:

NEW DRUG X is _____ absorbed *(Study Protocol/Report #s)*. The absolute bioavailability of the oral formulation is approximately ____% *(Study Protocol/Report #s)*. The pharmacokinetic parameters of NEW DRUG X in plasma after single *(Study Protocol/Report #s)* and multiple dose oral administration *(Study Protocol/Report #s)* as of ____ (date) were as follows:

(3) Pharmacokinetic Parameters:

(4) Distribution:

The protein binding of NEW DRUG X ranges from ____ to ____%. *(Study Protocol/Report #s).* NEW DRUG X is ____ distributed throughout the body with a mean apparent volume of distribution (VDss) of ____ *(Study Protocol/Report #s).* Distribution of NEW DRUG X into tissue *(Study Protocol/Report #s)*.

(5) Metabolism and Excretion:

NEW DRUG X is primarily eliminated _____ *(Study Protocol/Report #s)*. The mean plasma half-life is ____, the mean terminal elimination half-life is ____, and the mean apparent total body clearance of approximately ____ in patients with normal renal clearance. *(Study Protocol/Report #s).*

(6) Special Populations:

- Hepatic Insufficiency: *(Study Protocol/Report #s)*
- Renal Insufficiency: *(Study Protocol/Report #s)*
- Geriatric Patients: *(Study Protocol/Report #s)*
- Pediatric Patients: *(Study Protocol/Report #s)*

Data demonstrating effectiveness in animal or in vitro models. *In vitro data for anti-infective drugs should be preceded by the statement, "The following in vitro data are available but their clinical significance is unknown."*

(7) Microbiology:

NEW DRUG X exerts its activity by ____ *(Study Protocol/Report #s).* NEW DRUG X has been shown to be active against most strains of the following microorganisms **both *in vitro* and in clinical infection** as described in the "INDICATIONS AND USAGE" section.

(7a) Gram Positive Aerobes:

(7b) Gram Negative Aerobes:

(7c) Other bacteria:

The following ***in vitro*** **data are available BUT THEIR CLINICAL SIGNIFICANCE IS UNKNOWN.**

- **Gram Positive Aerobes:**
- **Gram Negative Aerobes:**
- **Anaerobic Bacteria:**

(7d) Susceptibility Tests

(7e) Dilution techniques - Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution method (REF 1, 2) (broth agar or microdilution) or equivalent with standardized concentrations of NEW DRUG X *(Study Protocol/Report #s)*. The MIC values should be interpreted according to the following criteria:

MIC (μg/mL)	**Interpretation**
	Susceptible
	Intermediate
	Resistant

A report of "susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard NEW DRUG X should provide the following MIC values *(Study Protocol/Report #s):*

Microorganism	MIC (μg/mL)

(7f) Diffusion techniques - Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. Once such standardized procedure (Reference) required the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with __μg NEW DRUG X to test the susceptibility of microorganisms to NEW DRUG X.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a ___ μg NEW DRUG X disk should be interpreted according to the following criteria *(Study Protocol/Report #s)*:

Zone diameter (mm)	**Interpretation**
	Susceptible
	Intermediate
	Resistant

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for NEW DRUG X.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the ___ μg NEW DRUG X disk should provide the following zone diameters in this laboratory test quality control strains *(Study Protocol/Report*

#s):

Microorganism **Zone Diameter**

(c) Indications and Usage

This section should include a statement that the drug is indicated in the treatment, prevention or diagnosis of a recognized disease or condition, i.e., Apenicillin is indicated for the treatment of pneumonia due to susceptible pneumococci@ OR a statement that the drug is indicated for the relief of symptoms associated with the disease or syndrome OR a statement that the drug is indicated for a particular indication only in conjunction with a primary mode of therapy. Because all indications must be supported by substantial evidence of effectiveness based on adequate and well-controlled trials (21 CFR 201.57(C)(2), this section is of primary importance in guiding the drug development program. The TPI should be as specific as possible with regard to the following: the intent to develop evidence to support safety and efficacy in selected subgroups; description of any tests needed for selection or monitoring of patients - i.e., susceptibility tests; whether safety considerations require the drug 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.

Example:
NEW DRUG X (tablets) is indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below in patients age X to Y.

- Acute bacterial exacerbation of chronic bronchitis due to: *(Study Protocol/Report #s)*
- Community - acquired pneumonia due to: *(Study Protocol/Report #s)*
- Pharyngitis/Tonsillitis due to: *(Study Protocol/Report #s)*
- Acute maxillary sinusitis due to: *(Study Protocol/Report #s) ETC. . .*

(d) Contraindications

The TPI should describe situations where drugs should not be used due to risk/benefit, including:

- *Known hypersensitivity to drug product*
- *Increased risk of harm due to age, sex, concomitant therapy, disease state, etc.*
- *Adverse reactions which would limit use*
- *KNOWN, not theoretical, hazards should be stated*

(e) Warnings

The TPI should include a description of serious adverse reactions and potential safety hazards and limitations of use imposed by them, as these become known through the drug development program. A causal relationship need not be demonstrated. Reasonable evidence should drive the listing. FDA may require a BOXED warning if the risk may lead to death or serious injury - this is derived from clinical data usually, but can be from animal toxicology.

(f) Precautions

(*1) General*

The TPI should 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.

(2) *Information for patients*

The TPI should include, when appropriate, information for patients; e.g., concern for driving, concern for concomitant use with other substances.

(***3) Lab tests***

The TPI should describe lab tests required to monitor patient response on drug or identify any adverse event. Normal values for tests should be provided.

(*4) Drug interactions*

The TPI should include practical advice on how to prevent drug-drug interactions; drug-food interactions (description of results from studies conducted or observations from the integrated safety summary); drug - lab test incompatibilities (known interference of drug with lab test outcome).

(*5) Carcinogenesis, mutagenesis, impairment of fertility*

Results of long-term carcinogenicity studies - species identified
Reproduction study results
Mutagenesis results
Precautionary statements required - if product shows potential for any of the above, then this information should be included under Warnings and Precautions.

(*6) Pregnancy*

This subsection may be omitted if the drug is not absorbed systemically
Teratogenic effects:
Pregnancy Categories: A, B, C, D, X
Nonteratogenic effects:
Other effects on reproduction are described here. Any information on the nonteratogenic effects on fetus or newborn should be included.

(*7) Labor and delivery*

The TPI should indicate if the drug will have recognized use during labor or delivery, effects on mother, fetus, duration of labor, delivery, effects on later growth or newborn.

(*8) Nursing mothers*

If the drug is absorbed systemically, the TPI should indicate if there is known information about excretion of drug in human milk and effects on the nursing infant. Pertinent adverse events in animal offspring should be described. A series of labeling statements should be provided if tumorigenicity is detected.

(*9) Pediatric use*

Pediatric definition is birth to 16 years of age. If there is a specific and relevant pediatric indication supported by adequate and well-controlled trials, then the TPI should include the statement regarding the indication in the INDICATIONS AND USAGE section and DOSAGE AND ADMINISTRATION section as well. This section should cite any limitations, need for monitoring, specific hazards, differences in response or other information pertinent to the referenced population.

(*10) Geriatric use*

Geriatric definition is age 65 and older. The TPI should include data relevant to the use of the drug product in the geriatric population. This section should cite any limitations, need for monitoring, specific hazards, differences in response or other information pertinent to the referenced population.

(g) Adverse Reactions

Definition - An adverse reaction is an undesirable effect reasonably associated with the use of the drug. The TPI should list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class. Adverse events may be categorized by organ system by severity, by frequency or by toxicology mechanism. Summary tables showing frequencies of adverse events can be a useful way to present such data.

(h) Drug Abuse and Dependence

The TPI should address in this section:

- *Controlled substance - abuse based on human data and animal data*
- *Dependence - Discuss potential for dependence*

(i) Overdosage

The TPI should describe the signs, symptoms, and lab findings of acute overdosage and the general principles of treatment. This section should be based on human data where available. Specific information should be provided for:

- *Signs, symptoms, and lab findings associated with an overdosage of the drug*
- *Complications that can occur with the drug, e.g., organ toxicity*
- *Oral LD_{50} of the drug in animals*
- *Concentrations of the drug in bio-fluids associated with toxicity or death*
- *The amount of drug in a single dose that is ordinarily associated with symptoms and the amount of the drug in a single dose that is likely to be life-threatening*
- *Whether the drug is dialyzable*
- *Recommended general treatment procedures*

(j) Dosage and Administration

The TPI should state the recommended usual dose, dose range, and the upper limit beyond which safety and efficacy have not been established. Dosages shall be stated for each indication.

- *Dosage intervals/titration*
- *Usual duration of treatment*
- *Modifications for dosage, i.e., pediatric patients, geriatric patients, or patients with renal or hepatic disease*

NEW DRUG X (tablets) (food effect statement)
Represent dosage schedule for NEW DRUG X in tabular form

Infection	Dosage	Frequency	Duration

(k) How Supplied

This section applies to the formulation (that the sponsor expects to market) and packaging. The strength of dosage form and the unit in which dosage form is available for practitioners (e.g., bottles of 100) are identified. Information for identification (i.e., scoring, shape, color, coating, NDC#), special storage and handling conditions should be described.

(l) Animal Pharmacology and/or Animal Toxicology (if necessary)

(m) Clinical Studies/References (if necessary)

References

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* - 4th Edition; Approved Standard NCCLS Document M7-A4, Vol 17, No. 2, NCCLS, Wayne, PA, January, 1997.
2. National Committee for Clinical Laboratory Standards. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria* - 3rd Edition; Approved Standard NCCLS Document M11-A4, vol 17, No. 22, NCCLS, Wayne, PA, December 1997.
3. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Sixth Edition; Approved Standard NCCLS Document M2-A6, vol 17, No. 1, NCCLS, Wayne, PA, January, 1997.