The Prospective Package Insert Guide

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THE PROSPECTIVE PATIENT PACKAGE INSERT

In the United States and other Western countries, the product label or package insert, characterizes the market for a drug by defining the indications and the appropriate patients population, informing prescribers, and serving as the basis for promotional material. Therefore, it should be self-evident that the package insert also drives development. In its most strategic context, clinical development is the process of generating the human data that populate the final package insert.

Recognizing the label's importance, many biopharmaceutical companies have instituted formal procedures for crafting and approving, early in development, a prospective patient package insert (PPI) for every new product. This is a key planning document that articulates those developmental goals that must be realized to maximize product value. It serves as the corporate statement of those attributes a new drug must possess for it to be considered a value-adding component of the overall portfolio. Selected practical considerations and characteristics of a prospective PPI are:

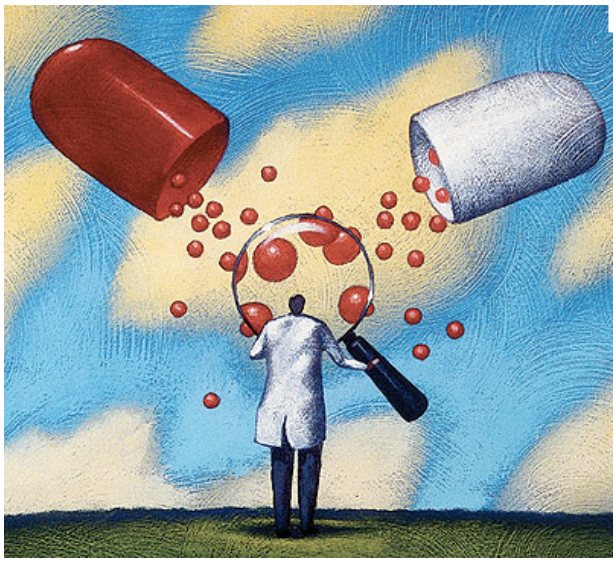
Characteristics of a Prospective Patient Package Insert	
Multidisciplinary	Input from the disciplines of chemistry, pharmacology, toxicology, pharmaceutical science manufacturing, clinical research, regulatory affairs, & marketing.
Aspirational	Presents labeling statements as a series of goals to be achieved through the life of the program.
Pragmatic	Acknowledges that clinical science often does not conform to aspirations, thus considers a range of possibilities and maintains room for flexibility.
Dynamic	Written in manner that can be updated on a real-time basis to incorporate and respond to new information
Evolutionary	Through the course of development, the document can serve as a component of the Clinical Investigator Brochure ("Summary of Data and Guidance for the Investigator" in ICH terminology); as more and more new data accrue, it can eventually transform into the actual label text.

The prospective PPI serves many audiences and addresses many important functions. For the development team, it provides a series of goals, raises new questions, and crystallizes thinking around central themes of development for a given product. For management, it initially serves to ensure that the development philosophy harmonizes with strategic goals; subsequently, it provides both a framework for capturing new knowledge and yardstick against which developmental progress and results can be measured. For the organization as a whole, it provides an invaluable communication and decision-making

tool; at every step of the way, actual results can be compared with aspirations, and reassessment can be made regarding the wisdom of continuing investment in the project.

Central to the process of developing the prospective PPI is determining the nature of the Indications Statement as specifically as possible. No drug is ever approved with an indication to "treat infection"; instead, it is approved with a label that specifies the site(s) of infection, the causative organism(s), and the characteristics of the patient population. A crisp articulation of the Indications Statement must be made at the outset of development to provide focus and direction to the clinical effort.

Two points about the prospective PPI are worth highlighting. First, not all the new data



that accrue during development and that influence decisions, emanate from clinical trials. Results are also generated by toxicology studies, manufacturing processes, competitors' programs, and the like. Certainly, negative information about a compound's chronic toxicity or carcinogenicity, high cost of goods, or inferior profile relative to a competitive compound will affect a company's view of that compound's value. Second, nota all label components lend themselves to being designed into a clinical trial but, rather, emerge from observations that are made during the course of a trial. In general, label data relating to pharmacology, efficacy, and dosing are subject to hypothesis formulation and therefore are directly designed into a protocol, whereas information relating to safety is obtained not by hypothesis testing but by careful empiric observation.

A DETAILED GUIDE TO THE PROSPECTIVE PATIENT PACKAGE INSERT

1. INDICATIONS AND USAGE	
• Indication(s), Usage	A clear statement of the specific indication(s) for which the drug will be approved together with any necessary claims one wants to make.
2. DOSAGE AND ADMINISTRATION	
• Dosage and administration	Recommended dose for each patient group based on clinical pharmacological data, and how the drug should be reconstituted if applicable and administered.
3. DOSAGE FORMS AND STRENGTH	
• Dosage forms and strength	Describes the physical characteristics of the drug. Appearance – color, shape, markings. Also describes the strengths available.
4. CONTRAINDICATIONS	
• Contraindications	List of situations when the drug should not be used, for example, medical conditions that may result in reactions, poor clearance or untoward events.
5. WARNINGS AND PRECAUTIONS	
• Warnings	List of serious side effects that may occur
• Precautions	Explains how to use the drug safely, any physical problems or drug interactions to be aware of.
6. ADVERSE REACTIONS	
• Adverse reactions	A list of adverse reactions and frequency.
7. DRUG INTERACTIONS	
• Drug interactions	Provides a listing of any drug interactions that have been observed or could be anticipated.
8. USE IN SPECIFIC POPULATIONS	
• Use in specific populations	Recommended use for each population such as pediatrics, adults, geriatrics, pregnancy, nursing mothers, etc.
9. DRUG ABUSE AND DEPENDENCE	

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• Drug abuse and dependence	Provide information regarding extended use and dependency if applicable only.
10. OVERDOSAGE	
• Overdosage	Provide information regarding the effects of over dosing and any treatment recommended.
11. DESCRIPTION	
• Description	Provide a detailed description of the drug.
12. CLINICAL PHARMACOLOGY	
• Clinical Pharmacology	How, where and on what the drug works, in the body, pharmacodynamics and pharmacokinetics; how absorbed, distributed metabolized, and excreted
13. NON-CLINICAL TOXICOLOGY	
• Non-clinical toxicology	Provide a summary of all non-clinical toxicology studies, and, carcinogenesis, mutagenesis and impairment of fertility studies.
14. CLINICAL STUDIES	
• Clinical studies	Provide a summary of all clinical studies, data and conclusions.
15. REFERENCES	
• References	Provide a complete list of published information relating to the drug.
16. HOW SUPPLIED/STORAGE AND HANDLING	
• How supplied/Storage and handling	Describes how the drug is supplied and any specific storage and handling requirements.
17. PATIENT COUNSELING INFORMATION	
• Patient counseling information	Provide patient counseling information as approved by FDA.

Further Information:
Federal Register /Vol. 71, No. 15 /Tuesday, January 24, 2006 /Rules and Regulations
http://www.fda.gov/ohrms/dockets/98fr/06-545.pdf
Guidance Drug Safety Information – FDA's Communication to the Public, March 2007
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072281.pdf