Good Practice Guide

Booklet Labels

Connecting a World of Pharmaceutical Knowledge

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Disclaimer:
This Guide is intended to provide guidance on the design, structure, use, and application of booklet labels to help with site and subject compliance. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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ISBN 978-1-936379-58-3

Preface

Fan-folded labels or booklet labels have been developed by the pharmaceutical industry over the past 15 years. The intent of this label type was to introduce greater efficiency in clinical trial production and to reduce the cost of packaging and labeling of investigational products for global clinical trials.

Technological improvements by label producers/label suppliers made it possible to accommodate global trials by moving from single panel labels to fan-folded labels or booklet labels.

The use of booklet labels in clinical trials is still growing for a number of reasons, e.g., flexibility and the reduction of packaging effort, cost, and time. However, considerations of how to use booklet labels have become increasingly important in maintaining site and subject compliance.

This Guide has been developed to provide guidance on how to design and structure a booklet label and how to standardize the use and application of booklet labels. It responds to the regulatory requirements and the practicability needs of the users. It is a result of a joint effort of representatives from the pharmaceutical industry and review by several pharmaceutical discussion groups. General support and professional insights also have been provided by representatives from the MHRA (UK).

This Guide is intended to provide direction for the pharmaceutical industry and to support further harmonization of labeling requirements, globally.

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The Task Team would like to give particular thanks to Rebecca Stanbrook and Graham McNaughton (MHRA) for general support and professional insights.

Many other individuals reviewed and provided comments during the preparation of this Guide; although they are too numerous to list here, their input is greatly appreciated.

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1 Introduction

1.1 Background

The ISPE Investigational Products Community of Practice (IP COP) presented an ISPE Concept Paper on Booklet Labels (January 2012) [1], which included assessments of any risk involved in using booklet labels for clinical trial materials and the results from an investigational site survey and pharmaceutical industry benchmarking. The survey and benchmarking were completed by:

- Sites that had participated in clinical trials
- Pharmaceutical organizations

Benchmarking showed clearly that the pharmaceutical industry uses booklet labels in several different ways; therefore, recommendations on how booklet labels can be standardized could be of value for both users and competent authorities.

The survey demonstrated that using booklet labels does not impact subject safety or compliance, nor was this the perception obtained from the investigators/sites survey. The survey also showed that booklet labels are considered to be only one source of product information for both sites and for subjects. For further information, see the ISPE Concept Paper on Booklet Labels [1].

Pharmaceutical industry benchmarking highlighted the variability in how required information is presented within booklet labels. These differences include:

- Whether or not text is printed on the base label
- Whether or not a sponsor logo is included
- Clarity of information on how to open the booklet label
- Amount of space for adding information manually at time of dispensing

The ISPE Concept Paper on Booklet Labels [1] acknowledged these differences and assessed potential risks introduced by the absence of standards in booklet label use. Concerns also were noted around the use of booklet labels, from both readability and training perspectives. These concerns and potential risks centered on several aspects of booklet labels, including those shown in Table 1.1.

Table 1.1

Risk	Possible Reason
Sites and/or subjects do not understand the booklet labels; therefore, sites cannot instruct subjects appropriately.	• Variety of designs of booklet labels: - Across industry - Within one organization • Lack of understanding on how to use the booklet label • Difficulty reading/identifying kit number
Sites/subjects do not read the information.	• Information not immediately visible on labels • Font too small • Booklet labels never opened
Pages of the booklet labels removed	• No information left on the container • Storage conditions not on front page • Too 'bulky' on small primary container: - May not fit in device - May make the container/device difficult to handle
Difficulty in finding the individual language pages	• Index of languages or countries not immediately visible

This Guide is intended to provide support to the pharmaceutical industry by presenting recommendations on using booklet labels in a standardized manner; helping to reduce or eliminate the risks and concerns expressed by investigational sites and competent authorities.

Although the pharmaceutical industry benchmarking and site survey on complaints received (as related to booklet labels) indicated that there is little evidence to support concerns that the use of booklet labels impact subject compliance or increases risks to subject safety, the ISPE IP COP felt that this Guide will be of benefit in addressing the risks listed above. See the ISPE Concept Paper on Booklet Labels [1].

The pharmaceutical industry benchmarking and site survey also indicated that the pharmaceutical industry could benefit by standardizing training of sites and subjects in product handling, especially on storage conditions, and in the use of booklet labels and use-by dates.

1.2 Overview

Multi-panel labels have been used in clinical trials since the mid-1980s. Booklet labels (fan-folded or glued) have been used both in the commercial pharmaceutical industry and in clinical trial supplies since the early 1990s. Both fan-folded and glued booklet labels were under development simultaneously, but the glued booklet label is currently more widely used due to its advantages in process efficiency for subjects.

The increase in the number of global clinical trials has increased the challenges for the pharmaceutical industry. These challenges range from increasing compliance and safety for subjects to the need to enhance packaging efficiency.

This Guide takes in account both the risk assessments and the results from the site survey (see the ISPE Concept Paper on Booklet Labels [1]), which provided findings on the most important issues to address. Standardization of booklet labels can benefit the pharmaceutical industry by eliminating variability and reducing confusion among users.

This ISPE Good Practice Guide: Booklet Labels provides recommendations to help to mitigate risks and issues identified in the pharmaceutical industry benchmarking and site survey (see the ISPE Concept Paper on Booklet Labels [1]), to encourage standardization of booklet labels across the pharmaceutical industry.

This Guide also includes recommendations to support using pooled products and eliminating use-by dates on labels when controlled using an Interactive Response Technology (IRT) system, as described in ISPE Good Practice Guide: Interactive Response Technology [2].

1.3 Scope and Purpose

This Guide discusses the relevant GMP and GCP concerns related to the use of booklet labels for global clinical trials. Although booklet labels are different from traditional single-panel labels, they must still comply with the same regulations and facilitate compliant use of Investigational Medicinal Products (IMPs) by subjects and sites.

This Guide provides recommendations for the effective use of booklet labels to support investigational products across countries, trial programs, and/or protocols.

In addition, this Guide provides recommendations on how to design booklet labels to:

- Improve their effectiveness for sites and subjects
- Meet the regulatory requirements of the participating countries
- Make them easy to follow and use for the pharmaceutical industry

Design will be discussed for both secondary packaging and small primary packaging, which have different challenges.

The Guide also includes recommendations for booklet labels applied to IMP for use in hospitals (in-subject) and at-home treatments (out-subject). Special consideration is given for clinical trial materials labeled for multiple protocols, known as pooled products, see the ISPE Good Practice Guide: Interactive Response Technology [2].

The Guide also recommends standards for the design of booklet labels that are expected to meet concerns raised by competent authorities. By promoting standardization across the pharmaceutical industry and eliminating variability and enhancing compliance, users and competent authorities should be less confused by booklet label designs and layouts.

Booklet labels are one of several options which pharmaceutical organizations can use to label clinical trial materials. This Guide does not cover the processes related to determining when it is appropriate to use booklet labels. Other options, such as single panel labels or other technological and process innovations are also not covered.

The method of constructing and/or printing booklet labels is **not** covered by this Guide. There are several options for producing booklet labels, some of which utilize proprietary technology that is available from suppliers to the pharmaceutical industry. This Guide applies only to technology which is currently available at time of publication.

1.4 Benefits

Booklet labels are a useful tool for clinical study sponsors and can be used to:

- Make supplies available for new subjects more quickly by eliminating both the time and resources needed to manufacture, package, and label supplies which are specific to individual countries
- Increase the amount of space available for text required by each participating country, such as that specified for the EU in Section 26 of the EU GMP Annex 13 [3]
- Increase the amount of space available on a label, allowing a larger font size to be used

- Create flexibility in the clinical supply chain, allowing sponsors to better supply multi-national clinical trials with fewer IMPs

- Improve distribution of IMP to ensure its availability at site in due time and reduce risk of stock-out. Reduce the likelihood of excess IMP being diverted or having a negative environmental impact if not stored, handled, and destroyed properly

The pursuit of business improvements to operate leaner and more cost efficiently by pharmaceutical companies, should not impact subject safety or exempt sponsor companies from complying with regulations enacted to protect subjects. The increased use of booklet labels is a testimony to their usefulness and their acceptance by the pharmaceutical industry. The recommendations in this Guide for the use of booklet labels by site personnel are intended to help to ensure that sponsor companies can continue to operate in the efficient manner required to be successful in their drug development pursuits without negatively impacting subject safety.

Guidance provided also can result in benefits to sponsors who use supplies labeled with booklet labels in clinical supply chains. Standardizing booklet designs, by placing the same text in the same location within booklets for all studies, can:

- Reduce errors in the design process

- Allow for standardization in the printing process

- Reduce the likelihood of delays during the distribution process

Similarly, standardization can help to reduce dispensing errors by sites and allow subjects and site personnel to become familiar with the label design, so they know where to look for pertinent information.

Providing justified recommendation on the removal of the expiry date from labels, coupled with guidance in the ISPE Good Practice Guide: Interactive Response Technology [2] can reduce potential for waste of IMP in the clinical supply chain. Without a requirement to re-label investigational product for which the expiry date has been extended, clinical supplies can be used longer “as labeled.” This approach can result in less product being sent for destruction, less labeling (or re-labeling) required at sites and distribution locations, and a reduction in the workload for site personnel. A risk assessment should be performed for each trial. An extension of the expiry date may not be needed due to a sufficiently long use-by date. Consideration should be given to printing the use-by date on labels, following recommendations for positioning this information, given in Table 3.1.

In addition, recognizing that many companies are pooling their IMPs either on a program or protocol level at time of distribution (or at time of dispensing), guidance is provided on the design of booklet labels for product pooling by recommending positioning of the trial identification (ID) in a manner that will make just-in-time labeling/identification of trial ID more feasible. This can result in more flexibility of supplies in the clinical supply chain, an increased rate of availability of clinical trial materials on site, and reduced waste and effort in supporting subjects taking IMPs in a clinical trial.

1.5 Objectives

This Guide aims to provide information and recommendations to the pharmaceutical industry for booklet label development and use. It addresses GMP requirements, as well as concerns of competent authorities regarding the use of booklet labels.

Safety of subjects is managed through increased compliance with the dosing instructions and this Guide aims to help to ensure greater safety and compliance for subjects participating in clinical trials.

Guidance is provided on the type of information that should be included within booklet labels, largely based on requirements in Annex 13 of the EU GMP [3], which is considered the most thorough definition of label text provided by a competent authority.

This Guide proposes a standard booklet label layout. It also suggests additional documentation (e.g., subject cards, and training documentation) that can support the information within booklet labels to enhance subject safety and compliance, as well as site compliance.

The proposed content and layout of booklet labels have been developed in order to maximize the readability/ understandability of the label, enhance subject safety, and ease of use by both subjects and sites.

1.6 Key Terms

Booklet Label

A combination of a label and a booklet containing multiple pages with country specific information in local language (a label with at least three pages).

Competent Authority

National Competent Authority, Ministry of Health. A body with authority to act on behalf of the government of the respective country/ state to perform the licensing of medicines for that country.

Interactive Response Technology (IRT)

Centralized electronic randomization system used in clinical trial for but not limited to randomization and medication management. Two methods included: voice and/or web.

Interactive Voice Response (IVR) System

Computerized technology which combines the use of databases and telephones to input, retrieve, and manage information.

Interactive Web Response (IWR) Technology

Computerized technology which combines the use of databases and the internet to input, retrieve and manage information.

Investigational Medicinal Product (IMP)

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization, but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form [3].

Synonyms: Investigational Product, Trial Product, Trial Medication, Clinical Supplies, and Study Drug, etc.

Kit Number

Unique identifier for a packaged unit used within a clinical trial.

Synonyms: Dispensing Unit, Box #, Pack ID, IRT Number, Med ID, and Kit Identifier, etc.