Use of Booklet Labels on Investigational Medicinal Products (IMPs)

A Concept Paper by the ISPE Booklet Label Task Team

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1 Introduction

It is current practice to use booklet labels for labelling of Investigational Medicinal Products (IMPs) to be used in multinational clinical trials.

Many companies use multinational clinical trials to locate potential subjects for testing new medications, and most countries require that labels on IMPs be in their local language.

Studies are performed in multinational and multilingual trials. Since there is no universal guidance covering the aspect of how to label, a broad range of approaches has been developed within the industry. An economic and flexible solution is booklet labels.

The ISPE IP COP Booklet Label Task Team was formed in order to respond to concerns in regard to content, readability, and correct usage of booklet labels. Their intention is to develop an ISPE Good Practice Guide for standardization of booklet label content and form in addition to driving improvement of user friendliness.

The objective of this concept paper is to reflect on a study site survey performed, to draw conclusions from an assessment on comparison of Booklet Labels versus Single Panel Labels performed, to discuss benefits of a Good Practice Guide, and to define the need for training on the proper use of booklet labels. The Good Practice Guide for Booklet Labels will be based on the conclusions and assumptions of the concept paper.

This report does not imply that a competent authority in any country agrees with the conclusions and assumptions of the concept paper.

2 Acronyms and Glossary

For the purposes of this technical report, the following terms are used and accompanied by their synonyms where applicable.

Base Label

The part of the booklet label which is applied to the primary or secondary packaging of the IMP.

Batch Number

Lot no., code no., requisition number, packaging run number, or equivalent.

Binding Area

Located left or right from the cover page on the booklet label.

Booklet Label

A combination of a label and a booklet/leaflet containing multiple pages with information.

Caution Statement

Covering Annex 13: “For clinical trial use only,” “keep out of reach of children,” etc.

Clinical Trial

Clinical study.

Clinical Trial Application

Regulatory submission to allow execution of a clinical trial.

Closing Area

Located right or left from the cover page of the booklet label, area where label is opened and closed.

Competent Authority

Health authorities, Ministry of Health; a body with authority to act on behalf of the government of the respective country/state.

Cover Page

Front page of the booklet label.

Direction for Use

Written information to the site and/or subject on how to use the investigational products.

Dispensing

Provision of IMP for subject use for home treatment or for hospital administration to subject. Refers to IMP which has been packaged in accordance with regulations and is ready for administration to the subject.

Expiry Date

Date by which the product expires and cannot be extended.

Inner Pages

Containing the table of content and the country specific translated pages, in the official local language(s) of the respective countries.

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 Products (IMP)

Investigational products, trial products, trial medication, clinical supplies, study drug, etc.

Kit Number

Unique identifier for a packaged unit used within a clinical trial; dispensing unit, Box #, Pack ID, IRT Number, Med ID.

Manual Re-Labelling Process

The process of creation, approval, and issuance of labels (IMP or auxiliary labels) for the purpose of updating retest dates currently on IMP containers at warehouses, depots, or clinical study sites.

Name of Investigator

Name of the principal investigator at a site participating in a clinical trial responsible for the clinical trial and emergency contact for the subject.

Pharma Industry

Life science industry, biopharmaceuticals, pharmaceuticals industry.

Primary Packaging

Immediate container with IMP.

Removable Panel

The part of the label that can be either removed or detached from the booklet label itself. A tear-off/peel-off label acts as a self-adhesive label used for documentation at the site.

Retest Date

Use period can be extended.

Secondary Packaging

Outer box/carton containing primary containers with IMP.

Single Panel Label

A label with just one layer; affixed directly onto the container containing one or more languages limited by size.

Site

Clinical site/centre/clinic/unit/hospital participating in a clinical trial.

Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Subject

An individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control; patient, volunteer.

Subject Number

Trial subject identification number.

Subject Safety

Patient care, patient safety.

Top Layer

The part of the booklet label visible when the booklet is closed.

Treatment Number

Treatment identification number assigned to the subject according to the randomization schedule and that relates to the investigational medicinal product(s) contained in the kit.

Trial Reference Code

Identification code of the trial, site, investigator, and sponsor; trial ID; protocol number, etc.

Use by Date

Indicates the period of use in month/year format and in a manner that avoids any ambiguity; retest date/expiry date.

Visit Number

Identification number of the protocol visit the investigational products are intended for.

3 Use of Booklet Labels with IMPs

3.1 Background

Labelling of IMPs to be used in clinical trials is, depending on the region in the world, usually regulated by national law to be complied with by the Pharmaceutical Industry. The most detailed guidance on IMP label content is found in the EU, where Annex 13 to the EU-GMP-Guide defines the information details to be labelled on IMPs, and responds to the fact of a multilingual EU community as follows:

"Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used. The particulars listed in Article ... should appear on the primary packaging and on the secondary packaging. ... . Other languages may be included."

Booklet labels have been established and used in clinical trials for more than 20 years. They reduce the amount of medication to be prepared and improve the efficiency of IMP use by optimizing commutability. By optimizing commutability of IMPs, there is a reduced risk of interruption to subject supply. However, since there is no guidance or standard on the design and structure of booklet labels, they vary greatly. The likelihood of errors which could negatively impact understanding the content on the booklet label is greatly increased by various designs of booklets that are sometimes very complicated, and contain vast amounts of information. Standardizing booklet label design would reduce confusion among site personnel including investigators, pharmacists, study nurses, and result in better usage of the label and ultimately, better patient care.

ISPE and the pharmaceutical industry have recognized that it would help the industry itself by standardizing the use of booklet labels. The ISPE IP COP Booklet Label Task Team has been established, aiming to introduce standardization of the booklet label contents and format, for improvement of user friendliness and finally to improve convenience for site and subject. The team identified three main tasks to be accomplished:

1. Conduct a customer survey (investigational site and if possible, patients) to obtain feedback on the current use and design of booklet labels.

2. Establish a concept paper assessing benefits versus risk of booklet label use, summarize the survey feedback, explain the benefits of a Good Practice Guide, and propose recommended training on booklet labels.

3. Develop a Good Practice Guide with recommendations on how to standardize the structure and design of booklet labels.

4 Survey Feedback

This section contains feedback and associated conclusions from a recently conducted pharma industry benchmarking as well as a survey.

The benchmarking took the form of a series of questions related to IMP labels/booklet labels.

The survey was an investigational sites survey, conducted by the ISPE Interactive Response Technology (IRT) Good Clinical Practice (GCP) Sub Team with input from the ISPE Booklet Label Task Team.

4.1 Pharma Industry Benchmarking

Complaints: A number of pharmaceutical companies were asked whether they had received any complaints related to the use of booklet labels on IMPs. 12 responses were received:

- 9 companies had no record of specific IMP booklet label related complaints.
- 3 companies had received complaints related to booklet label quality (damage, font size, and text smudging). Incident rate appears no higher than seen with single panel labels.
- Only one cited a complaint related to confusion caused by booklet label design – subject was confused on how to open label.

Conclusion: Of companies polled there is little evidence to suggest that the use of booklet labels versus the use of single panel labels leads to an increased incidence of customer complaints that could be extrapolated to risk to subject safety.

General Booklet Label Related Questions:

A number of pharmaceutical companies were asked a series of booklet label related benchmarking questions. These questions included:

- Whether companies used booklet labels and whether they used them on small containers.
- How companies provided information on IMP to sites and subjects.
- Whether sites received training.
- Whether companies used pictograms.
- What information appears on their cover page and whether it was translated.
- How variable text was added to the booklet.
- Various formatting questions.

Consistently positive responses were received for the use of booklet labels, including on small containers (with translated text), and for the provision of supplemental IMP information, although how this information was provided, varied.

Most companies also indicated that they did not provide site training, nor did they routinely use Pictograms. Varied responses were received for the remaining questions indicating a diversity of booklet label design and format.

4.2 ISPE IRT Investigational Site Survey

This survey was conducted by the ISPE IRT GCP Sub Team with specific input from the ISPE Booklet Label Task Team, on the booklet label related questions [Appendix 1]. Responses were received from more than 250 investigational sites around the globe with significant participation from sites located in the EU (34%), Asia (27%), and North America (23%). Site composition of respondents:

- 45% located in large state run hospitals
- 22% located in Independent Clinical Trial Research Units
- 15% located in clinical trials units in private hospital
- 3% located in GP surgeries
- 15% located at other types of sites
- 80% of sites who responded supported Phase III/IV studies

Comments and Conclusions from this Survey:

The number of sites who indicated that they had not encountered booklet labels previously was surprisingly high, particularly in light of the number of sites who indicated they supported Phase III/IV studies. In evaluating this response rate, it was concluded that respondents may not have fully understood the use of the term “booklet labels” and that perhaps with the inclusion of an associated definition, a significantly higher positive responses would have been secured.

Site Training: 65% of respondents indicated that they had received training in the use of booklet labels either at investigator meetings, initiation meetings, or contained within pharmacy manual. Site training in use/understanding of booklet labels should be a recommended good practice.

Additional (to IMP Label) Reference Sources for Sites: the most consistently provided reference sources providing guidance on the use/storage of the IMP are the protocol, pharmacy manual, and the investigator brochure. Only a small percentage of sites **(4%)** indicated that the sponsor provided no additional guidance on IMP storage or use other than that on the IMP label.

Demonstration of Booklet Label Use: 80% of respondents indicated that they demonstrate the use of the booklet labels to subjects and half of those, also ensured that they did this at each dispensing visit. Good practice would suggest that subjects are made aware of how to use the booklet labels on their first dispensing visit, as a minimum.

Subject Instruction to Open and Read Label: 70% of sites instruct subjects to open and read the booklet label with **44%** of sites confirming that this action has been completed.

Additional IMP Information for Subjects: 45% of responders rely on the label as the primary source of product information for subjects. **55%** provide subjects with additional information to supplement the IMP label. Supplemental reference sources vary by study, but include informed consent form; diaries; leaflets; and additional labelling (by pharmacy). Some provide additional verbal instruction to the subjects.

Booklet Label Challenges: 78% of respondents indicated that the information contained within a booklet label is hard to read (print/font too small). With both Kit ID/Container Number not being obvious and information not being clearly positioned or structured were rated as a challenge by approx **30%** of respondents. It was noted that the provision of additional IMP information mitigates some of these challenges.

Customer Complaints: 83% of respondents indicated they had not received complaints from study subjects related to booklet labels. For those who had received complaints, they typically related to the clarity of the information contained within the label and ease of use.

Subject Compliance: 90% of respondents indicated that they have not observed any impact on study subject compliance when using a booklet label versus a single panel label.

Conclusions: From this somewhat limited responded site survey, the responses clearly indicate that in general the vast majority of sites are informing the subjects on how to use or take their IMPs. Therefore, by extrapolation it seems justifiable to conclude there is little evidence to support concerns that the use of booklet labels (versus the use of single panel labels) in IMPs impact subject compliance or increases subject safety risk. However there is clearly room for improvement in a number of areas of booklet label creation and use including the clarity of booklet label content:

1. Training of sites and subjects on how to use booklet labels, and confirmation of subject understanding of use of IMP, should be recommended as good practice. Documented evidence of training is also recommended.

2. The content of booklet should be sufficiently clear and understandable to avoid the need for supplemental labelling of duplicate information at point of dispensing, e.g., through recommendation on optimal design and minimum font size for text.

3. Opportunity to provide guidance on booklet label structure to promote ease of use/dispensing, e.g. recommend consideration is given to the number of pages included in a booklet label versus ease of use, to avoid label being “too bulky” resulting in damage or being torn off; recommendation on Kit ID font size.

In addition, a subject survey is planned to demonstrate how much (or little) training improves compliance in the use of IMPs labelled with booklet labels. It is expected that the results from this survey will support the conclusions made in this concept paper and will be addressed in an additional concept paper.

Summary

This feedback from the pharma industry and from investigational sites provides valuable input for the ISPE Booklet Label Task Team to create the Booklet Label Good Practice Guide, intended to promote consistency and introduce standardization across the industry on booklet label creation and use.

5 Assessment of Booklet Label versus Single Panel Label

Based on the great variability in booklet label design and use, a pharma industry benchmark on product complaints related to labels and the ISPE IRT Investigational Site Survey assessment has been performed to assess the potential increased risk associated with the use of booklet labels. The assessment is provided in Appendix 2.

The following scenarios have been assessed for single panel labels and booklet labels:

1. Site and/or subject can not interpret or understand information on cover page of booklet label.
2. Site does not understand information on label.
3. Subject does not understand information on label.
4. Subject cannot find language.
5. Subject does not read information on the label.
6. Damaged Labels due to transport or use.
7. Subject and/or site remove pages they do not consider applicable.
8. Booklet on primary container is removed by the subject.
9. Poor label design.

The assessment of booklet labels versus single panel labels in Appendix II shows that booklet labels can be used in clinical trials as long as the following standard practices are applied:

- Good design and quality of the booklet label according the Good Practice Guide.
- Training of site personnel on the use of the IMP label.
- Mandatory review of the label of site personnel with the patient.

Additionally it should be taken into account that IMPs are used in a highly controlled environment. Investigational product information on the use and storage of the product is not only provided via the IMP label, but also via the protocol, pharmacy manual and/or the investigator brochure. Patients (or caretakers) are personally instructed on the use and storage of the product and in many cases they receive additional information via supplemental sources.

Conclusion

Provided the booklet label is appropriately designed, the site personnel are sufficiently trained and subjects receive instruction on how to use the IMP (including the label), the use of booklet labels should not lead to an increased inconvenience or reduced user-friendliness for the investigator site personnel or the patient in comparison to a single panel label.

6 Benefit of a Good Practice Guide on Booklet Label Content and Structure

As a result of the site survey feedback and assessment of booklet label versus single panel Label [Appendix 2] as outlined in previous chapters, the ISPE Booklet Label Task Team has initiated the process to develop a Booklet Label Good Practice Guide (GPG) on Booklet Label Format/Structure and Content.

The major goal for the GPG is to improve quality and convenience/user friendliness and to provide guidance on the design, format, structure, and content of booklet labels used in Clinical Trial Supplies.

Annex 13 is used as a foundation for the recommendations in this section in order to provide the most comprehensive and compliant set of label requirements.

The aim of the GPG is to define a global standard for booklet labels used to provide information on IMPs within a clinical trial. A global standard will:

- provide a clearly defined interpretation of regulatory requirements
- increase subject safety and compliance by:
    - reducing the risk of providing confusing information
    - reducing the risk of not providing required information
    - providing IMP information to subjects in a clear and comprehensive manner
- reduce confusion experienced by investigators, pharmacists, and individuals who may have to deal with varying layouts/designs
- address quality concerns raised by regulators by introducing quality standards for booklet label content and design
- assist regulators in understanding how the actual label will look based upon information in applications

The guide will cover the following areas:

1. Information that must be included on the label to
    - ensure protection of the subject
    - ensure traceability
    - enable identification of the product and trial
    - facilitate proper use of the investigational medicinal product based on the requirements outlined in Annex 13 [1]
        - Standard information to be included on a regular booklet label
        - Minimum requirements for small containers and/or special shaped containers/devices
        - Justification for absence of certain information in case IRT system is utilized [5]

2. Recommendations to support a user friendly booklet label

    - Content
        - Mandatory information
        - Other information
    - Structure and design, how information is arranged on/within the label
    - Layout, physical construction of booklet labels (base panel, booklet, cover page, and removable panels)
        - Good Practice Solutions
        - Alternative Designs
    - Graphical elements, such as pictograms
    - Font Size

Through the publication of the Booklet Label Good Practice Guide, a reference source will be available for companies or individuals responsible for generating and using booklet labels in clinical trials to create consistent, compliant and user friendly labels.

7 Recommended Training

It is the responsibility of the sponsor to ensure sites and subjects review the booklet label content prior to use of the IMP. Using the Commission Directive 2003/94/EC [2] and Annex 13 to the EU Guidelines to GMP as a reference:

- The sponsor (or designee) should appropriately train all personnel involved with the handling of the IMP on the use of booklet labels and ensure understanding of the label contents. Personnel includes, but not limited to: investigators, study staff, pharmacist, and monitors.

- The sponsor should review the label contents to personnel and also instruct the site personnel to complete the empty fields on the label with the relevant information.

More importantly ensuring the sites and subjects are instructed in the label contents will result in better compliance with the protocol and more consistent results overall.

Prior to the first subject enrolled in the study at the clinical site, the sponsor or designee (in many cases this will be the monitor), is responsible for reviewing the label contents with any personnel that are providing prescriptions, dispensing, and or administering the IMP directly to the subjects. The personnel that have direct contact with the subjects when dispensing the IMP should instruct the subject on the content of the label.

In addition, it is recommended that documented evidence of the label content reviewed and understanding of the label content for both site staff and staff responsible for dispensing IMP to the subject is kept.

8 Conclusion

Through evaluation of the benchmarking, site survey, and an assessment of booklet labels versus single panel labels performed, it is concluded that booklet labels are considered to be a useful, GMP compliant, and cost efficient information tool for the concerned parties such as pharmaceutical and clinical personnel of clinical study sites as well as subjects receiving the investigational medicinal product.

It has been shown that there is a great variability in the design and phrasing styles of booklet labels. A certain degree of standardization of the booklet structure has been recognised as helpful and therefore recommendable for both the pharma industry and the recipients of the investigational medicinal products. A detailed outlook on the objectives and the benefits to be achieved by a standardization initiative has been given.

Training of booklet usage has been proven to add a relevant contribution to the appropriate use of study medication and should form an integral part of considerations on standardization and improvement processes of booklets.

This concept paper forms the basis for the ISPE IP COP Booklet Label Task Team to develop a Good Practice Guide for Booklet Labels, for standardization of Booklet label content and form, for improvement of user friendliness, as well as for recommended training including documentation.

9 References

1. EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13 Investigational Medicinal Products.

2. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.

3. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

4. 21 CFR 312.6 Labelling of an Investigational New Drug.

5. ICH E6 5.18.4.

6. *ISPE Good Practice Guide: Interactive Response Technology*, International Society for Pharmaceutical Engineering (ISPE), First Edition, November 2011, www.ispe.org.

Appendix 1 – Site Survey Booklet Label Questions and Responses

Questions and Responses	% Response
1. Have you encountered Booklet Labels	
• Yes	37%
• No ***Note:*** *"No" respondents did not proceed with the rest of the questionnaire*	63%
2. Indicate below the answer which best describes how you were trained on the use of booklet labels	
• Training received at Investigator Meeting	32%
• Training received at Initiation Visit	45%
• Pharmacy manual	24%
• Other Please specify	4%
• No training provided	35%
3. In addition to the Investigational Product label, what other reference sources are provided by the sponsor which gives guidance on the use/storage of the product? ***Note:*** *Most respondents cited more than one additional reference source. Most prevalent combination was IB/Protocol and Pharmacy Manual*	
• Protocol	29%
• Pharmacy/Training Manual	20%
• Investigator Brochure	19%
• IP Instructions/Card/Template	9%
• Investigator Meeting and Site Training	5%
• Release documentation e.g., QP Release Note, Certificate of Analysis	4%
• Product Monograph/SPC	3%
• Clinical Trial Site File	3%
• CRA/Monitor	2%
• None	4%

Questions and Responses	**% Response**
4. Do you demonstrate/review the booklet label with study subjects? Do you do this with each dispensing activity or only initially?	
• Yes – Initially	40%
• Yes – With each Dispensing	39%
• No – we do not. 23 responses received - Research nurse provides meds /explanation to subjects (8/23) - Not applicable – don't see subject (6/23) - upplemental info/labeling provided (4/23) - Booklet too complex and text too small /not useful (3/23) - Other (2/23)	21%
5. Do you instruct the study subject to open and read the booklet label? Do you confirm they have read it?	
• Yes – I instruct the subject – Don't confirm	26%
• Yes - I instruct the subject – do confirm	44%
• No – I do not usually instruct the subject	30%
6. Do you rely on the container label to be the primary source if product information or do you provide the study subject with other reference information?	
• Use label as primary source of subject information	45%
• Use other forms of reference in addition to the label (explain e.g. leaflets, diaries etc) – 30 responses received. ***Note:*** *a number of respondents cited more than one additional reference source* - Diaries (7/30) - Verbal explanation (7/30) - Supplemental labeling (7/30) - Informed consent(3/30) - Leaflets(3/30) - Other (3/30)	55%
7. What challenges do you most frequently encountered when using booklet labels?	
• Information is not clearly positioned or structured	29%
• Information on cover page is not sufficient (what is missing – explain below) - Relevant language should appear on top of booklet label - Administration information should appear on cover page - Drug name and storage condition should appear on cover page - Layout satisfies regulatory requirements but is unfriendly to patients	16%
• Information is hard to read (print font too small)	78%
• Kit ID/Container Number is not obvious	31%
• Other – please explain below - Not always easy to locate the right language - Too many pages to search through - Can be awkward to open sufficiently to read contents - Can lead to serious safely issues	9%

Questions and Responses	**% Response**
8. Do you receive complaints from study subjects related to booklet labels?	
• Yes (please explain why below) - Font size too small – too hard to read text (7/17) - Label too bulky – interferes with DP use/accidentally torn off once opened ***Note:*** *7 of 17"Yes" respondents indicated they were not in a position to provide a response*	17% *(10% – See Note)*
• No	83% *(90% – See Note)*
9. Have you observed any impact on study subject compliance when using a booklet label versus a single panel label?	
• Yes (please describe how compliance was impacted) - Single panel more clear for patient - Text too small to read and sometimes no detail of how to use - Patients can get confused leading to poor compliance ***Note:*** *6 of 10 " Yes" respondents indicated they no patient contact and so were not is a position to provide a response*	10% *(4% – See Note)*
• No	90% *(96% – See Note)*
10. How might we better meet your needs and expectations regarding clinical trial supplies? (Booklet Label related comments included only)	
No column/space to indicate serving instruction (i.e., no. of tablets to take, frequency) Wordings are too small, esp. container number, batch, and expiry.	
Study medication is labelled in accordance with internal guidelines in order to ensure patient safety and appropriate oversight. In the case of some study medication, this requires removing the original booklet, and thereafter taping the country specific information page (from booklet) and a separate label with information necessary for medication control (batch number, expiry, Patient UPN) to the medication bottle. This process is inefficient and also does not present the medication to the patient in a professional form	
Spacing of information – clearly displayed – not too close – one label.	
We need larger letters on label	
Usually make a leaflet to instruct subject. It's useful to instruct how to take medication to the subject, especially elderly subject. In the leaflet, I can manage the size of font and make an instruction more easily and understandable.	
TGA Australia Annex 13 GMP labelling recommendations are the minimum standard. However, drug name (or placebo) should appear clearly on the label. This is not always the case.	

Appendix 2 – Assessment Booklet Label versus Single Panel Label

				Single Panel Label	***Booklet Label***
Number	**Scenarios Assessed**	**Causes**	**Possible Impact**	**Mitigation**	**Mitigation**
1	Site and/or subject cannot interpret or understand information on **cover page** of label	• Subject and/ or site staff do not understand references on cover page • Confusing design • Cover page of booklet written in English (relevant only for booklets)	• Wrong IMP dispensed (e.g.,strength, treatment) • Labels perceived as non-compliant labels • Non-compliant storage of product	Not applicable	a. Include guidance on how to design a user friendly booklet label in Booklet Label Good Practice Guide b. Training of site personnel c. Review and verify information on the label with subject to explain the set-up of the label
2	Site does not understand information on label	• Content is described in a way (e.g., abbreviations) that site does not understand • Font size too small • Does not understand language visible on the label	• Site may not know how to use and/or store the IMP • Site may not deliver the IMP to the Subject • Site may not be aware that they do not fully understand (difficult to detect)	a. Training of site personnel b. Include particulars on self-explaining pictograms in Booklet Label Good Practice Guide c. Include particulars on the definition of minimum font size in Booklet Label Good Practice Guide	See mitigation single panel label.
3	Subject does not understand information on label	• Content is described in a way (e.g., abbreviations) that site does not understand • Font size too small • Does not understand language visible on the label	Subject may not know how to use and/or store the IMP	a. Obligation of site personnel to review the label with the subject and to confirm subject understands the contents b. Include particulars on self-explaining pictograms in Booklet Label Good Practice Guide c. Include particulars on the definition of minimum font size in Booklet Label Good Practice Guide	See mitigation single panel label.
4	Subject cannot find language	No indication or unintelligible information available where to find label text in different languages	• Subject does not know how to use the IMP • does not know how to store the IMP • cannot provide emergency information	Not applicable	a. Include guidance on the usage of booklet labels in Booklet Label Good Practice Guide b. Training of site personnel c. Review label with subject to explain the set-up of the label

				Single Panel Label	*Booklet Label*
Number	**Scenarios Assessed**	**Causes**	**Possible Impact**	**Mitigation**	**Mitigation**
5	Subject does not read the information on the label	• Lack of understanding of the importance of information. • Font size too small	• Subject does not know how to use the IMP • does not know how to store the IMP • cannot provide emergency information	a. Review label with subject to explain the set-up of the label; site to ensure proper understanding of IMP use by the subject (either by supplemental or a dialog) b. Subjects receive additional IMP information via e.g., informed consent, subject card or leaflets c. White paper 3.5 – Sponsor training of site, obligation of site personnel to review the label with the subject d. Include particulars on the definition of minimum font size in Booklet Label Good Practice Guide	See mitigation single panel label.
6	Label and/or information on label is damaged during transport and use	• inappropriate quality of labels (e.g., construction, print quality, laminate, color • inappropriate packaging design • Shipment package not optimal	Information not available/readable for subject and sites: • do not know how to use the IMP • do not know how to store the IMP • cannot provide emergency information	a. Include guidance on the contents of the base label in Booklet Label Good Practice Guide b. Sites are instructed to report damaged IMP/ labels to Sponsor	See mitigation single panel label.
7	Subject and site remove single pages out which they do not consider applicable	Information not clear how to use the booklet	• IMP may be unidentifiable (in case of emergency) • Reconciliation of IMP at site may not be possible • May accidently tear-off the cover information, and therefore remove IMP identification	Not applicable	a. Include guidance on the contents of the base label in Booklet Label Good Practice Guide with information necessary in order to identify IMP b. Training of site personnel not to tear-off any pages of the booklet label c. Include guidance on how to design a user friendly booklet label in Booklet Label Good Practice Guide
8	Booklet on primary container is removed by the subject	A relatively thick booklet is not considered handy	• IMP may be unidentifiable (in case of emergency) • Reconciliation of IMP at site may not be possible	Not applicable	a. Include guidance on the contents of the base label in Booklet Label Good Practice Guide b. Training
9	Inappropriate label design	Multiple sponsors; no guidance for label designs	Confused sites and subjects	a. Applicable, however more straight forward to resolve and not part of Booklet Label Good Practice Guide	a. Include guidance on a standardized and user friendly label design (including an appropriate design) in Booklet Label Good Practice Guide

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