Clinical Trial Labelling – more than just labels

Deciding which label is best for a particular trial project is not always easy. Labels have become multifunctional tools which are able to convey variable data in different languages, indicate first opening, product originality, support ease of use or blind study drugs. They are no longer used as mere carriers of specified contents.

Legal bases

In the European Union, label contents are specified in Annex 13 to the Guidelines whereas structure and other aspects such as layout, font size and symbols are defined in the *Guideline on Readability.* Clinical trials in the US have to meet the requirements of the *Code of Federal Regulations*.

Several countries, different languages

Clinical trials are usually conducted in several countries. The labelling of investigational medicinal products has to accommodate an increasing number of languages. Labels may have to be printed in up to 40 different versions. Each language is having its own label, this means having to produce 40 label variants in the volume required before applying and distributing them. The paperwork involved is immense: separate batch documentation is required for each label version. If the medication labelled accordingly is not available for a particular country. Then significant delays will affect the distribution until subsequent production can ultimately ease the bottleneck. Re-using medication that has already been labelled but is no longer needed will require an equally high amount of time and effort.

Multilingual booklet labels with index

Another option is to integrate several languages into a single product. This can be achieved by using booklet labels, now available in up to 113 pages. These provide an all-purpose solution that can be applied in every country. Booklet labels are a combination of self-adhesive labels and leaflets. Thanks to their large volume, they can accommodate all languages in a clear structure and readable font size.

In April 2013, ISPE (International Society for Pharmaceutical Engineering), a non-profit association operating worldwide, published a new guide for standardizing the use of booklet labels in global clinical trials. The purpose of this standardization is to establish a uniform design and a universal structure for booklet labels across markets. In addition to tables of contents, thumb indexes can help users find their way through booklets. Direct access to user-specific data is to be facilitated by intuitive handling, which enhances patient compliance durably. High compliance has an immediate and positive impact on the validity of the studies.

Unusual shapes

Labels should always match the shape of primary packaging. For instance, vials, pens, syringes and inhalers can be labelled in different ways. Wrap-around labels – regardless if they are a one-layer, multilayer or booklet label – are particularly suitable for small-diameter cylindrical containers. Wrapped around cylindrical bodies several times, these labels can be resealed after each opening.

Unusual shapes tend to require a high level of creativity, know-how and experience from label manufacturers. Departments dealing with research and development are therefore becoming increasingly important. Labels are developed individually and tested for criteria such as adhesion and adaptability as well as user-friendliness. Label performance during application can be simulated at Faubel or tested at the drug manufacturer's facilities.

Booklet labels are often enhanced by additional functions. For example, booklet labels are supplemented by one or several documentary stickers to provide complete and accurate documentation, for example in patients' medical reports. Another way of optimising the subsequent use of investigational products is to integrate a hoop into the label itself for hanging an infusion bottle. The Hanger Label offers improved ease of use.

Tamper-evident features

A label can fully or partly cover the area around the mouth of the container. Opening the product will damage the label badly and make tampering clearly visible. So staff or customers are able to assess the integrity of trial products.

Child-resistant packaging

Whenever subjects take home drugs, there is another type of security to be considered by the pharmacist. Child-resistant packaging should protect children against improper use. Depending on the type of primary packaging used and the level of safety required, there are different ways of securing packaging. As a matter of example, blister packs can be covered with labels. Blister-label combinations contain mechanical and logical barriers which make them child-resistant on the one hand, but easy enough for adults to open, on the other.

Material properties

Investigational products are usually stored in cool places or even temporarily frozen. As a result, product labelling must be capable of withstanding temperatures as low as -196°C without damage while retaining full adhesion and legibility after the trial products are heated. To exclude label deterioration caused by water, grease or chemicals right from the start, it is recommended that synthetic materials be used to manufacture labels.

Printing variable data

Ultimately labels primary purpose is to convey information. Printing variable data is a time-consuming task. Personalised data is, however, not specified until very shortly before drug labelling takes place. This is why some label manufacturers tend to offer variable data printing at short notice.

The GMP Guidelines are complied with by using validated software, stand-alone camera inspection, non-contact printing systems and trained staff when printing variable data. A possible source of error can be eliminated by replacing faulty labels during printing in order for pharmacists or contract packers to process label reels of a consistent quality. UV-inkjet print technology delivers high-quality print with outstanding surface adhesion and high light fastness. Besides, UV-inkjet prints are highly waterproof, alcohol-resistant as well as wear-, scratch- and smudge-proof. The quality of such prints will not even be affected by temperatures as low as -196°C.

Data routing

If trials are to be international and the participating countries are supposed to only receive the pages pertaining to them, label manufacturers often compile the country-specific contents and obtain the corresponding approvals. A weekly or monthly overview of the current project status will give medicine manufacturers the transparency they need.

Blinding clinical trials

Pharmaceutical manufacturers sometimes face the challenge of having to blind their study drugs adequately to make sure that trial investigators, nursing staff,

participating patients as well as the persons in charge of handling the data are unaware of the treatment administered to individual patients. Unwanted biases can only be avoided in this manner.

Some blinding solutions can only be used for single-blind trials, some others for double-blind trials. They may be completed with various options such as Braille embossing, variable data, security features such as tamper-evident features or a code-break function, and documentary sections.

The type of product selected for blinding depends on the primary packaging of the study drugs. Vials, bottles, pots, jars and tubes can be fully covered. Optimal blinding can make the time-consuming colour matching between liquid placebo and active substance unnecessary.

Pharmacists and contract packagers often use labels to blind tubes, jars or pots. Once labels are glued on tubes, it is impossible for trial staff and volunteers to tell the placebo from the active substance.

Blinding boxes

Vials can be blinded by using boxes made of opaque and robust cardboard. As a result, the volume and the height of the containers as well as the colour of the contents are entirely masked and therefore unidentifiable. Boxes can be printed on the inside in colour in order to give the active substance and the placebo groups the impression that both trial products are the same colour. Furthermore, a control window can be added to these boxes. If it needs opening for some reason, it will become immediately visible. In addition to the blinding box, there is another option featuring an opaque or a transparent plastic cup with a separate lid, into which the container to be masked is placed. Finally, the cup can be partly or completely covered with a label. Placed directly across the opening area, the label can, at the same time, fulfil a tamper-evident purpose.

If trial-specific data needs additional masking, printable laser fields, scratch areas and sections with code-break function can be subsequently incorporated into the secondary packaging.

A compact solution

Labels traditionally used as secondary packaging for trial products have changed into flexible, though compact, multifunctional tools. Increasing demands on quality and user friendliness, shorter lead times in development and production describe the significantly general conditions of clinical trial labelling.

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