Behind the Mask

With blinding requirements for clinical trials continuing to grow, primary and secondary packaging and labelling must become ever more sophisticated to help mask the shape, size, colour, texture, weight and taste of drugs being tested – helping to restrict bias and improve study compliance

Frank Jäger at Faubel

About 5,000 clinical studies are initiated every year. Drug candidates are tested in the form of capsules, tablets, drinking solutions, salves, injections, sprays and even plasters, depending on the area of application. In addition to the product under study, participants may receive a placebo, a comparator, and an additional or substitute drug – for preventative, diagnostic or therapeutic reasons.

Figure 1: The success of a clinical trial is improved by first-class blinding for the study medication

The manufacture of investigational medical products for research-based pharmaceutical companies and CROs is viewed as more extensive than that of approved drugs (1). According to the European Directive Annex XIII, this is due to the lack of routine, the variability of the study design within the various phases of the clinical trial and the packaging processes associated with this, as well as the randomisation and blinding.

Generally speaking, blinding serves to avoid unwanted influencing. The varied assessment of treatment results – often labelled as informational, judgement or ascertainment bias – is thus restricted.

Furthermore, blinding can improve compliance in study participants and their willingness to remain in the trial, while reducing the use of additional care or treatment measures (2).

Either the primary packaging masks the shape, size, colour, texture, weight, smell and/or the taste of the drugs, or the secondary packaging assumes this task. Blinding is a substitute for repackaging, which is often not possible. This may, for example, be the case if sterile filling cannot be ensured during the repackaging, or if use requires the original packaging, as is the case with an inhaler.

Single or Double Blind

Blinding can take place on a single- or double-blind basis; the term triple-blind is also used occasionally. The degree of blinding is determined by whether individual or multiple participants in the trial are unaware of the allocation of test subjects to treatment or control groups (1).

Single blinding involves test subjects not being informed about the assigned intervention, while double blinding means that the trial physicians, the nursing staff, the monitors and,

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sometimes, the data analysts have no knowledge of the identity either. If the individual treatment allocation/ randomisation list is disclosed, this is referred to as an unblinding.

Measured in terms of volume, Germany is the world’s second most important market for clinical studies, behind the US (3). The German Federal Ministry of Education and Research recommends the double-blind study design as the optimum procedure. It stipulates that, where a double-blind study design is not possible, single blinding should be selected, and only in cases where it is not feasible, or it is ethically unacceptable, should the trial be carried out openly. In addition, the reasons for the selected degree of blinding, and the measures for minimising systematic errors resulting from this, should be described in the trial protocol (4). The effectiveness of the blinding should be checked and this inspection documented (1).

Given this complex initial situation, the requirements for the packaging and labelling of study medications are extremely high. Capsules and tablets are often packaged in blisters, wallets or tins, salves in tubes, jars or sachets, drinking solutions in bottles or cans, injections in vials, syringes, ampoules or bags, sprays in aerosol cans or inhalers, and plasters in boxes.

Label Flexibility

Many primary packaging methods – for example, syringes or tubes – can be simultaneously blinded and marked using labels. Not only are labels incredibly flexible in their design, format and scale, but their material and adhesive properties can be adapted to filling, storage and transport conditions. Indeed, labels – with their strongly adhesive glues, special films or resistant colours, among other aspects – can survive contact with alcohol-containing liquids, high humidity levels during application, or freezing in dry ice, without sustaining any damage. This means the blinding measures are spared damage. Film, paper and ink give the package an opaque and light-proof cover.

When it comes to multinational clinical studies, different countries’ languages usually need to be factored in.

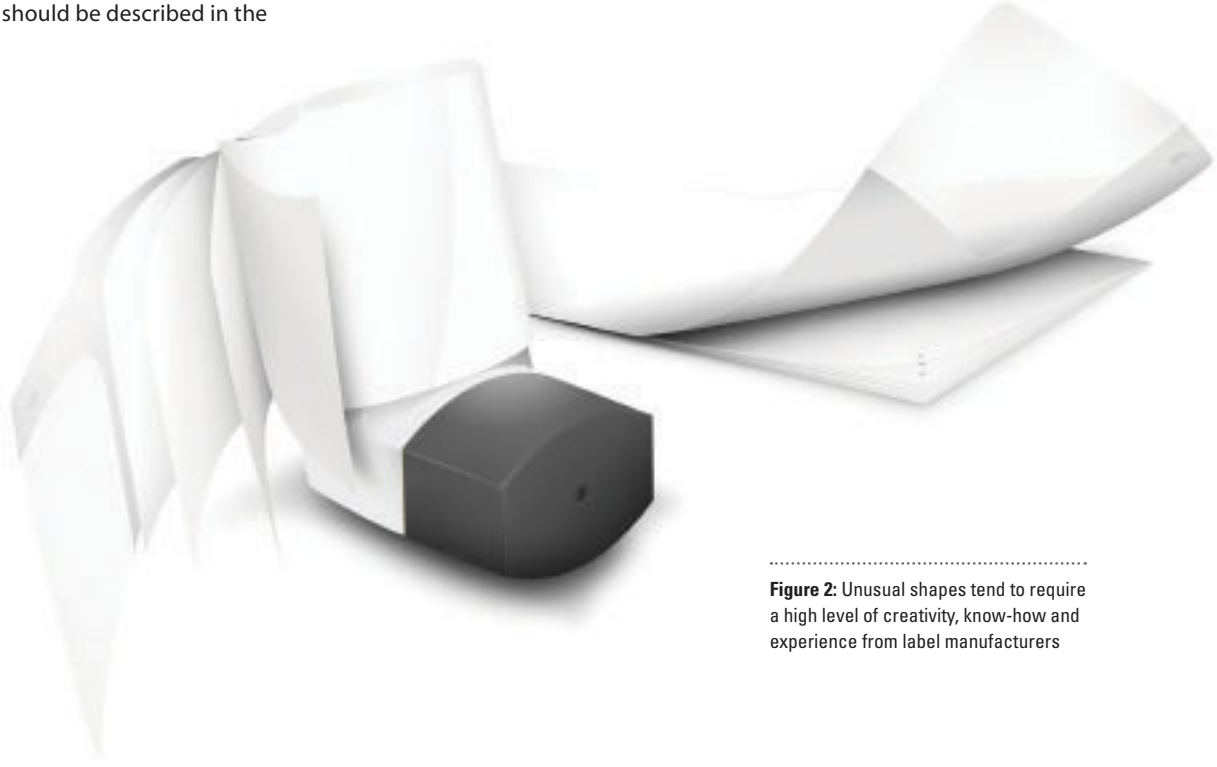

Figure 2: Unusual shapes tend to require a high level of creativity, know-how and experience from label manufacturers

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In this case, the use of a booklet label is ideal – one which can hold up to 113 pages, while still offering quick and wrinkle-free application. If the radius of the primary packaging is very small, neutralisation of the base label in some patches will allow it to be wrapped around the package several times.

Reader-friendly fonts should be used and an index should be added in order to encourage patient compliance. This way, labelling meets the requirements of Annex XIII while being sufficient for all participating countries and/or markets; there is then no need for an extra wallet or box either. The booklet label helps to bring packaging costs and logistical expenditure down, as well as reducing timescales for subsequent deliveries or repeat production.

Secondary Concepts

Regardless of whether single-layer, multi-layer or booklet labels are used to standardise the products, further properties can be added by the secondary packaging:

- Data blinding by using a laser field, scratch field or a code-break function
- Variable overprinting and serialisation
- QR and data matrix codes
- Documentation sections for full and accurate data collection
- Tamper-evident elements and authenticity features
- Child safety and Braille
- Application aids – for example, integrated bands for attaching infusion bottles

Particularly in the case of blisters for tablets and soft capsules, the bottom label layer should be perfectly matched to the aluminum foil, to ensure that the functionality of the blister is not compromised and the drug is not destroyed. The labelling of inhalers poses just as much of a challenge when it comes to accuracy of fit. Their special shape requires a high degree of specific and project-related development work on the part of suppliers.

A label does not always succeed in covering all trial product, placebo or comparator features which require masking. If shape, size and weight are to be disguised for the study participants and the trial staff, overall concepts from various secondary packaging materials are often used.

Consistent Solutions

One less common blinding solution is a concept that consists of a cylindrical plastic container with removable caps at both openings. The cylinder is usually put over the package and sealed with a label on the caps. Participants cannot see the qualities of the internal package. Perforation will cause the individual elements to be separated again – tampering with or initial opening of the blinding concept is clearly visible.

The CRO or pharma company achieves complete masking of shape, size and weight of the primary packaging and the colour of the trial products using tailor-made boxes. These can be used in single- and double-blind studies primarily for cans, vials, bottles and bags. The opaque and rigid cardboard of the boxes allows an insert to provide unseen compensation for a difference in height or volume, and permits the container to be immovably centred.

Product Function

If there is a vial in the box, the cap can be removed by the care staff or trial physician first, before disinfecting the insertion point and then sticking the cardboard together. In this case, clinical trial personnel know about the treatment allocation as soon as the extra blinding is not used for the primary packaging. The trial is therefore single-blind. However, it is also possible that the box has already been sealed upon delivery to the trial centres. Disinfection is not carried out until after the blinding – so the trial proceeds on a double-blind basis.

In both cases, the hypodermic needle can be easily inserted into the package vial due to a small punched-out hole. Another film protects the insertion point from external impurities. This is particularly useful when the fluid in the vial is to be used for more than one injection. A perforated tab in the box is used as an integrated control window. This enables the product to be identified in an emergency. The initial opening is irreversibly visible.

Printing on cardboard can be just as elaborate or simple as printing on a label. In order to prevent any conclusions from being drawn as to the liquid content of the vial, the cardboard box must be printed in such a way on the inside that the colour of all products appears standardised. As with a label, optional properties

can also be selected for the box – for example, a tamper-evident function using seal labels or an attachment band. One advantage of using the box is that it can easily be further processed without using tools or even configuring the packaging line.

Optimum Blinding

Requirements on blinding solutions for clinical studies will continue to grow. The possibilities described cover only a fraction of the day-to-day requirements with which packaging manufacturers are confronted.
It is generally recognised that this increase in regulation, individual customer demands, new materials and innovative technologies are driving the capacity to develop.
After all, only those who can offer their customers sophisticated concepts can guarantee efficiency in blinding and the usability of treatment results – thus saving CROs and pharmaceutical companies effort, time and money on a sustainable basis.

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About the author

Frank Jäger is the Managing Director of Faubel, a German and global provider of solutions for clinical trial labelling that focuses on manufacturing booklets for multinational trials. After completing his studies at the University of Bochum, he held various positions in the medical device industry for nearly ten years. Since joining Faubel in 2012, Frank has played an important role, based on his international experience and following the Six Sigma philosophy, in expanding global activities in the US and Asia. He leads the company's Business Development and Marketing team, as well as R&D.
Email: marketing@faubel.de