A Question of Standards

Packaging investigational medicinal products plays a significant part in patient compliance and, therefore, in the quality of clinical trial results. The labelling of drugs is an equally important and inherent aspect contributing to patient adherence

Nurdan Citamak at Faubel Pharma Services

In 2013, the International Society for Pharmaceutical Engineering (ISPE) launched a survey to analyse the relationship between patient compliance and packaging (1), in which subjects of clinical trials were asked about their experience when applying investigational medicinal products (IMPs). An overwhelming 77% found their medication easy to use. Since the questionnaire was almost exclusively based on responses by patients from the US, it was expanded in 2015 to include the UK, the EU and Asia. The favourable opinion was, again, confirmed: the majority of participants gave positive feedback regarding the overall ease of application of their IMPs – both in the EU (85%) and in China (88%).

The more user-friendly the labelling of IMPs is, the simpler they are to use. This equation takes centre stage considering the growing demand from subjects for medication to be delivered straight to their homes (75% in the EU; 78% in China; 78% in the US in 2013). In contrast to briefing on the phone – which always means extra work for site personnel – dosing instructions on the package are directly and durably attached to the drug. To be accessible, additional digital information usually requires analogue placeholders on the packaging – such as QR codes – which can only be read by means of technical devices. Having functioning hardware and software is, therefore, a prerequisite.

Just-In-Time Labelling

The labelling of IMPs is subject to demands that are specified in the Good Manufacturing Practice (GMP) Guide within the EU (2), and in the Code of Federal Regulations (CFR) in the US (3). They mostly apply to blister packs or bottles as far as the primary packaging of clinical IMPs is concerned, and to labels on secondary packaging. Label content is governed by EU stipulations in Annex 13 to the Guide, with layout, font size and symbols laid down in the *Guideline on Readability* (4).

Images: © Faubel Pharma Services

Image 1: Booklet label: Unusual shapes require a high level of creativity, know-how and experience from label manufacturers

Clinical trials are often conducted in more than one country. According to Annex 13, there is a variety of information to communicate in the official languages of the countries concerned, but it is possible to accommodate each language in a single-layer label (2). In so-called just-in-time (JIT) labelling, this approach is the basis needed to increase both speed and flexibility in clinical supply fulfilment and distribution.

"Pharmaceutical companies are multiplying their efforts to establish JIT labelling. This is only feasible if we can assume that all trial participants, such as sites, clinical trial monitors, local depots, regional distribution centres and, ultimately, contract manufacturing organisations share the same high quality standards," explains Nurdan Citamak, Director of Business Development and Sales North America at Faubel Pharma Services. Yet regarding standards, there is a wide range of requirements to meet first, in order to secure the quality necessary in all supply and distribution chain participants.

Ideal versus Reality

Preferably, verum, placebo and comparator drugs arrive at the depot where they will only be labelled as needed before being shipped directly to the trial site, or even to the subject or patient; the label only contains information that is relevant at that time, and all instructions are exclusively printed in the official language of the recipient country. This process sounds simple, but there are still many uncertainties to resolve. Are IMPs still unmarked when they arrive at the depot? How high is the risk of confusion? Should they already be labelled to allow clear identification, and should extra secondary packaging be readily purchased and applied in addition to the primary packaging? How effective and cost-saving would relabelling be? If one of the participating countries happens to be China, for example, one has to bear in mind that importing unlabelled drugs is prohibited by Decree No. 650 of China's FDA (5).

Regardless of whether IMPs have already been labelled or not, adequate resources should be made available in different areas to ensure final labelling. Further points will then have to be clarified: does the depot have skilled staff that are able to carry out printing and application according to GMP? Are air-conditioned storage areas available for IMPs and bulk goods? Can the technical equipment – from PCs to presses – meet the high demands placed on safety and quality? Is the road network good enough to allow flexible and smooth distribution?
If one of these prerequisites is not met, there may be

Image 2: All types of labels will continue to exist in parallel

unpredictable disruptions within the supply chain. For example, it might be impossible to obtain exploitable trial results because of sloppy documentation triggered by incomplete data transmission to the monitor. This may be caused by incompetent staff; so far, it has not been possible to eliminate mistakes resulting from language barriers entirely, because not every depot worker has a good command of English.

Therefore, documentation, printing and application operations must be checked continuously by internal quality control at the depot. Poor print quality can lead to delays within the supply chain and, in turn, to financial losses for the sponsor. However, it would be much more serious if an illegible number or a blurred printed image in the dosing instructions caused harm to patients' health. Even though print quality is high in all participating depots, the actual print image may still differ. Minor discrepancies occurring when labels are fed into the press could be identified by site staff and subjects as soon as a trial site is supplied by several depots, following logistics bottlenecks.

Blinding Challenges

Labels are often employed both for blinding and marking bottles and blisters. They should be adapted to minimise the risk of unblinding. Reliable blinding solutions presuppose know-how, experience and precision.

In clinical trials, the purpose of blinding is to avoid undesirable bias. Differences in the evaluation of treatment outcomes – often referred to as information, assessment or ascertainment bias – are limited by this. Moreover, it can enhance compliance in study subjects, as well as their willingness to continue participating; it also helps reduce the need for additional care or treatment measures (6).

The shape, size, colour, consistency, weight, smell and/or taste of the medication are either masked by primary or secondary packaging. Blinding is a substitute for repackaging verum medication, placebos or comparator drugs. Repackaging is often impossible if sterile filling cannot be guaranteed, or when the type of primary packaging used – for inhalers, for example – is conditioned by the way the medicine is administered.

Every unusual shape of primary packaging will require custom design and execution. Properties such as adhesiveness, apply capability and user-friendliness should be tested, too. This is why it is the label manufacturer's job to develop a coherent blinding solution, as the most cost-effective and time-saving option is when the label manufacturer also deals with producing and printing labels after the development phase.

Tried and Tested

Until now, booklet labels have been used for labelling IMPs in different languages. Thanks to the large number of pages these labels can contain, it is possible to convey all the

required information in up to 40 different languages in a reader-friendly font size. This way, they can be used in any participating country. In 2013, the ISPE published *Good Practice Guide Booklet Labels* to promote a market-wide uniform design and a universal structure for booklet labels by standardising them (7). Among other subjects, it addresses the topic of font size, which has often been criticised for being too small. The ISPE recommends using points 6 or 7, while the European Commission even considers point 9 as adequate. When you have small-diameter vials, it can be extremely difficult to meet this requirement if you use single-layer labels. Opting for booklet labels seems to be the only solution.

The ISPE survey also investigated the experience of trial participants with booklet labels. Only 23% of European patients surveyed actually saw one; 45% opened it; 54% were able to view their language quickly; and font size was deemed adequate by 71%. Among the Chinese subjects, 41% took notice of the booklet label; more than 80% opened it; and 75% were able to find their way through it easily.

The demand for comprehensive information is growing. For the time being, it is met by booklet labels; however, there seems to be room for optimisation in user-friendliness. This is why it is strongly recommended to add clearly visible arrows, as well as partly rough or rubberised surfaces to the opening section. Such visual and tactile features draw attention to the content fitting on several pages. Furthermore, these surfaces give users a good grip – especially with IMP bottles. The special design of the easy-peel opening section also helps when separating individual layers in the label; once the label is open, a thumb index can be employed to facilitate navigation through the booklet. The index can be presented in contrasting colour so that the user is able to quickly get to the relevant section, and pictograms or QR codes linked to user videos can be viewed as text supplements alone. All of these significantly enhance patient compliance.

Booklet labels are often enriched by other features – for example, integrated brackets for hanging infusion bottles or detachable documentary sections. The self-adhesive part usually carries trial-related data and supports accurate documenting in patient reports. It is even possible to add documentary stickers to booklet labels designed for vials. Once the safety aspect of the documentation is satisfied, further protection can be achieved by incorporating a tamper-evident feature. Labels with such a function guarantee the integrity of IMPs by sealing the opening area of the primary packaging. Attempts to tear it open would cause so much damage that site personnel and subjects could easily identify any type of tampering. This development in booklet labels is driven by users' needs. Patient compliance has improved greatly, and the quality of clinical trial results is maintained as a result.

High Standards

Given the extensive demands placed on labelling, the standards required for JIT labelling can neither be implemented in every single depot, nor in every single participating country. Expectations on depots are high because they have to be – but it is unrealistic to think that they can quickly catch up with the standards of secondary packaging manufacturers and contract manufacturing organisations that have been optimising them for decades. In the transition period, JIT labelling seems to be unable to compete with the quality of conventional labelling.

Booklet labels are irreplaceable for small containers like vials. When it comes to blinding, cooperating with a label specialist is the most effective way to proceed. Both processes have their place and will continue to exist in parallel, and both will continue to develop. In recent concepts, analogue and digital elements are combined in booklet labels: such hybrids also make late-stage customisation possible.

References

1. **ISPE, Report on the ISPE project concerning patient experience with clinical trial materials, 2013**
2. **European Commission, EudraLex, The Rules Governing Medicinal Products in the EU, EU Guidelines to GMP Medicinal Products for Human and Veterinary Use, Annex 13 (3), Volume 4, 2010**
3. **US FDA, CFR Title 21, Part 210-211, 1978**
4. **European Commission, Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use, Revision 1, 2009**
5. **China FDA, Decree of the State Council of the People's Republic of China No. 650, 2014**
6. **Schulz KF and Grimes AD, Verblindung in randomisierten Studien: Wie man verdeckt, wer was erhalten hat, *Reihe Epidemiologie* (8): p630, 2002**
7. **ISPE, Good Practice Guide Booklet Labels: pp18-19, 2013**

About the author

Nurdan Citamak joined Faubel Pharma Services in 2013 and was appointed Director of Business Development and Sales for North America. She graduated in Business Administration from Würzburg-Schweinfurt University, Germany, and majored in International Business at Bond University, Australia. Prior to joining the company, Nurdan spent nearly seven years in New York working in the technology industry.

Email: n.citamak@faubel-ps.com