

Improving Patient Compliance in Clinical Trials Smart Packages or Smart Design?

By Martin Lamb, Head of US and EU Business Development at Clinical Trial Services

Martin Lamb received a BSc in Pharmacology from the University of Leeds and has postgraduate qualifications from Queen's University, Belfast and the Chartered Institute of Marketing. He began his career in 1992, working in marketing communications for a pharmaceutical marketing communications consultancy and a clinical diagnostics company. He arrived at Clinical Trial Services in 1996, working in their business development department, and in 2001, he became Vice President of Business Development.

For marketed products in the US, poor compliance with treatment regimens is estimated to cost the health care system around \$100 billion each year. More than 100,000 patient deaths and one million hospital admissions each year, in addition to increased antibiotic resistance, are believed to be due to poor patient compliance. The cost of poor compliance in clinical trials is equally serious. Data from non-compliant patients can affect trial results to such an extent that they can make or break a candidate drug. While measures are in place to monitor compliance and avoid this (paper diaries and pill counting, for instance), these are far from perfect.

Many of the reasons for poor compliance are especially applicable to clinical trials (see Table below). Packaging designed to improve production efficiency rather than patient compliance can add to the problem. Designing packs with the patient in mind has proven benefits in improving compliance. New RFID-based technology provides tools to accurately measure compliance and can even remind patients to take their medication. While both of these approaches can potentially add to the cost of clinical trial medication, we need to consider the cost of poor compliance when making packaging decisions. The cost of packaged drug for clinical trials accounts for less than 10 per cent of the cost of a trial. By overlooking patient-compliant packaging, are we gambling the other 90 per cent of costs in favour of an incremental reduction to a minor portion of our total spend?

DESIGNING-IN COMPLIANCE

Many of the reasons quoted below for poor compliance are especially applicable to clinical trials. The reasons for this are stated in the table below. Many of these can be addressed through the design of clinical trial packs.

Choice of Blinding Method

For double-blind clinical trials, it is often necessary to blind products by over-encapsulation. While product size often dictates the size of capsule chosen, it is important to choose the smallest capsule size possible. The larger a capsule is, the more difficult it is to swallow and the more likely it is for compliance to become an issue. Double-dummy designs can also increase the number of units a patient needs to take each day. In addition, a double-dummy trial can increase the complexity of a dosage regime, especially if bottles are the chosen packaging form (see below). As discussed in Table 1, complex dosing is a key cause of non-compliance.

Packaging Materials

Packaging materials can have a huge impact on the size of the finished pack and the ease with which patients can remove medication. This is particularly true in the case of blister packaging materials. This point is demonstrated by the use of coldform (alu/alu) and thermoform packs. For moisture-sensitive materials, it is common for standard coldform materials to be used in clinical trials. Due to the forming characteristics of this material, blisters are significantly larger than the equivalent blisters in thermoform materials. While this may not present a huge problem for commercial packs, for clinical trials (especially double-dummy) where multiple doses are presented in the same pack, the resulting blister packs can be huge. Choice of a high-barrier thermoform film such as Aclar could afford similar product protection, while at the same time improving compliance by providing the patient with a smaller, more convenient pack.

Improving Patient Compliance in Clinical Trials

Table 1

Reason for Non Compliance	Relevance for Clinical Trials/Possible Solutions
PATIENT-RELATED	
Misunderstanding of prescribing instructions	<p>Are clinical trial labels designed to meet regulatory requirements, or to aid the patient? Has the investigator/pharmacist been trained in correct use of medication by the sponsor? Has this been relayed to the patient during visits?</p>
Denial/embarrassment	<p>Patients may feel that a large, indiscreet pack advertises their ailment to others. Drug may be removed in advance and transferred to other containers, affecting compliance.</p>
Forgetfulness	<p>In calendar-type blister packs and cards, it is more obvious to the patient whether or not they have taken their medication at the correct time. Is there any kind of follow up to remind the patient to take their medication as directed?</p> <p>Smart packaging or use of an IVR-based diary solution (for example, as provided by Interactive Clinical Technologies Inc (ICTI) or Clinphone) could help.</p>
No faith in drug's effectiveness	<p>This may be especially true in a clinical trial, but may be addressed through investigator counselling and other forms of patient education.</p>
Reduction, fluctuation or disappearance of symptoms Apathy	<p>Not specific to clinical trials.</p> <p>Patient education programmes are becoming commonplace in encouraging patients to participate in clinical trials and can help alleviate this.</p>
PHYSICAL DIFFICULTIES	
Swallowing tablets or capsules	<p>Blinding products by over-encapsulation can result in large unit doses that may affect compliance.</p>
Opening packages	<p>Small packs/medication units can be difficult for elderly patients to manipulate. Some blister designs (for example, alu/alu) can make it more difficult to remove medication. Large packs are inconvenient. Patients may remove drug and transfer to more convenient packaging, affecting compliance. Child resistant packages are generally more difficult for patients to open.</p>
DRUG RELATED	
Adverse events	<p>Not specific to clinical trials, though patients may be more suspicious of adverse events if they do not know what they are taking. Patient/physician education can help.</p>
Complex regimens	<p>Especially true in clinical trials when comparator products and double-dummy designs are used. These cause the number of units taken each day to increase.</p>
Inconvenient or restrictive precautions	<p>Not specific to clinical trials, though they could be amplified if insufficient knowledge of the trial medication leads to an 'avoid everything' approach.</p>

Blisters Versus Bottles

Packaging in bottles offers significant financial and timeline advantages over blister packing. Unfortunately, this gain can be offset by the negative impact on patient compliance. Blisters provide the patient with a visual aid to taking their medication correctly. In addition, graphics and dosing instructions can be incorporated into the blister to further aid compliance. From a doctor's perspective, it is far quicker and easier to assess compliance through the presence of unused medication present in a blister card than to start counting leftover tablets in a bottle. This makes the process of identifying, and acting on, poor compliance much easier. Several clinical trials have shown that compliance in blisters is superior to that in other forms of packaging (1,2,3)

Clear Labelling

Multilingual booklet labels are used increasingly for multinational clinical trials, largely because they maximise the utilisation of product by avoiding the need to make it country-specific. Booklet labels have been both praised and criticised in terms of their contribution to patient compliance. Careful design of these labels, however, can avoid compliance issues.

Improving Patient Compliance in Clinical Trials

- Use an index to enable patients to locate their language quickly
- Make the most of the extra printing space afforded by the multipage design. Use larger fonts to convey important information
- Consider the information needs of the patient when writing label text – not just the minimum requirements of the regulators in a particular country
- If a particular country is resistant to the use of booklet labels, place their language at an easy-to-find location (such as front or back page)

Child Resistance and Patient Compliance

In the US, clinical trial medication must be presented in child resistant and senior friendly packaging. While it is easy to make a pack child resistant, there is a fine line between making a drug too accessible to children and making it so difficult to remove from the pack that it may affect compliance. The difficulty in making blisters child resistant has further reinforced the position of bottles as the clinical trial package of choice, despite the advantage of blisters as described above.

User-friendly child resistant blister designs are available on the market. For example, MeadWestvaco's Dosepak is widely used for packaging both marketed and clinical trial products. It offers an easy-to-use child resistant design. In 2003, the Healthcare Compliance Packaging Council awarded its compliance package of the year to a pack employing this design (P&G's Actonel 35mg). Other child resistant mechanisms used with blisters include Keystone Packaging's KeyPak F1 and labels that can be fixed to the back of blister packs to add an additional barrier to removing medication. While all designs meet the standards required by the Regulators, the user-friendliness of these designs varies greatly. Careful consideration of the patient population in a clinical trial should be made when selecting the type of child resistant pack to be employed.

NEW TECHNOLOGIES – SMART PACKAGING

The introduction of RFID-enabled computer chip technology has introduced the possibility of monitoring that a patient has taken medication, and when the medication was taken. Technological advances (for example, conductive inks) mean that these packs look the same as standard packaging to the patient, and can be produced using standard packaging equipment.

Smart Blister Packs

Examples of smaller blister packs include:

- Med-ic ECM (Information Mediary Corporation, Canada)
- Cypak (Sweden) and Cerepak (MeadWestvaco, US Licensee)
- Medicaid (Bang and Olufsen, Denmark)

While the exact mechanisms employed by the above packs vary slightly, they work on the principle that removing medication from a blister breaks the flow of current to a microprocessor. This break in the current is recorded as an event, and the date and time of each event is recorded by the microprocessor. When a patient returns their package to the physician, information from the microprocessor can be downloaded onto a PC using a wireless RFID reader. The physician can then make an instant assessment and, if necessary, work with the patient to improve compliance. Information can also be uploaded to a secure website where it can be used in subsequent data analysis by the CRO or study sponsor.

Further enhancements to these systems include the addition of alarms to remind patients to take medication through the audible or visual alerts, or even through digital means (SMS messages, emails). It is also possible to include an integral electronic diary/questionnaire pad that prompts the patient to enter information on adverse events or quality of life scores at the time of taking their medication.

MEMS Caps

This system is based around the inclusion of a microprocessor in a bottle cap. When the bottle is opened a mechanical spring mechanism is activated, completing an electronic circuit and recording an event. The cap records the time and date of each event. MEMS caps cost from \$50 for MEMS IV caps and from \$84 for MEMS six caps. To minimise the number of these required for each trial, pharma companies often supply only a single cap/set-of caps per patient. These are re-used each time a patient is re-supplied during follow-up visits. As with smart blister packs, the MEMS system requires the use of appropriate software and readers.

Improving Patient Compliance in Clinical Trials

Information gained from this type of pack will give a clear picture of when the drug was removed from a package (but not necessarily when it was taken). As a result, they give a clearer picture of compliance than traditional methods, such as pill counting and paper diaries that do not record the time of dosing. This information is available to the physician, allowing them to target counseling and other measures specifically at non-compliers. It also allows poor compliers to be eliminated from the final trial analysis, removing the possibility that trial results will be compromised.

There is limited evidence of early adoption of this new technology by most pharma and biotech companies for clinical trials. One of the major reasons cited is the cost of the technology. While it is true that a Smart package costs significantly more than a standard blister card (such as the Cypak device costs \$20-\$30 each from US licensee MeadWestvaco (4)), careful consideration of how these devices are employed can help minimise the risk of poor compliance, while still keeping costs under control. For example, if Smart packaging is used during the run-in/screening period of a trial, non-compliers can be identified before they are enrolled into the main study. Standard packages can then be used for the remainder of the treatment period. While this approach does not eliminate non-compliance, it greatly reduces the risk of this problem without the need to use higher-cost packaging for the full duration of the trial.

It can be argued that Smart packaging identifies poor compliance after the event – too late according to some. Rather than being used as the sole method of improving compliance, Smart packaging should form part of the armoury of compliance-improving measures available to trial sponsors.

THE FUTURE

The real power of Smart packaging technology is that it has the potential to increase the statistical power of clinical trials. Through use of this technology, clinical events can be tied precisely to medication use history. Data captured through Smart packaging can be integrated with data collected through other sources such as EDC, patient diaries (paper- or IVRSbased) and that collected by physicians.

The key reasons for not using this technology remain cost and the time it takes to implement. As the above technologies become more widely used, the price of the technology will drop through economies of scale and increased competition as newer devices enter the market. Even if a sponsor company has no short-term plan to begin using Smart packaging, it should not be ignored. As mentioned above, the real power of compliance data will be realised when it is integrated with other data collected from clinical trials. This integration process will not happen overnight, so the potential use of the Smart packaging should be borne in mind when planning long-term data capture strategies for clinical trials.

As discussed above, monitoring technology records compliance rather than encourages it. It allows poor-compliers to be recognised and corrective actions to be taken. However, it is not a complete replacement for measures such as good pack design and physician-patient relationships. Good compliance can, therefore, only be achieved through a combination of the tools available. This is best summarised by Jo Carol *et al.* “The most reliable method for research purposes, although not practical in a clinical setting, may be a combination approach that includes pill counts, patient self-report, and electronic monitoring (5)”.

The author can be contacted at martin.lamb@cts-almac.com

References

1. Huang HY *et al*, Impact of pill organizers and blister packs on adherence to taking in two vitamin supplementation trials, *Am J Epidemiol*, 152 (8) pp780-787, October 2000
2. Simmons D *et al*, Can medication packaging improve glycemic control and blood pressure in type 2 diabetes? Results from a randomized controlled trial, *Diabetes Care*, 23 (2), pp153-156, Feb 2000
3. Wright JM *et al*, Evaluation of the use of calendar blister packaging on patient compliance with STD syndromic treatment regimes, *Sex Transm Dis*, 26 (10), pp556-63, Nov 1999
4. WWW. idtechex.com/smartheatkcareuse/4.asp
5. Carol J *et al*, Patterns of Adherence to Antiretroviral Medication, The Value of Electronic Monitoring, *AIDS*, 17 (12), pp1,763-1,767, Oct 2003