Contract Clinical Trials Packaging

Setting the Stage for Clinical Trial Success

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In the vastly expensive process of bringing a new drug to market, the cost of clinical trials packaging is miniscule. Yet, this seemingly minor component of the drug development operation bears impressive responsibility for the success or failure of a new product. The time it takes for a contract packaging company to design, develop, and produce an individualized package; the professionalism with which it maintains the efficacy of the product; the degree to which the packaging complies with federal regulations; and the overall efficiency of the packaging process are but a few of the considerations that will make or break the success of a drug’s clinical trials phases and ultimately the completion and marketing of the drug.

Excellence on time

As world populations become increasingly aware of advances in health research and the possibilities for treating disease, pharmaceutical companies are under growing pressure to develop and launch new drugs. The upshot is an increase in the number and scope of clinical trials and therefore the expectation that packaging companies will quickly produce well-designed containers. By the time a drug is ready for trials, its developer will have invested a tremendous amount of R&D dollars in the product and will have risked the narrow probability that it will survive from candidate status to registration. The sooner a company can get its product into clinical trials, the sooner it can use the data from the trials to submit a new drug application (NDA).

Getting started. A contract packaging provider must negotiate a complex set of hurdles as it works with a pharmaceutical company to ready a drug for clinical trials. It must learn the results of stability studies before choosing the kind of packaging that will most effectively protect the product throughout the trial and comply with International Conference on Harmonization and FDA-mandated stability criteria. If not much stability data are available, then the packager may automatically opt for a container that offers the best protection against moisture vapor transmission or other environmental factors. It must consider the complexity of the proposed drug regimen to determine the best packaging design for various dosages (e.g. two tablets a day, multiple dosages of more than one drug) as well as the time period during which the drug will be taken (e.g., weekly cards, monthly kits). The packager must learn the doctor–patient visit schedule to know how many dosages each package should con-
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tain. The packaging must be tested to ensure that it is durable enough to survive normal storage, transporting, and handling. For example, companies may conduct burst tests or assess the strength of heat seals.

**Safety regulations.** Beyond basic package durability is the challenge posed by US Consumer Product Safety Commission (CPSC) regulations governing child-resistant (CR) attributes. The 1974 guidelines codified in 16 CFR 1700.14(a)(10) were later stiffened when outpatient clinical trials dosing increased, thereby exposing children to the risk of serious injury. On 23 May 2000 CPSC issued a statement mandating CR packaging for all oral-dosage clinical trial drugs dispensed for home use that are toxic enough to harm a young child. Manufacturers whose primary packaging was not CR were allowed to put packages into a CR outer container. They were then given two years in which to bring all primary packaging up to regulation standards. After that date, any firm conducting a new clinical trial, regardless of the phase, could no longer package the drug in a CR outer container to satisfy CR requirements. As a result, packagers have developed a variety of blister pack designs with features such as tear-resistant laminates and peel-and-push components.

In response to industry warnings that a required CR test protocol for every clinical trial blister package would cost manufacturers far more than they could financially justify, CPSC agreed that as long as a package design incorporated a CR feature described in ASTM D3475, a manufacturer could forego the protocol—a move that saves the contract packaging industry precious time and substantial amounts of money. Nevertheless, contract packaging providers that demonstrate that their package designs have been tested and meet CR requirements are definitely ahead of the game.

**Meeting deadlines.** As consequential as the previously described considerations are, they mean little if the packaging supplier cannot meet production deadlines and the sponsor company is left hanging. By the time a product has reached the clinical trials phase, speed to market is a top priority among drug manufacturers. Contract packagers must strategize carefully to accommodate the various timelines for each trial phase. Phase I trials require smaller volumes and quick turnaround; Phase II trials are large, randomized, and often long; and Phase III trials sometimes require a range of treatment doses to identify the optimal dosage amount. Phase IV trials, which follow NDA approval, may be used if a company wishes to add another indication for the drug or institute a broad look at the safety of the drug.

Contract packaging providers can get ahead of the game if a client works with them to develop packaging designs long before they expect their drugs to be approved. Some packaging companies are provided with the client’s long-term distribution, shipping, and marketing requirements and consequently can design packages for the final product as well as for the clinical trial stages. Sufficient lead time for producing blister cards is especially critical because of their often-complicated and specialized design. Contract manufacturers are in the best position when they can work with the client as it is identifying its trials protocol; then the contract organization can help design the most workable packaging solution.

The forward-thinking contract organization will invest considerable energy in planning before the project is actually awarded. The company that has its design capabilities, timelines, teamwork plans, and equipment resources firmly in hand is much more likely to be called on for a project, and once the project is assigned, the packaging company can start right in. Admittedly, however, risk is involved: the contract company may spend significant time, effort, and money on planning and development only to find out they have not been assigned the project.

**Robotics.** One way some packaging companies are speeding their response time without compromising accuracy is with the use of robotic packaging systems. Robotic systems are designed to eliminate time and personnel otherwise needed to produce, handle, and inventory product as well as hand assemble final unit-dose packages. For a unit-dose package with multiple drugs, a robotic system can work with each drug simultaneously and create the final package in one step (1). If the system detects an error, then it rejects the blister package.

Overall, there is no room in the clinical trials arena for packaging errors and late delivery. Participants’ health and even their lives are at stake, and pharma companies’ millions of dollars in investment are on the line. Excellence delivered on time by the contract packager is crucial to the ultimate success of the product.

**Promoting patient compliance**

The outcome of a clinical trial itself depends upon patient compliance, and compliance depends largely upon effective packaging. A package that has text or design that confuses patients or that does not allow convenient access to the therapy can create noncompliance and thus a failed clinical trial—a disastrous result for the pharma company. The simplicity or complexity of the dosing regimen determines the packaging design, and making it easy for the patient to use it is the goal. Clear instructions, icons, portability, the way the drug is organized in the package, convenience, and color coding are a few of the top considerations for keeping the number of clinical trial dropouts low. For example, a pocket-sized package is a logical choice for a daily regimen, and icons are necessary for patients who don’t speak English. Thinking in terms of worst-case scenarios can help packaging engineers devise a container that is best suited to the contract company’s client.

**A clinical trials packaging primer**

Pharmaceutical products typically are tested in tandem with comparators and placebos. Clinical trial testing also often requires different dosage amounts than the final product may require. These factors affect the way packaging is designed for clinical trials.

**Packaging for blinded studies.** Blinded studies are conducted so that participants do not know whether they are in the experimental or the control group. The experimental group receives the medication being tested and the control group gets a standard treatment or no treatment. In a double-blind study, neither the participants nor the study staff knows which participants are receiving the experimental treatment and which are getting either a standard treatment or a placebo. Sometimes
color-coded labels are the only thing that identifies the packages for blinded studies. Products must be manufactured to look identical, and packages must be produced to eliminate tampering and breaking of the blind. Some companies have the capability to blind tablets and caps by overencapsulation—the quickest, lowest-cost way to blind a study—thus eliminating the need to outsource a matching placebo. In some cases the packaging company is the only group that knows the dosing regimen that patients are using. The sponsor company may choose to remain blinded so it can avoid creating bias in any of the practitioners or patients.

**Multiproduct blister packs.** Companies such as Almedica (Allendale, NJ) and Blistech (Fairfield, NJ) have automated equipment that can package multiple products in one blister pack especially for clinical trials. This capability eliminates the need for the patient to dose from multiple containers, a system that can confuse the patient and lead to incorrect dosing, thus skewing the trial. In addition to the convenience a blister card offers, the visual cues it provides make correct dosing much easier. The multiproduct blister pack also reduces the number of packages a company must provide for one dosing regimen.

**Packaging format changes.** The clinical trials packaging format is likely to change as the product is amended through the trial phases. The form in which the drug is used for a Phase I trial may evolve to a more-developed form for Phase II studies. For example, the medication may first be administered in powder form and then be developed into a capsule, and finally a tablet. Participants in adjuvant trials receive a different medication that aims to prevent reoccurrence for those who have recovered as a result of the medication they took during a clinical trial. Packaging companies must be prepared to amend the type of medication package to suit each need.

**Labels.** Labeling acts as a crucial guide for the clinical trials participant. Labels must contain language that cannot be misinterpreted, not only to protect the safety of the participant but also to ensure the success of the trials. A government-sponsored 1992 National Adult Literacy Survey concluded that nearly 50% of Americans “read too poorly to understand most printed health information” (2). The pharma and packaging partnership must take this sobering fact to heart when it composes the labeling language.

Labels may have to include randomization codes. Open-label trials in which both the doctor and the patient know what treatment is being administered demand yet another kind of labeling. Some packaging companies offer blinded labels and treatment unblinder reports. Packagers often can incorporate multiple fonts, styles, bar codes, and graphics in the labels. Multiple-panel labels enable sections of the labels to be removed and placed in a case report for a record of dispensing.

**Global language.** Designing a label can become complicated by a multicountry clinical trial. The contract packager must not only design a regulation-compliant package, but the package
must have international language capabilities. Booklet labels with instructions in as many languages as needed are one way to minimize having to design and print separate labels for each language in global trials. Overlabeling, in which a basic label with a unique reference number is applied in a production run and then a clear overlabel with the language of the country in question is applied as needed, also is a popular solution. Approvals from within companies’ regulations departments in accordance with local regulations must be granted for each language, however, and being forced to wait for approval of one or two languages on a multilanguage label may delay the entire project. Some large pharma companies have opened GMP-approved packaging facilities in numerous countries, giving them allocation flexibility when recruitment is low in a given area. To complicate the multilanguage problem, the packaging may have to meet not only FDA standards, but also EU standards for accuracy of translation, compliance with the regulations of countries in which the study is taking place, and CR requirements.

Communication is the key. A contract organization and a sponsor company must work together closely on text approval for medication labels. Sometimes only the pharma company’s regulatory and medical departments are involved, and other times text approval must go through a hierarchy of departments. It behooves the contract packager to allow ample time in its production schedule for this step.

Why contract packaging?
The contract clinical trials packaging industry commands an estimated total market value of $400–500 million, a comparatively moderate sum. A small handful of companies accounts for approximately 50% of the market (3). A 2000 study found that 56.6% of pharma companies surveyed use contract packagers for some or all of their packaging requirements (4). To gain a foothold in the industry, packaging companies must win partnerships with Big Pharma and remain in its good graces. To do so, companies generally offer the services described earlier in this article as well as provide more-specialized services such as

- training clinical site staff about product dispensing and inventory and record keeping
- compliance-related services such as maintaining audit logs and providing print-run batch records
- distribution and study monitoring
- outsourcing of packaging of comparator drugs
- repackaging, relabeling, inspection, and assembly
- interactive voice response systems to minimize inventory
- tracking of location, status, and retest and expiration dates
- information storage (e.g., history reports)
- import and export services
- shipping directly to study sites.

Most pharma companies that choose to outsource packaging for their clinical trials do so because their production sched-
ules are overburdened, product demand is capricious, and competition is tough. All the while they are fully aware that the sooner they can use clinical data to support an NDA, the better. Established contract packagers have the advantage of having their systems in place; logistics worked out; a proven production track record; and easy access to equipment, facilities, and staff. Often these advantages will convince a pharma company that it’s well worth its while to outsource the clinical trials packaging. On the other hand, contractors must be flexible enough to serve all clients regardless of the study size and complexity. No matter how sufficiently in place their staff and equipment may seem, inevitably they will run up against a company with a project that will test its limits.

Contractors that have identified the size of their permanent staff must also anticipate how many more personnel must be hired should the company take on a larger-than-usual assignment. Almedica, for example, adjusts for the “ups and downs of demand,” said spokesperson Martin Noblet. When the company must hire additional staff, “we then use established well-trained operatives from agencies that specialize in GMP operations.” Knowing that adaptability is key, the company may institute flexible hours, overtime, and weekend hours and add and subtract personnel as needed. Companies also must appraise their equipment resources to determine if special equipment must be fabricated, calibrated, qualified, and validated. A company’s information technology systems must be capable of maintaining secure job documentation and data, including randomization codes and other number schemes, inventory records, history reports, audit logs, lot status, and distribution records.

Conclusion
Effective clinical trials packaging is the gateway to NDAs and ultimately to the successful distribution of health-enhancing therapies. Close collaboration between pharma companies and contract packaging firms can guarantee the efficiency and success of a trial, safeguard the safety of its participants, and speed the drug’s time to market, benefiting both companies as well as millions of patients whose recovery will rely on the success of this little-known partnership.

References