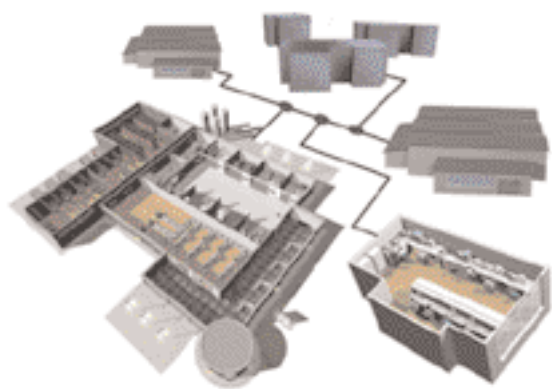


# Connecting Clinical Trial Management to Pharmaceutical Manufacturing

Marcia Walker



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Companies that leverage collaborative technologies to address challenges in their clinical supply chain are better positioned to reduce their time to market.

**H**igh research and development costs and lengthy time-to-market challenges make it difficult for pharmaceutical companies to successfully introduce new drugs to market. To expedite the process, these companies rely on a highly structured clinical trial system to collect, analyze, and categorize data about a new drug as it progresses through development, testing, and trials in the field.

Yet like a massive pipeline that's equipped with a myriad of inbound and outbound valves and conduits, the clinical trial system depends on precise timing, monitoring, and coordination efforts as well as a cataloged flow of information and materials. If just one critical step in the clinical trials process goes awry and slows or stops the pipeline, the drug manufacturer could lose tens or even hundreds of millions of dollars in potential revenue and profit. The longer it takes for a new drug to go through clinical trials, the shorter the amount of time is available to enjoy protected sales on the market before its patent expires—an industry rule of thumb pegs the opportunity cost as high as \$1 million per day in lost revenues.

To help keep the new-drug pipeline flowing freely and improve time-to-market and profitability, pharmaceutical manufacturers often rely on various technologies to help connect clinical trial management with manufacturing. Among the most popular systems are those that aid collaborative communication and planning, simulation and subject compliance, clinical supplies, packaging, and manufacturing.

## Integrated communication is key

The clinical trial system requires the input, output, and cooperation of diverse groups, including personnel from the pharmaceutical company's medical department, biostatisticians, investigators, trial subjects, representatives of domestic and nondomestic regulatory organizations, manufacturing personnel, packaging personnel, and sometimes representatives from contract research organizations (CROs) and other third-party vendors.

To juggle the needs and requests of these groups during the clinical trial process, a pharmaceutical company relies on the knowledge, experience, and involvement of its in-house clinical supply group or CRO packaging and clinical supply group. Often, this job requires as much explanation as it does exper-

Marcia Walker is the Application Center team leader, Clinical Trial Management, at Rockwell Automation, tel. 919.465.1741, ext. 302, mwalker@ra.rockwell.com.

tise. For instance, even the most experienced pharmaceutical personnel may be unaware that decisions made at the study-design level can have a significant effect on manufacturing and packaging operations and profitability down the line. It's the job of those in clinical supply to explain the cost- and time-effectiveness of alternative decisions, as demonstrated in the following group-specific examples.

**Medical personnel.** When medical personnel design a clinical study, they often request complex packaging designs that will take a significant amount of time to produce; for example, blister packs with detailed instructions printed on each blister. Bottles that contain a preprinted instructional leaflet are usually less expensive and faster to package. Moreover, medical personnel often do not understand the extensive lead times for formulation, validation, and stability efforts that are needed to obtain and blind comparative products (i.e., to develop a product that is visually identical to a competitor's drug).

**Biostatistics personnel.** Biostatisticians who work closely with medical staff to design a clinical trial hold considerable sway over how a clinical drug is packaged and distributed. However, their decisions may not always be optimum. For example, they may request a randomization scheme that could inadvertently make the setup of packaging runs difficult, time-consuming, and expensive.

**Clinical investigators.** Clinical investigators—the physicians who provide the drug to the patient—may have difficulty keeping track of various standard operating procedures, storage conditions, minimum inventories, and other rules related to a range of studies and products. In addition, investigators are sometimes responsible for reordering new-drug supplies. They may assume that a product is sitting on a shelf in a warehouse and is ready to be distributed when in fact a reorder may require a full manufacturing and packaging run because of limited available supplies.

**Trial subjects.** Responsible for taking the investigational drug, trial subjects present multiple challenges to the packaging and clinical supply group. For example, subjects might misplace their drug supplies or not take the product as labeled. The clinical supply group must carefully consider the packaging with trial subjects in mind as well. Historically, clinical materials were exempt from regulations concerning child-resistant pharmaceutical packaging. However, today's clinical materials often must adhere to the same guidelines as those for marketed products. Thus, trials for certain demographic groups such as arthritis patients may require special packaging materials to ensure that the packaging will comply with both trial and regulatory requirements.

**Regulatory organizations.** Regulatory organizations during the clinical trial process are critical stakeholders. The documentation, tracking requirements, and import-export considerations for clinical supplies are extensive. Insufficient or inaccurate documentation during a trial can delay or cancel it, thereby resulting in huge losses to the study sponsor.

**The manufacturing group.** The manufacturing group within a pharmaceutical company is unique in that it is both a supplier and a customer of the clinical trial materials. The facility that supplies the clinical trial material usually is not the same facil-

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ity or even the same company that will manufacture the drug for the market. However, the manufacturer must know how the drug is produced and, therefore, will be a customer for the production data from the clinical material facility. For this reason, the manufacturer also may want to be involved in decision-making for producing the trial formulations.

**CROs and third-party vendors.** CROs and third-party vendors hired by the pharmaceutical company to assist with manufacturing, packaging, labeling, and distributing clinical materials rely on data about the clinical trial and supplies to plan and execute their work. Any break in the process such as a delay in the delivery of the investigational drug from the pharmaceutical company can seriously disrupt the timing and success of their work.

### **Challenges of international production, marketing, and distribution**

The packaging and clinical supply group must design ways to cost-effectively meet the needs of multiple groups involved in the process. In addition, it must deal with the unique challenges of manufacturing and distributing an investigational product. Because pharmaceutical companies typically plan worldwide marketing and sales of a new drug, this poses a host of issues related to international production and testing.

Before a drug can be sold in a country, it may first need to go through a clinical trial under the rules that are specific to that country. Sourcing issues for new drugs are complex because many countries do not permit the use of certain compounds. For example, most European countries require excipients, capsule shells, and bulk drug products to be certified as free of bovine spongiform encephalopathy and transmissible spongiform encephalopathy. Country-specific requirements such as these pose unique challenges when drugs are still in research and development because it is typically not cost-effective to manufacture different batches for each country. Thus, most pharmaceutical manufacturers follow the requirements of the country having the most-strict regulations.

However, drug companies often do not decide which countries will participate in a clinical trial until late in the process. By that point, it may be difficult to obtain sufficient quantities of the drug material in time to make and deliver the first batch to the first investigator in time for the first patient visit.

Sometimes, a company will manufacture different clinical trial batches for different countries. However, this can lead to supply challenges if the sites in one country are running short on the drug while another country has an oversupply. Often, the oversupply cannot legally be sent to the sites that are in need. Thus, companies must track which batches may legally go to which site and ensure that material is not sent to the wrong location. Mistakenly sending the wrong batch to the wrong country not only may result in a large fine from the regulatory agency for that nation, it also may invalidate the clinical study data.

The clinical manufacturing and supply group also must pay close attention to batch-release issues. Countries that belong to the European Union (EU) specify that a “qualified person” (QP) must certify each batch. If the batch is manufactured in a non-

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EU country, then the QP still must certify it, which may require that the QP visit each facility where trial samples are being produced, thus adding extra time to the clinical trial process.

### Sourcing challenges

The availability of the active pharmaceutical ingredient (API) in the trial material also may pose a challenge. Because the API often is in limited supply and is manufactured using technology that's still being developed, it can be difficult for the clinical supply group to scale up a research and development production facility sufficiently to produce the larger quantities that may be needed as the trial progresses. It's not easy to forecast the demand for a trial product as the number of trial subjects that enroll increases. In addition, stability data about the API often are limited. To ensure the quality of an investigational drug being tested when the clinical trial must take place over several years, the clinical supply group may require multiple production runs of the investigational drug.

When a pharmaceutical company wishes to compare its new drug with that of a competitor, this poses an additional sourcing challenge. Specifically, the company must determine how it will obtain sufficient quantities of the comparator drug quickly enough to be used in manufacturing and packaging. Even if a source for the comparator drug is found, in some cases, it still must be "unpacked" and blinded without affecting the orig-

inal manufacturer's product-release standards. This extra step also may severely limit the shelf life of the repackaged supplies.

### Product protocol challenges

An additional unique challenge faced by clinical production and packaging facilities is the need to blind products so that neither the investigator nor the subject/patient can determine whether the subject is receiving the investigational drug, a placebo, or a comparator from a competitor. The manufacturing complexity of blinding can be significant and costly.

For example, although it may be relatively easy to match the exterior appearance of tablets or capsules, matching the taste or weight of certain formulations can be extremely difficult. Liquids are notoriously difficult to blind. The clinical production group must consider any characteristic that might potentially "unblind" the product. For example, if the investigational product requires refrigeration, but the comparator product does not, it would be fairly easy for an investigator to determine which product was which if one package arrives in a refrigerated container and the other does not.

Additional blinding challenges include

- patented processes. Because some comparator drugs are manufactured using patented processes, the pharmaceutical company sponsoring the trial may need to pay license fees to use the patented technology.

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- stability data. Many methods of blinding products also require the clinical production group to establish the expiry data through stability testing.
- manufacturing protocols. To ensure that the products being blinded are appropriately labeled (i.e., not likely to be mistaken for the wrong drug), the clinical production group must design robust production processes that ensure the

correct product is in the correct container with the correct label when it goes out the door to a clinic.

Blinding also presents international challenges such as dealing with ever-changing rules about import licenses. For example, because the blinded nature of a clinical trial may be unclear to a customs official, it could mean that a clinical trial sample is delayed at a customs checkpoint.

However, if the trial material is not delivered on time to subjects, the investigators may not be able to complete the trial in accordance with the study protocol, thus invalidating the results.

### **Leveraging collaborative technologies**

The most useful and urgently needed technologies available to clinical packaging and supply groups are those that allow clinical trial teams at multiple sites in multiple countries to communicate and plan more effectively. Technologies range from simple team-room systems that are based on shared computer servers to complex planning tools that are accessible to users worldwide. These systems allow users to input their expected study dates and manufacturing needs, which reduces the likelihood of surprises down the road.

Surprisingly, few clinical groups use these collaborative technologies. However, by encouraging medical planning personnel and biostatisticians to effectively communicate their clinical trial expectations to manufacturing personnel early in the process, a pharmaceutical manufacturer will have a cleaner and more cost- and time-effective link between clinical trials and manufacturing.

Similar technologies make it easier for a clinical packaging and supply group to collaborate with investigators and subjects. In the past, paper-based systems of communication with investigators and subjects led to problems such as long wait times and lost data. Although paper-based systems are still widely used, many pharmaceutical companies and CROs are accelerating their data gathering and analysis by using technologies such as interactive voice-response systems and Web-based technologies.

Increasingly, pharmaceutical companies are using software to simulate trial results early in the life of a product and to help determine whether trials should continue. In some cases, the simulation software even helps the company reduce the number of trial subjects that must be enrolled, thus further reducing costs. Other types of simulation software help companies better predict events under various manufacturing, packaging, and/or distribution scenarios, which in turn help



stakeholders better understand the impact their decisions will have on the clinical supply chain.

Technologies that ensure subject compliance are relatively new to the market. For example, some compliance-agreement products use a light sensor to indicate when a patient has opened the trial bottle and has taken the medication. Interactive voice response systems can “call” sub-

jects to remind them to take their trial medication or can allow patients to complete symptom diaries over the phone according to the schedule set for the study.

Packaging technologies can help manufacturers solve common packaging and distribution challenges. For example, new packaging materials that are both child-resistant and senior-friendly are popular in trials for older adults. Some current

package designs include radio-frequency transmitters to help companies track the inventory of materials at investigative sites and reduce the workload for managing material supply.

To improve manufacturing processes, pharmaceutical manufacturers can now integrate manufacturing execution systems software with clinical packaging software systems to manage recipes, packaging designs, and randomization data that fully comply with 21 *CFR* Part 11. Such systems also allow users to execute what-if scenarios to help determine the effect of various packaging designs such as whether the use of blister packs or bottles for product packaging would be most efficient and cost-effective.

Shipping challenges are simplified with the use of software that helps users track import licenses and materials to ensure that supplies intended for one country are not inadvertently shipped to another. The same systems allow users to view all components for a blinded trial, including the design and execution of the manufacturing and packaging for the blinded materials, so that quality control departments can confidently release blinded batches of materials.

### Staying on the cutting edge

It's clear that software and technology resources allow pharmaceutical companies to more effectively address and improve their response to the challenges specific to the manufacturing, packaging, and distribution of clinical trial materials. The companies that most effectively leverage the benefits of these new technologies will be best positioned to reduce their time to market, boost product profitability, and gain a critical market advantage. **PT**

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