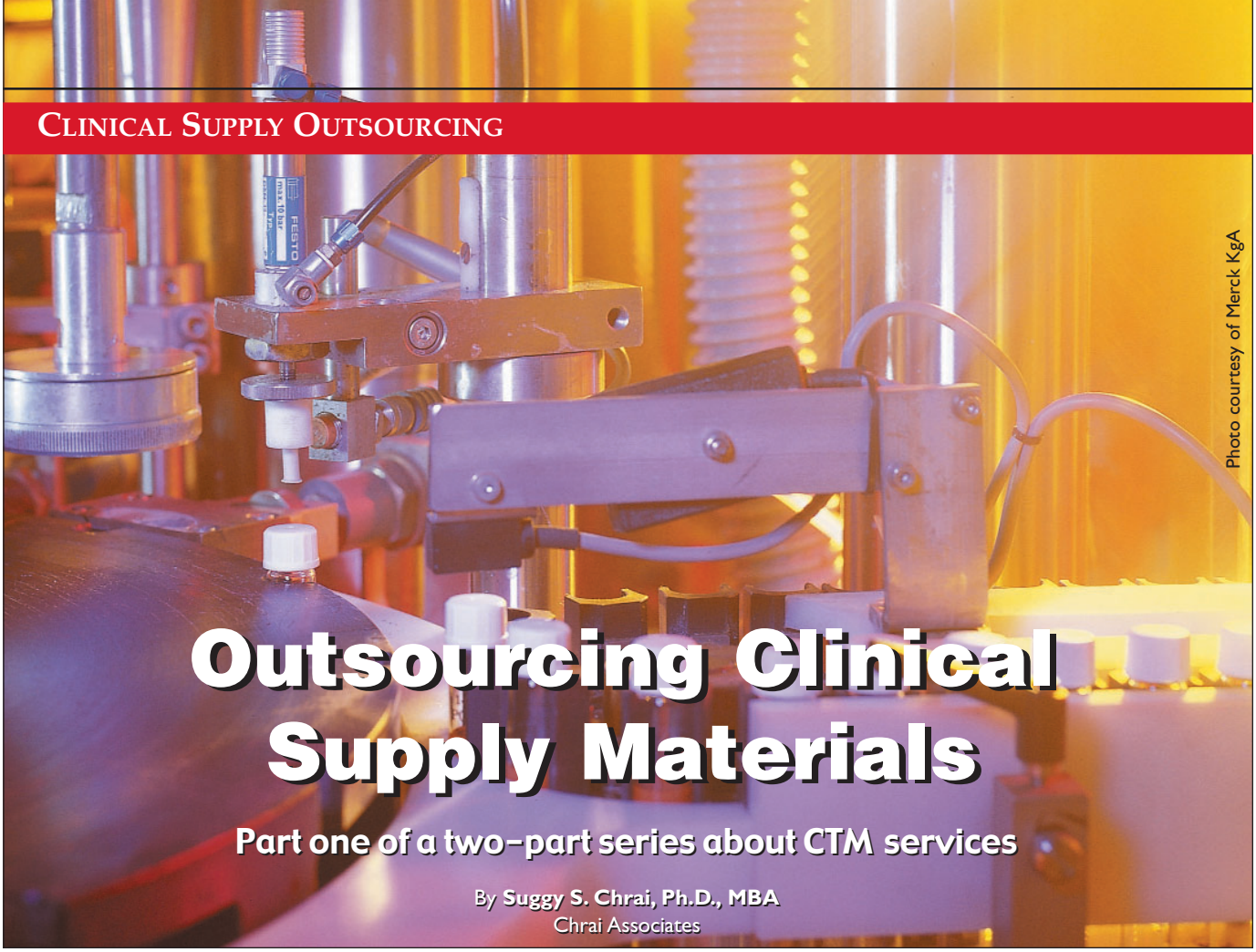

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Outsourcing Clinical Supply Materials

Part one of a two-part series about CTM services

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MANY INTUITIVELY APPEALING arguments have been offered both for and against outsourcing as a means of achieving sustainable competitive advantage. By allowing outside specialist organizations to concentrate on certain tasks, firms may increase their performance by focusing more narrowly on the things they do best. This is especially true for the area of Clinical Supply Materials (CSM), where the complexities of study designs make it difficult to have all the required core competence elements in house. However, outsourcing may reduce organizational innovation, may shift knowledge to supplier organizations, and may reduce control over a firm's activities.

Approximately 60% of research and development is spent on human clinical trials[1]. Every year, costs of clinical trials increase by 9-10% due to their growing complexity. High throughput screening (HTS) has made it possible to have more new chemical entities undergo clinical trials, contributing to the annual marked increase. The FDA is also demanding sample populations, which requires more time and money. The FDA wants Pharma companies to collect more data, particularly on possible side effects. The mission of the FDA is to safeguard and promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products. In comparison to just 10 years ago, clinical trial populations have increased two- or threefold. The pharmaceutical industry's increasing need for outsourcing drug development has resulted in the explosive growth of the practice. Outsourcing now accounts for more than 20% of drug development expenditures, about $5 billion annually.

It is important to understand the evolution of R&D outsourcing for both the pharmaceutical companies and Contract Research Organizations (CROs). In the past, the outsourcing was too insignificant in both volume and scope to warrant much management attention. Today, with pharmaceutical companies outsourcing 20-40% of their development budgets, the cost of inadequately managing outsourcing—measured in delays to market and potential development risks—is too high to ignore.

Organizations are increasingly turning to outsourcing of clinical supply materials in an attempt to enhance their competitiveness. At present, the pharmaceutical industry is still focusing on outsourcing specific, short-term tasks rather than seeking partnership with contract service providers (CSPs) that can help them break through the next level of innovation and process improvement. One major change is to focus internally only on core activities that can create strategic advantages, and more proactively outsource activities that other companies can perform more efficiently. Operationally this means that large parts of R&D and manufacturing can be outsourced. The contract drug development and manufacturing is a $30-plus billion industry. This increased growth is a result of an industry-wide strategic shift to outsource more manufacturing and research services to save money and get products to market faster.

What are Clinical Supplies?

All pharmaceuticals start out as little more than an idea in a drug company laboratory. To test the idea, the company needs small quantities for in vitro and toxicological studies. Rather

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than prepare the material in-house as was done traditionally, pharmaceutical companies are increasingly interested in suppliers from the very early stage. Next, a slightly larger quantity is needed to fund the Phase I and II clinical trials. Then even larger quantities are required for Phase III trials and finally full-scale, long-term supplies for commercial launch would be needed by the pharmaceutical companies. The materials needed for the in vitro and toxicological studies and to perform the Phase I to Phase III are the "clinical supplies" required for the trials. Clinical supply material for Phase IV trials is generally provided from commercial supplies. It is in the best interest of the CSP to have the capability to supply pharmaceutical companies from grams to tons and everything in between. Also, it is always costly to alter production and supplier, because of required regulatory approval for both process and material changes. Thus, companies would like to streamline their supplier chain so that only a few partners are needed to ensure adequate supply with acceptable quality of materials.

Table 1: Important Differences Between Clinical Supply Material and Commercial Material

Description	Commercial Material	Clinical Supply Material
Methods	Fully validated	LOD, accuracy and precision
Process	Fully validated	Establish preliminary specs; verify lot-to-lot
Cleaning verification	Fully validated	Verification of cleanliness
Batch records	Complies with master; derivative of the validation study	Follow manufacturing production record
Manufacturing area	Full scale arena	Pilot facility; lab scale
Expiry dating	Established via stability testing	Preliminary data; retest date
Raw materials	Qualified/established component specs and suppliers	Varies according to protocol guidelines; document and adequately justify
CMC parameters	Established via validation	Evolving parameters
Packaging	Range for reconciliation and accountability	100% reconciliation and accountability
Stability	Support label claim; established	Support study period; evolving
Handling deviation	Formal QA system	Formal QA system
Planning	Formalized; fairly consistent	Study specific; unpredictable
Operating costs	Very high with profit	Very high without profit
cGMP adherence	Strict; rigid enforcement	Flexible; loosely enforced

What CSM Services are Available?

- Product formulation and development
- Manufacturing (clinical, pilot and finished product)
- Laboratory (method development, in-process, release testing, stability, microbiology)
- Stability storage
- Packaging/labeling
- Shipping (including import/export)
- Return goods
- Destruction
- Special handling for controlled substances
- Package development/design
- Over-encapsulation for clinical supplies
- Storage and site distribution
- Clinical/inventory management

Types of Clinical Study Drug Materials

- Injection – aqueous, lyophilized, powders, oils, suspensions, liposomes
- Ingestion – tablets (regular and controlled-release), capsules, liquids, syrups
- Inhalation – MDI, DPI, Nasal
- Suppository
- Topical – cream, ointment, lotion, gel, paste, patches
- Radioactive
- Biologics
- Others

What's So Hard About Clinical Supplies?

Labeling is more complicated with global trials than those conducted only in specific geographic regions. Different countries require different amounts of text and languages. In order to supply clinical trial material to Canada, for instance, the label must sometimes be in both English and French (see Table 1). This means someone would need to procure labels large enough to contain both languages. However, the clinical trial may involve both the U.S. and Canada. Perhaps the Purchasing group will opt to procure smaller labels to minimize confusion at the U.S. clinical sites and during packaging.

To go a step further, the package and design group may develop a design, in collaboration with the project manager, to use different colored labels. Each treatment period will be assigned a different color. One would now need to divide the total number of labels by the different treatment group colors. As the study design gets more complex, the quantity, color, size, shape, texture, material of the labels will all have to be exact. Specifications for each label and the content of each label are often already established and approved for use. These are called label copy approvals, which QA may review for information purposes (see Table 2 for label requirements).

Manufacture of a Clinical Kit: Possible Pitfalls

Next, one must get the investigational drug to the packaging site. This bulk material may either be obtained domestically, in house (i.e. with a pilot plant), or overseas[2,3]. The clinical supply coordinator will order the material and will follow up when and where the drug product is to arrive. Clinical trials tend to start up very quickly, so such investigational drugs would need to be procured expediently. In going about procuring the investigational bulk drug material and comparators, it is also important to ensure that the supplier can certify that each lot does not contain any animal derived product possibly linked with

Table 2: Label requirements for Canada and Europe

Canada	• Statements "Investigational Drug" and "To be Used by Qualified investigator Only"; or "Drogue de recherché" and "Reservee uniquement a l'usage de chercheurs competents." • Name, clinical investigator name or number • Protocol code • Lot number and expiry date • Storage conditions • Name and address of manufacturer
Europe	• "For clinical trial use only" and "Keep out of reach of children" • Investigator name and site number • Dosage form, route of administration, quantity • Lot number for contents and packaging run • Expiry or retest date • Patient study number • Directions for use • Storage conditions • Sponsor name

bovine spongiform encephalopathy (BSE)[4]. Preferably, one should attempt to obtain products comprised of vegetable sourced ingredients. In addition to this certification, one should also specifically request that the material be shipped with a certificate of analysis stating that it meets GMP requirements.

At the same time, there exists the need to order the packaging components, comparator products (if necessary) and any ancillary supplies. All procured packaging components must abide by the pre-existent specifications (i.e. size, color, material, closure style). The group would need to be advised in terms of the appearance of the material. Typically, the company that sells that product is solicited to see if it would produce a batch for clinical trial use. For instance, an interested company would ask whether a certain cream packaged in tubes could be packaged into blank tubes. Understandably, the comparator company will most likely reject the request. In such a circumstance, someone should aid in attaining a packaging service (if it cannot be done in house) that could rework the tubes into tubes of the same color, material, luster, and crimp as the investigational drug. Perhaps the investigational drug manufacturer may supply extra empty tubes. Ultimately, there should be two sets of tubes consisting of different products, yet which are absolutely indistinguishable from one another.

In addition to ordering the comparator drugs, the group shall also procure the ancillary supplies (needles, syringes, alcohol wipes, saline, etc.). The group may collaborate with the QA group to better understand the level of quality needed of these supplies.

Earlier, we provided a glimpse of what packaging services may be necessary. Depending again on the complexity of the protocol design, the bulk product may need to be blistered.

Table 3: Examples of Clinical Trial Designs

Objectives	Means
Safety	Open label
Efficacy	Single blind
Pharmacokinetics	Double blind
Bioavailability	Crossover
Bioequivalency	Double dummy
Titration	

Furthermore, packaging services would need to be secured for manufacturing child resistant packaging for U.S. clinical trials. This is mandatory especially if the patient intends to take the medication home with them.

In shipping the material overseas, the material may not be imported back into the U.S. unless it is for clinical drug return purposes. Nevertheless, the group may choose to send the finished clinical material in bulk to overseas qualified warehouses. This will diminish the number of interactions with customs on a kit-by-kit basis. Although such shipments will be via express delivery, the group plays a key role in furnishing the special components to send the material in a qualified shipping container.

Design of Patient Kits

- **Blisters**
  - Card design
  - Resupply intervals
- **Parenterals**
  - Bulk pack
  - Labeled kit
- **Bottles**
  - Kit layout
  - Color coding

Preparation of a Subject Kit requires the following items:

1. Approved Clinical Protocol and Randomization Code
2. Ordering Clinical Trial Materials
3. Inventory Management
4. Labeling and Packaging
5. Training
6. Review of Executed Documents
7. Distribution

CTM and the EU

IN MAY 2001, THE EU WROTE up its review of the Clinical Trial Directive, which goes into effect this month. The Directive covers ethics and regulations for the protection and privacy of clinical trial subjects, and also deals with manufacture, import, and labeling of clinical trial materials, which must meet GMPs. As one outsourcer recently remarked, "The biggest hurdle in the EU Directive for packagers and exporters of clinical supplies has to do with the need for a QP (qualified person). A QP needs to release the supplies in that particular country—they need to obtain all the batch records, certificates of authenticity, everything. This isn't a problem for large organizations like Pfizer, but for smaller biotechs it can be a real pain. Another problem is that member states can have subtle differences with respect to the EU directive. They may all agree in principle but they all have these subtle changes that they like to add. For example, Sweden needs upfront stability data, while Germany doesn't. All you need in Germany is IRB approval. In Sweden it's more like the FDA requirements." ■—Gil Y. Roth

Ordering Drug Product
- **Sources**
  - ❑ Pharmaceutical Technology (Pilot Plant)
  - ❑ Vendor
- **Order is based on amounts required for:**
  - ❑ study
  - ❑ overage
  - ❑ analytical samples and packaging retains
  - ❑ stability

Ordering Packaging Components: Package Design
- Bottles, closures, subject kit boxes
- Determined by the study design
- Are customized for each study
- Can influence patient compliance
- Additional resource - Package Design & Development

Inventory Management
History of use is documented
- Accountability
  - ❑ At the point of use
  - ❑ Physical inventory of bulk materials in storage
  - ❑ Distinct Quarantine, Released and Reject areas
  - ❑ Returns
    100% inventory of material received from site
  - ❑ Disposal
- Receipt and Log-in Process
  - ❑ Inspection
    damage
    correct quantities
    checked for correspondence to protocol
  - ❑ Lot number assigned, shipment is labeled and quarantined for release by CQA
  - ❑ Samples deducted
    Analytical testing and demonstration
  - ❑ Forward documentation to Clinical QA for release

Labeling
- Label copy - circulated for review and approval to Clinical R&D, DRA, CS and CQA
- Items required to start label printing:
  - ❑ Approved label copy
  - ❑ Randomization Code (if applicable)
- Use of different colored labels to aid in patient compliance
- Capability of printing different languages.

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(Part 2 of this article will appear in the June 2004 issue of CONTRACT PHARMA, and will cover CTM labeling requirements and the development of outsourcing criteria for CTM suppliers.)