Encyclopedia of Pharmaceutical Technology

Volume 3

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ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY

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VOLUME 3

CLINICAL SUPPLIES TO DERMAL DIFFUSION AND DELIVERY PRINCIPLES

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Clinical Supplies

Overview

Clinical supplies are dosage forms containing investigational drug substances that are produced, packaged, and labeled specifically for testing in clinical trials in humans, prior to market approval or prior to approval for a new claim for a previously approved product.

To test a new drug substance in humans, a drug sponsor must obtain approval from the U.S. Food and Drug Administration (FDA). The drug sponsor must follow a predetermined route to test the product, first in a few healthy volunteers and eventually in perhaps thousands of actual patients. This process is conducted under an Investigational New Drug (IND) application. Testing under the IND goes through several stages (Phases I, II, and III) leading to the filing for approval from the FDA to market the drug product under a New Drug Application (NDA) and continued testing under Phase IV, often referred to as post-marketing surveillance, under the IND. This whole testing process can take many years to complete and cost the sponsor millions of dollars.

Information pertaining to the drug product dosage form contained in the IND for clinical trial supplies includes, among other things, a listing of the components used in the dosage form; the quantitative composition of the dosage form, both as a unit formula and a typical batch formula; a brief statement describing the manufacturing process; test methods and specifications; and an indication of the stability data gathered to date.

A more thorough explanation and examination of the regulatory process is given in "Clinical Evaluation of Drugs," in Volume 2 of this Encyclopedia.

Current Good Manufacturing Practices

Throughout the dosage form development and clinical testing process, the manufacturing of clinical supplies must comply in all aspects with the same controls and regulatory agency requirements as commercial, marketed products.

The manufacture of a clinical dosage form must be completely and accurately documented every time the product is produced. The sponsor must be able to show written proof that all raw materials, components, processes, testing, storage, and distribution of the product meet appropriate standards of quality and that the product complies with the Current Good Manufacturing Practices (CGMPs) regulations—Code of Federal Regulations, Title 21, Part 211.

Because there can be rather significant differences in processing and control requirements for clinical supplies, compared with commercial products, it was not always obvious as to how and where the CGMPs applied to clinical supplies. Therefore, in February 1988, the FDA issued a document "Draft Guidelines on the Preparation of Investigational Drug Products." The guideline was issued to inform interested parties of practices that would permit users to be in compliance with certain parts of the CGMPs—at least to the extent that those practices would be acceptable to the FDA. It should be noted that these guidelines are still *draft* guidelines as of the date of this publication.

The pharmaceutical industry in the United States is highly regulated. Part of that regulatory control is the requirement that drug sponsors maintain and follow written procedures known as Standard Operating Procedures (SOPs). SOPs are written documents that describe the many processes, procedures, and controls related to the manufacturing of pharmaceutical dosage forms. They are intended to help ensure that the drug sponsor has the necessary controls to consistently produce a quality product. The need for SOPs also applies to the manufacture of clinical supplies. The basis for these SOPs are the CGMPs. Procedures must be written and followed concerning:

Equipment cleaning, maintenance, and use
Equipment calibration
Receipt, storage, sampling, identification, and approval or rejection of incoming components of drug products
Production and process control
Label control and issuance
Expiration dating
Warehousing procedures
Stability testing
Reserve samples
Records and reports generation and storage
Release or rejection of finished products
Returned goods handling

This list is very general. Each individual or firm wishing to manufacture, package, and label clinical supplies must examine its own situation and ensure that the operation is in strict compliance with the CGMP regulations.

In addition one must have separate and unique areas for:

Receipt of incoming items
Quarantine of nonreleased products and components
Storage of released drugs and components
Storage of released finished goods
Storage of rejected and outdated materials
Storage of controlled substances
Packaging and labeling operations

The Pharmaceutical Manufacturers Association (PMA) has also issued guidelines concerning the CGMPs, specific to clinical trial materials. These guidelines, issued September 28, 1983, can be acquired from the PMA.

Manufacturing and Control

Bulk Clinical Manufacturing

Before a new drug product can be approved for marketing, it must undergo a rigorous testing process, initially in animal models or preclinical testing and then in human clinical trials.

The testing process in humans is initially designed to prove that the drug substance in the dosage form presentation is safe and to define the maximum tolerated dose in a limited number of healthy volunteers. Having done this, the drug sponsor then must test the drug product in much larger numbers of actual patients in order to prove efficacy...or that the drug does what the sponsor claims it will do.

A product's profile is very likely to change several times before it becomes a marketed product. In early Phase I studies under a new IND, the dosage form may be very simple in nature. For example, the dosage form for first testing a new chemical entity (NCE) or new biological entity (NBE) in humans often consists of the drug substance being hand-filled into hard gelatin capsules. That is, the dosage form is not formulated with excipients. In later clinical studies, Phases II, III and IV, and as more and more data on the product are gathered, the formulation will likely change to provide a final product that is safe, efficacious, stable, and designed with patient dosing compliance and convenience in mind.

In the manufacture of clinical supplies, the drug sponsor prepares a written manufacturing batch record. All steps in the manufacturing process must be described and documented in sufficient detail to permit the process to be repeated by qualified personnel to yield the same product in future batches.

The batch record contains a listing of the raw materials and components used to produce the bulk dosage form. All components are tested and/or evaluated against approved specifications and released for use by Quality Control (QC). Typically, the raw materials are compendial-referenced items (e.g., USP/NF, BP, EP, etc.) because these materials have a known quality and specification.

The batch record shows not only what components are to be used, but also how much of each is to be used for the intended batch size. The batch size may vary, depending on the stage of development or IND phase. Normally, the later one is in the development stage, the larger the batch sizes are likely to be.

Since manufacturing experience with investigational materials has yet to be gathered, it is generally recognized that there may be differences between the clinical dosage form and the eventual commercial product—especially in the early stages of dosage form development. Therefore, it is imperative that the manufacturer of a drug product intended for use in clinical trials maintain well-documented written records of the manufacture of each clinical batch. Important details to be described include: the specific locations of operation; the specific pieces of equipment used;

and the specific processing parameters such as processing times, temperatures, speed, humidity, and pressure. Furthermore, any change in any one of these parameters needs to be noted in the batch record, with a brief explanation of the reason for the change. This information is accumulated over the dosage form development process and is ultimately useful in defining the criteria for manufacturing the commercial product. This information is also used to be define the master formula for the product against which all future clinical batches will be compared.

During the manufacture of clinical supplies, in-process testing will help ensure that the end product will be the desired one. In the early stages of clinical supply manufacturing, in-process controls cannot always be predicted. But, through the experience gained with the manufacture of multiple batches, the drug sponsor adds, adjusts, deletes, or manipulates those controls to make it possible to reproduce the same product.

Contract Manufacturing

Sometimes a drug sponsor may not have the capability or time to manufacture clinical supplies. Therefore, the sponsor may consider using a contract manufacturer.

Generally, the drug sponsor's Quality Control/Quality Assurance unit will audit the contractor prior to having the work actually performed. In this way the sponsor is assured that the product, and conditions under which it is produced by the contractor, will meet its standards.

The contract manufacturer must comply with all aspects of the applicable CGMPs. However, the sponsor's Quality Assurance (QA) or Quality Control (QC) unit has the ultimate responsibility of approving or disapproving the use of a particular contract manufacturer based on the results of the audit.

It is also common practice to have a knowledgeable representative from the drug sponsor on-site at the time the contract manufacturing actually occurs. This is the "man in the plant" concept, whereby someone familiar with the product and/or process is present and available to answer any questions, make suggestions, or help solve any problems during processing. In making arrangements with the contractor, the drug sponsor generally describes the desired end product and the required processing parameters. The sponsor also is responsible for identifying or pointing out to the contractor any special precautions for handling the drug substance. The contractor can then use this information to generate a manufacturing batch record describing the process to be followed. That batch record is generally reviewed and approved by the drug sponsor prior to actual manufacturing. Once the supplies have been manufactured by the contractor, the final release of the supplies for use in clinical trials remains the responsibility of the sponsor.

The sponsor may have the contract manufacturer do the bulk product testing and the sponsor only do routine incoming QC testing upon receipt of the bulk product, or the sponsor may take responsibility for all final testing and release of the bulk product using its own analytical facilities. In either case, the sponsor must assure itself that the product meets specifications and that it has not been altered or tampered with during transit from the contractor or otherwise been adversely affected by environmental conditions during shipment.

Expiration Dating/Stability Testing

Just as for commercial products, clinical supplies must be tested periodically to ensure that the drug product in clinical trials meets the sponsor's standards—at the time of use and in the container/closure system used.

The sponsor is required to establish an expiration date or, more appropriately, a reevaluation date for the product. Through a written testing program, the sponsor collects physical and chemical data on the product, under a variety of environmental storage conditions. These data are used to determine whether the drug substance and drug product will be within established specifications until the proposed expiry or reevaluation date. Using the accumulated data and perhaps good scientific judgment, the sponsor may periodically extend the assigned reevaluation date. However, the sponsor must continue to gather physical and chemical data, through continuing stability studies, to confirm the assigned date.

Quality Assurance/Quality Control

As indicated in the CGMPs, the QA or QC unit of a drug manufacturer, or drug sponsor in the case of clinical supplies, has the ultimate responsibility for assuring the quality of the dosage forms. The QC unit is intimately involved in all aspects of clinical materials manufacture. The unit's involvement covers literally everything—from the time the raw materials and components are received and released for use until the bulk product is manufactured, tested, and released for clinical packaging. Some drug companies in the United States have an assigned QC staff responsible for the release of clinical materials while others use the same staff that reviews, approves, and releases commercial products. In either situation, the review and approval by QC/QA personnel throughout the manufacturing process are necessary to help ensure that the clinical supplies are of known, specified, and reproducible quality.

To help in this process, the QC unit performs a valuable periodic internal audit function. The unit can be instrumental in ensuring that the records and documents, the facilities, and the equipment are adequate and appropriate for the product(s) produced. The audits can be extremely useful in detecting and recommending areas for improvement to enhance the quality of the clinical dosage form.

Facilities/Equipment

The facilities and equipment used for manufacturing clinical supplies must be in compliance with the CGMPs. This can cover such things as:

Equipment use, cleaning, and maintenance programs
Room use and cleaning
Water and air system design and maintenance

The facilities must be designed and maintained in a state appropriate to ensure product integrity and to preclude product mix-ups and/or cross-contamination.

Cleaning procedures for the facilities, as well as for the equipment, must be written and followed; each cleaning exercise must be documented. Sometimes the cleaning procedures to be followed are specific to a particular product, while at other times they can be general in nature.

Some drug sponsors use their commercial product manufacturing facilities for producing clinical supplies, while others use the same facilities in which they conduct their dosage form development activities. If commercial product manufacturing facilities are used, special care must be taken throughout the manufacturing process to ensure that none of the investigational material finds its way into the commercial product. This means that the equipment and facilities must be adequately cleaned to preclude mix-ups and/or cross-contamination with any subsequent commercial products produced in the facility.

Similarly, if the sponsor's development facilities are used for manufacturing clinical supplies, the sponsor must do everything possible to prevent product mix-ups or cross-contamination.

Comparator Products

Matching Placebo (for Oral Solid Dosage Forms)

During development of a dosage form, and when attempting to prove efficacy, it is common practice to compare the effects of a new drug product with those of a matching placebo. Therefore, the drug sponsor must make a placebo that has the same appearance as the active drug product and study the two side by side in double-blind studies. (See definitions and comments in the Packaging and Labeling sections that follow.)

Because developing a matching placebo for oral liquids, for controlled-release oral solids, and for nonoral dosage forms each presents special problems, they should be handled on a case-by-case basis.

Manufacturing a matching placebo for the new drug product can look simple in theory, but can be quite difficult in practice. Because the placebo needs to match the appearance of the drug product, making a placebo appears to be an easy task. Indeed, that is the case if one needs to make a hard or soft gelatin capsule or if the dosage form is a white tablet. The difficulty arises when the sponsor needs to produce a color-matched dosage form. Even this requirement is not insurmountable given sufficient time to develop the color match.

Positive Control Drugs (Oral Solid Dosage Forms)

It can be extremely difficult for the sponsor of a new drug product to make an existing commercial product (positive control drug) match the new product. It is common practice to conduct double-blind clinical studies whereby the new product is compared side by side with products that already exist in the market place.

There are several options available for preparing matched comparator products, each with its own set of requirements. Methods and procedures vary from firm to firm, but the importance of ensuring that the integrity of the competitor's product is

not compromised is the ultimate concern. Following is a list, in descending order of preference, generally considered acceptable by most firms:

1. Obtain the commercial dosage form and matching placebo from the competitor. This is by far the preferred option. In this case, the supplies would be packaged and labeled in "double dummy" fashion. That is, the sponsor's new drug product and matching placebo would be compared with or against the competitor's product and its matching placebo in a container/closure system suitable and approved for both products.
2. Obtain in-process material from the competitor and compress it or encapsulate it according to the competitor's instructions. The drug sponsor may then prepare color-matched placebo tablets or capsules.
3. Reprocess the competitor's product by inserting the *intact* dosage form into an opaque hard gelatin capsule, with or without filler excipients. This capsule can match the appearance of the test article, or a placebo can be made to match the appearance of the capsule containing the competitor's product. In this case, a double-dummy study would also be employed.
4. Remove or obscure the markings on the competitor's printed tablets or capsules and prepare a matching placebo tablet or capsule.
5. Reprocess the competitor's product by grinding and recompressing or re-encapsulating, and prepare matching placebo dosage forms. This method is the least desirable and should be avoided if at all possible.

NOTE: When any change is made to a competitor's product, including packaging components, the firm making the change and conducting the trial is ultimately responsible for the integrity of that product. This responsibility also includes the stability and bioequivalency of that product.

Inventory Control

Just as with commercial products, the distribution of clinical supplies must be controlled and monitored. However, in distribution, once the supplies are packaged, labeled, and distributed to study sites, they are considered still under the direct control of the sponsor. The sponsor can determine where the supplies are located and can effect a quick and complete retrieval of those supplies if necessary.

Whether the supplies are in the bulk state or packaged, they must be stored under the appropriate storage conditions as determined by the stability testing.

Once the bulk dosage form is produced, the sponsor must conduct a reconciliation/accountability of each batch. The sponsor is required to determine the yield and be able to account for any manufacturing losses. It is generally understood that for early Phase I trials, the batch sizes are likely to be small. Consequently, the manufacturing losses can appear quite large when calculated on a percentage basis. However, as the batch sizes become increasingly larger, and the process begins to be finalized, the sponsor can establish predetermined limits on manufacturing losses.

Then, any losses beyond these predetermined limits should result in an investigation into the cause.

The sponsor's records must ensure that each batch can be traced. These records should cover the complete cycle, starting from the raw material and continuing through the manufacturing, packaging, and distribution to study sites. Once the clinical trial is complete, the materials are returned and reconciled to complete the documentation.

Packaging and Labeling

Clinical Supply Packaging

Clinical supply packaging is not unlike any pharmaceutical packaging environment. The ultimate goal of producing the correct package with the correct components and labeling is a constant. However, clinical supply packaging is complicated by look-alike drugs, labeling, and packaging configurations. However, the complexity of the situation cannot be allowed to loosen controls or lessen the need to follow CGMP regulations. With few exceptions (to be examined later), only one product and its appropriate labeling should be in the packaging/labeling operation at any one time.

Most clinical trials are conducted in a double-blind fashion, often with comparative products and placebos. The dosage regimens may be alike or different. However, when the packaging is complete, all supplies must *appear* to be the same. In general, this is best accomplished by examining a total clinical supply requirement and breaking it into groups of like operations. These smaller groups can be packaged and labeled strictly following CGMP regulations. Once these groups have been labeled and identified, they can be collated into the final packaged product.

In a time when the pharmaceutical industry is facing an alarming number of packaging- and labeling-related recalls, the FDA has pushed for such safeguards as:

1. No look-alike products
2. Use of "roll" labels (often electronically checked) as opposed to "cut" labels
3. Packaging lines dedicated to specific products

It may be difficult to successfully package clinical trial materials using all these cautions. Instead, sponsors must carefully choose the critical combination of personnel, procedures, documentation, and ongoing training programs to ensure that clinical trial materials and, subsequently, the integrity of the trial to follow are of the highest possible quality.

Initial Considerations

The primary initial considerations in determining packaging plans are:

(1) the dosage form of the drug (i.e. solid, liquid, cream or ointment, parenteral, aerosol/nebulizer, etc.); (2) the type of study (open label, double-blind, etc.); (3) the

recommended dosage regimen (once a day, twice a day, etc.); (4) the use of placebo or comparative products; (5) the stability and physical characteristics of the drug products involved; and (6) the use of child-resistant container/closure systems.

Packaging Schemes

The most important consideration in developing a packaging scheme is maintaining the integrity of the product or products involved. One must also carefully assess the ability of the patient or subject to correctly take or administer the clinical supplies as needed for the success of the study. Some of the more frequently used schemes are:

1. Open Label. Identity of the drug is "open" or disclosed on the label. This is equivalent to commercial pharmaceutical packaging. This packaging is usually reserved for the Phase I, early Phase II, and open long-term safety trials. In some cases, very little is known about the physical and chemical properties of the drug during early trials. Therefore, special care must be taken in choosing the correct components. Amber glass usually offers the best protection for the product.
2. Double Blind. The majority of Phase II and Phase III trials are conducted in a double-blind fashion. In this case, more is usually known about the drug product, which may offer greater flexibility in the packaging scheme choice.
3. Study Site Packaging. In some studies, difficult dosage regimens, flexible dose designs, or economics of the trial may require packaging the study drug at the study site. On-site packaging requires a qualified person or persons at the site to be unblinded and follow a prescribed randomization and packaging scheme for investigational articles. Study site packaging is risky and must be monitored closely by the sponsor firm.

Bottling Operations

Many clinical trials are conducted using oral dosage forms; therefore, the clinical supplies are typically packaged in bottles (glass or plastic). The containers and closures should be carefully chosen and be suitable for all products to be used in the trial.

Counting Methods. Dosage form accountability is often used in measuring patient compliance with the prescribed dosage regimen. Therefore, accuracy of count during packaging is critical to the completion of a successful clinical trial. Methods include:

Hand counting—should be checked by a second individual for accuracy.

Machine counting—machines used for clinical trial counting must be flexible to the size and shape of the dosage form to be counted. Ease of cleaning between operations should also be a factor in machine choice. Commonly used machines are the King Model TB4, the Versacount Model 721, and the Kalish Count. Figure 1 shows a King Model TB4 Tablet/Capsule Counter.

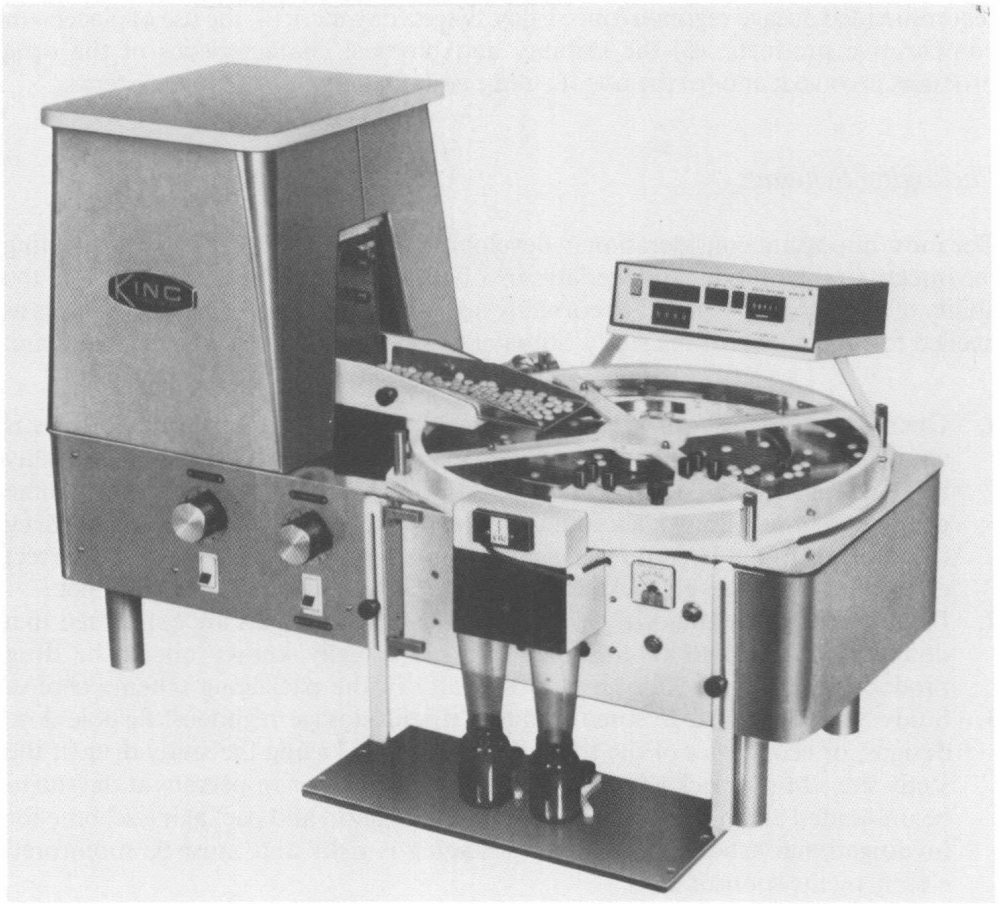

FIG. 1. King Model TB4 Tablet/Capsule Counter.

Counting by weight—may be suitable for bulk supplies. Caution should be used if exact counts are necessary. Product and container weight variation may lead to inaccurate counts; however, counting by weight can be a valuable method to verify counts done by another method. Many commonly available scales and balances can be equipped for small-piece counting.

Tamper-Evident Considerations. Although clinical trial materials are stored and dispensed under strict controls, some form of tamper-evident packaging is usually preferred. This not only decreases the chance of tampering, but also helps in monitoring the use of the clinical trial materials. Tamper-evident methods include PVC shrink banding, tamper-evident cartons, or tamper-evident cap liners (induction seal).

NOTE: Controlled substances in clinical trials must be sealed per Drug Enforcement Agency (DEA) regulations.