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MANUFACTURE OF CLINICAL SUPPLIES

John W. Bettis, Ph.D.

Pharmaceutical Research and Development Laboratories
Burroughs Wellcome Co.
Greenville, NC 27834

INTRODUCTION

Clinical testing under a modern drug development program requires the manufacture of a variety of dosage forms and drug delivery systems in a wide range of batch sizes. Accordingly, a clinical supply system must be flexible to meet these varying needs, but its procedure must be consistent and controlled to insure product quality and integrity. At Burroughs Wellcome Co., the Pharmaceutical Research and Development Laboratories (PRDL) are responsible for the manufacture of all dosage forms used in our clinical studies. This paper describes how clinical supplies are manufactured and controlled at Burroughs Wellcome Co., following the process from the initial request through manufacturing, packaging, and labeling.

FACILITIES

PRDL's manufacturing facilities occupy approximately 6,000 sq. ft. and includes areas for manufacture and testing of solid dosage forms and fluid preparations. Use of portable equipment permits flexible use of the manufacturing areas. The solid dosage form area consists of individual granulating, encapsulating, tableting, and

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coating rooms. Use and clean-up of each room is documented in a logbook; two signatures are required to verify clean-up between batches.

The fluid preparation area has separate rooms for the manufacture of sterile and non-sterile dosage forms and a clean room with laminar flow work stations. Air supplied to the clean room is also HEPA filtered, and air pressure is positive with respect to adjacent rooms. The fluid preparation area houses a double-doored autoclave and a double-doored dry heat sterilizer.

Clinical supplies are packaged and labeled in a separate 4,000 sq. ft. facility with separate rooms for storage of Quality Assurance (QA)-released products and packaging components and labels, isolated packaging rooms, an in-process quarantine room, double-blind assembly room, blister packaging rooms, and computer areas. Exhaust from all product filling rooms is HEPA-filtered to prevent cross-contamination.

Standard Operating Procedures (SOPs) describe the cleaning, disinfection, and use of the clean room and environmental monitoring of the clean room during aseptic operations using settling plates, swab tests, and an air particle counter. Water used in the manufacture of clinical supplies is carefully monitored by QA. Purified water samples from PRDL are taken daily and tested according to USP specifications. Water for injection is obtained from the Burroughs Wellcome Co. Pharmaceutical Production Division, and each batch is USP tested and released for use in manufacture of clinical supplies.

In addition to the manufacturing areas, PRDL also has the following facilities: general laboratory facilities, in-process quarantine, QA-released product storage, stability-testing laboratory, equipment storage, and office areas.

PROCEDURES AND CONTROLS

Request

The Medical Division requests the manufacture of clinical supplies by submitting a Bulk Clinical Trial Material Order (Figure 1) to PRDL. The Bulk Order, signed by the Medical Monitor and approved by the Medical Section Head, specifies

MEDICAL DIVISION
BULK CLINICAL TRIAL MATERIAL ORDER

INSTRUCTIONS: Complete appropriate sections of the TOP part of this form, obtain signature of the Section Head, send ENTIRE form to the CTM Coordinator - Medical

Columns indicated by an asterisk (★) will be completed by PRDL.

BULK Order # _____

Requestor: _____ Section: _____ Department:

Section Head's Initials: _____

This Order Pertains To: _____ (Res. Comp.# or Product Name)

( ) Clinical Research
( ) Clinical Investigation

Requested Completion Date for BULK Materials: ___ / ___ / ___ (Mo / Day / Yr)

Proj # _____
IND# ____ NDA# ____
Res. Comp. # or Product Name _____

Unit Conc. (Potency)	Dosage Form	FB	B.I.N. ★	Immediate Container (Not Required for Solids)		Quantity Ordered	Quantity Available ★	Date Submitted for Pass ★	Date Passed ★	Repass Date ★	Special Characteristics/Comments
				Type	Fill Wt. or Vol.						Indicate here if this request pertains to a placebo, and give the FB of the active drug which it matches.

Cleared to CTM Coord. (G) ___ / ___ / ___ _____ (Mo / Day / Yr / Initials)

BOTTOM OF THIS FORM TO BE COMPLETED *ONLY* BY PRDL.

1. Assigned to: _____ (Group Leader) _____ (Responsible Scientist) Confirmed Due Date: _____

2. Re-established Due Date: _____ Reason: _____

3. Date Submitted for Pass / Quantity Available (See Above)

4. Date Passed / Repass Date (See Above)

DISTRIBUTION: CTM Coordinator (RTP), CTM Coordinator (G), Medical Requestor, PRDL Group Leader, PRDL Data Entry

MDF#8

FIGURE 1. Form used by medical personnel to request manufacture of clinical supplies.

the product, its IND or NDA number, the required formulation (identified by a unique formulation number), the quantity to be manufactured, packaging information (for liquid and semi-solid dosage forms), and the requested completion date.

A development scientist in PRDL is assigned the manufacture of the product or products specified on the Bulk Order. The PRDL scientist reviews the Medical Bulk Order request and confirms or re-establishes the due date in consultation with the Medical Monitor. The responsible PRDL scientist then completes line 1 at the bottom of the Bulk Order form and distributes copies to inform appropriate individuals of the confirmed due date. Typically, the due date allows one month for product manufacture and one month for analytical testing and QA release.

Formula and Manufacturing

Before initiating manufacture of a batch, the responsible PRDL scientist completes the first three pages of a five page Clinical Trial Material Record (CTM Record) which is then checked by another PRDL scientist. This document provides the working formula for the clinical trial batch. A detailed SOP describes the procedures to be followed for manufacturing clinical supplies at Burroughs Wellcome Co. This lengthy SOP contains detailed instructions for using the five page CTM Record and other control procedures. Each PRDL staff member involved in the manufacture of clinical supplies receives special training and a personal copy of the SOP.

Page 1 of the CTM Record (Figure 2) lists the quantitative composition of the active ingredient and excipients as per the formulation number specified by the Medical Monitor. PRDL maintains a central computerized file of Formulation Numbers. Each Formulation Number is a seven digit alpha-numeric code (i.e., AAA00A0) representing a unique formulation. The first three letters designate a particular product, dosage form, and potency. The next two numbers represent a unique component mix; the next letter specifies a unique composition of that component mix;and the last number specifies the product's appearance. Accordingly, the number for two tablet formulations of the same potency and appearance, but with different binders, would differ in digits 4 and 5; the numbers for two tablet formulations of identical composition,one compressed on coded

PHARMACEUTICAL RESEARCH AND DEVELOPMENT LABORATORIES
CLINICAL TRIAL MATERIAL RECORD

Formulation Number	Product	Theoretical Quantity	Date Started

Batch Identification Number (B.I.N.)	Bulk Order No.	Storage Statement	Date Completed

ITEM NO	INGREDIENTS	RAW MATERIAL B.I.N.	PER UNIT mg	PER BATCH kg	WEIGHED BY (Signature)	CHECKED BY (Signature)
	TOTAL WEIGHT OR VOLUME					

Precautions:

Calculations:

Prepared by: _____ Date: _____ Checked by: _____ Date: _____

Page of

FIGURE 2. Page 1 of CTM Record which is used to list quantitative formulation.

Formulation Number	Product	B.I.N.

Step No.	MANUFACTURING INSTRUCTIONS	Performed By: (Signature and Date)	Checked By: (Signature and Date)

Prepared by: _____ Date: _____ Checked by: _____ Date: _____

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FIGURE 3. Page 2 of CTM Record which is used to list manufacturing instructions.

Formulation Number	Product	B.I.N.

SPECIFICATIONS AND TEST RESULTS

TABLETS:	Specifications	Results
Color		
Punch Size		
Punch Design		
Monogram		
Score		
Weight		
Gauge		
Hardness		
Friability		
Disintegration Time		
Cont. Uniformity		
Dissolution		

CAPSULES:		
Size		
Color		
Gross Weight		
Fill Weight		

COATED TABLETS:		
Color		
Weight		
Gauge		
Hardness		
Friability		

LIQUIDS:	Specifications	Results
Color		
Odor		
Clarity		
pH		
Specific Gravity		
Viscosity		
Sterility		
Eye Irritation		

SEMI-SOLIDS:		
Color		
Melting Point		
Viscosity		
Penetrometer		
pH		
Particle Size		

LYOPHILIZED PRODUCT:		
Cake Color		
Moisture Content		
pH of Solution		
Solution Clarity		

ACTIVE INGREDIENT(S):	Specifications	Results	Assay Procedure

Prepared by: _____ Date: _____ Checked by: _____ Date: _____

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FIGURE 4. Page 3 of CTM Record which is used to list product specifications and test results.

punches and the other on plain punches, would differ only in the last digit. The Formulation Number system has proved valuable in ensuring that the proper formulation is used in the clinic.

The first page of the CTM Record also lists the unique Batch Identification Number for the batch to be manufactured, theoretical quantity to be manufactured, and quantity of each ingredient required per batch. Each ingredient is assigned a unique item number as a double check that only correct ingredients are added to the batch. Later, as each ingredient is weighed, the raw materials batch identification numbers are added to the form as well as the " weighed by" and "checked by" signatures. Each ingredient must have been passed or repassed by QA within the past twelve months before use. Inventory cards, completed for each ingredient, provide a mechanism for tracing use of each lot of active ingredient and excipient.

Page 2 of the CTM Record (Figure 3) lists specific stepwise instructions for manufacturing the batch. As each step is performed, the CTM Record is signed and dated by two responsible individuals. The identification numbers of each major piece of equipment (e.g., blenders, granulators, mills, dryers, tablet presses) used to manufacture a particular batch are also recorded on this page, and a logbook assigned to each piece of equipment is signed as the equipment is used and after cleaning. Thus, all equipment used to manufacture any batch is completely identified and traceable.

Page 3 of the CTM Record (Figure 4) lists the specifications for the product to be manufactured. The specifications are obtained from the Analytical Standards or are developed in cooperation with QA and Analytical Development Laboratories. Lines are drawn through the dosage forms listed on page 3 that do not apply to the product being manufactured. Test results are added to this page after the batch has been released by QA.

Because clinical supplies must be produced in many forms and in highly variable quantities, a variety of techniques and kinds of equipment are used in their manufacture. SOPs describe set-up, operation, and clean-up for each piece of equipment. For example, the SOP for the H&K 400 capsule filler (Robert Bosch Corp., 15 Steeley Ave., Piscataway NJ 08854) is 27 pages long and references 164 slides to aid

Formulation Number	Product	B.I.N.

BATCH RECONCILIATION

BATCH ACCOUNTABILITY	Kg or l
1. Total Batch Wt. or Vol	
2. Available for Filling or Compressing	
3. Processing Loss	(%)
4. Volume Filled or Wt. Compressed (Avg. Fill Vol x No. Units or Weight)	
5. Processing Rejects	
6. Not Filled or Compressed	
7. Total (4,5,6)	
8. Unaccounted Material (2 minus 7)	(%)

EXPLANATIONS (Use reverse side if required):

UNIT ACCOUNTABILITY	No. of Units
Number of Units Obtained (Count or #4 + Avg. C.W.)	
Number Rejected	
Actual Yield	

DISTRIBUTION	No. of Units
Analytical Tests	
Physical Tests	
Stability Evaluation (Study No. _____)	
PRDL Retained Sample	
CTM Stock	
Other _____	
Total (Actual Yield)	

% of Theoretical Yield

$$\frac{\text{Actual Yield}}{\text{Theoretical Quantity}} \times 100$$

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FIGURE 5. Page 4 of CTM Record which is used for batch reconciliation.

Formulation Number	Product	B.I.N.

LABEL SPECIMEN (Include packaging precautions)	PACKAGING SPECIFICATIONS

Final CTM Batch Records:

Checked by: _____ Date: _____ Approved by: _____ Date: _____

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FIGURE 6. Page 5 of CTM Record which is used to record bulk product label, packaging specifications, and CTM Record approval.

in set-up and operation. A 7-page SOP describes set-up and operation of the Manesty Beta Press (Thomas Engineering Inc., Central & Ela Roads, Hoffman Estates, IL 60195) and another 21-page SOP gives detailed instructions for operating instrumentation to measure compression and ejection forces. Detailed equipment SOPs aid in employee training and help insure proper operation and maintenance.

To illustrate how PRDL meets the varying needs of a clinical trial program, the manufacture of powder-filled capsules is described in more detail.

Typically, batch sizes for powder-filled capsules vary through the stages of clinical testing:

Clinical Test Phase	Number of Capsules Per Batch
Phase I	400 to 5,000
Phase II	2,000 to 200,000
Phase III	100,000 to 1,500,000

The number of units required for a new chemical entity at various phases of testing depends on its therapeutic class and on how objectively clinical parameters can be measured. Thus, the batch sizes and the numbers of batches required for each phase of clinical testing span a wide range.

Capsules for Phase I studies are usually filled manually, because of the relatively small batch sizes and limited availability of the active ingredient. Preformulation studies are conducted to eliminate excipients that are obviously incompatible with or adversely affect the stability of the new chemical entity. A formulation is then proposed and stability studies initiated. Although capsules can be filled manually with only active ingredient and a filler, we attempt to include all excipients in the formulation that would be required for machine filling. This sometimes allows a machine-filled formulation to be developed using the same components as in Phase I testing, with only minor adjustments in quantitative composition.

Frequently, Phase I clinical trials require several capsule potencies for use in rising dose safety studies. If more than two potencies are required, development batches are manufactured in only the lowest and highest potencies to obtain stability data for filing in the Investigational New Drug (IND) application. When the clinical batches are manufactured, samples from batches of each potency are taken for stability studies.

Manually filled capsules are manufactured with the aid of a ChemiPharm capsule filler (ChemiPharm, 225 Broadway, NY, NY 10007), usually size #1 or #0. The final formulation powder blend for 200 capsules is weighed and subdivided among 200 empty capsule shells. After filling, each capsule of the entire batch is individually weighed on a Scientech balance (Scientech, c/o W.L. Schoonover, Inc., 6840 Roswell Rd, 2-A, Atlanta, GA 30328), and capsules above and below predetermined weight limits are rejected. Because of the inherent inadequacies of manually filled capsules (e.g., variability due to differences in operator technique), the 100% weight inspection of each batch ensures that each capsule meets weight variation requirements. A computer printout of individual capsule weights and a statistical analysis of the data are attached to the batch record. We have found that this technique also reduces variation in active ingredient assays and content uniformity data.

As increased quantities of the new chemical entity become available and Phase I and early Phase II clinical trials are encouraging, a formulation is developed for encapsulation on a H&K capsule filler. We attempt to use the same components as in the manually filled capsules and to encapsulate blended powders without granulation.

Before Phase III clinical trials begin, we attemp to develop a final formulation that can be scaled up using commercial production equipment. If Phase II trials are encouraging, we undertake an intensive development effort to study formulation and manufacturing variables in depth.

Capsule dosage forms for late Phase II and early Phase III clinical trials are manufactured using the H&K 330 or 400 capsule fillers. Filled capsules may be passed

through a Mocon Vericap capsule sorter (Modern Controls, Inc., 6820 Shingle Creek Parkway, Minneapolis, MN 55430) to ensure acceptable weight control. Typically, batches of up to 500,000 units can be encapsulated and sorted in five to ten days. Later Phase III trial requirements for more than 500,000 capsules are normally met using the production model H&K 1500 capsule filler. This provides scale-up experience and allows clinical data to be obtained using product manufactured with equipment to be used in commercial production.

The manufacture of tablets, sterile solutions, suspensions, or any other dosage form must meet similar requirements and follows a similar sequence of stages.

Page 4 of the CTM Record (Figure 5) aids in accounting for all material used in producing the batch, both in-process and when manufacture is complete. The left side of the form accounts for material lost in process (e.g., during filtration, granulation, filling, or compression). Although batch size greatly affects processing loss, unaccounted material loss must be less than 5 %. The right side of the form compares actual yield with theoretical quantity. Because theoretical yield also depends upon batch size, minimum yields cannot be predicted. However, the batch reconciliation form explains material balance in detail, and any abnormalities are investigated and documented before samples are sent to QA for release.

The distribution of product is also recorded on page 4 of the CTM Record. Samples are submitted to QA for testing according to the Analytical Standard, and samples are also retained for future reference. Other samples are used in a full shelf-life stability evaluation. This allows product stability to be monitored during the clinical phase and bulk material to be repassed as additional data are generated.

The product for clinical trial use is quarantined in a locked limited-access area while QA release is awaited. The bulk containers are labeled with product name and batch number, and a copy of the label is affixed to page 5 of the CTM Record (Figure 6) which also lists packaging specifications. For solid dosage forms, the bulk container is described; for liquid and semi-solid dosage forms, the individual package is described. Item numbers are specified for all components to ensures that only QA-approved components are used to package the product.

When the batch is released by QA, a printout of the analytical results is attached to the CTM Record. Actual results are added to page 3 to confirm that all specifications were met. A copy of the QA "pass label" is affixed to each bulk container, and one copy is attached to the CTM Record. In addition to releasing each batch of product, QA also performs in-process manufacturing checks, batch record reviews, and internal quality audits. These additional QA checks may be conducted at any time either with or without prior notice.

The scientist responsible for the batch now reviews the CTM Record and attachments, verifies that all information is complete and correct, and signs and dates page 5. The PRDL Group Leader responsible for the batch also reviews all documentation and signs and dates page 5 of the CTM Record.

The approved CTM Record and the properly labeled bulk product are then transferred to the CTM Packaging and Labeling Group within PRDL. The product is placed in a Passed CTM storage area which is locked and has limited access, and the CTM Record and attachments are filed.

Packaging and Labeling

Bulk product is packaged and/or labeled as required by the Medical Division for a specific clinical trial. Solid dosage forms are packaged and labeled; whereas, fluid preparation dosage forms, having been filled into final containers, are only labeled.

Burroughs Wellcome Co. uses the computerized Almedica Drug Labeling System (Almedica, 15 Industrial Park, Waldwick, NJ 07463) to format studies, generate labels, and track patient medication dispensed and returned. Currently, most solid dosage forms are dispensed in glass bottles; however, we are beginning to use the Almedica unit dose blister card because this form of packaging improves patient compliance.

For each specific clinical trial, the Medical Division defines exactly how clinical supplies are to be packaged and labeled. Basic information required for each trial includes the number of study centers, patients, treatment groups, and drugs to be

investigated (including placebo) and the name of principal investigator(s). The drug information required includes product, dosage form, potency, batch number, directions, storage conditions, and disclosure panel information for double-blind studies. Four standard label sizes are used: 0.75, 1, 1.75, and 2.5 inch. Both double-blind and open labels, preprinted with Burroughs Wellcome Co. logo, are available in each size. After all information is keyed into the Almedica software package, sample labels are generated and sent to Medical and Drug Regulatory Affairs for approval signature. A Protocol Dialog (a printout of all information for a specific clinical trial) is also sent to Medical Division for signature. After approval, all labels required for the study, including bottle, carton, and shipper labels, are printed by the computer. Computer printing allows each label to be unique, including a specific patient or subject number, dose level, and code number. The labels are cut, inspected, and stored in a secured area until needed in the packaging room. Strict accountability is required for all labels.

Concurrently with label generation, the appropriate packaging order is generated. The packaging order, in a standarized format, identifies the product, potency, dosage form, batch number, repass date, quantity per unit to be filled, and packaging components to be used. All packaging components are obtained from our Pharmaceutical Production warehouse. For each clinical order, components are requested by item number and description via a personal computer linked with the company's mainframe computer system. Use of stock warehouse items for packaging ensures a continuous supply of QA-approved components, because the Inventory Control and Purchasing Departments maintain minimum inventories specified by PRDL.

A specific drug to be packaged, appropriate labels, packaging components, and the packaging order are taken to a packaging room. Only one product is allowed in the room at a time, and all materials in the room must correspond to the packaging order requirements. All items are checked and double checked before the packaging operation is allowed to start. Also, QA performs intermittent checks during all packaging operations.

The Kalish Lectro counter (H.G. Kalish, Inc., 165 Oneida Drive, Pointe Claire, Quebec, Canada) is used for most tablet or capsule filling. Accurate fills at filling

rates of 2500 tablets or 1500 capsules per minute are possible, depending on product size and shape. Bottles are sampled throughout packaging and checked for accuracy of fill. Currently, bottles are handled and capped manually, but a minature assembly line with automated filling, cottoning, and capping is planned.

The computer-generated labels are applied manually as bottles are filled. After all steps of the packaging order have been completed, the labels and bulk material are reconciled and documented using a special form. QA checks the work and retains samples of filled and labeled bottles. Each filling room has a logbook to document use and cleaning. After each packaging operation, the room and equipment are cleaned, and the logbooks are signed by two responsible individuals before the next product is filled in that room.

For double-blind studies, the Medical Statistics Department generates a randomization list specifying which patient receives active product or placebo. Individual bottles containing either active product or placebo are separately filled, labeled, and reconciled. Appropriately labeled and identified active product and placebo are taken into the assembly room, and the randomization list is checked as each bottle is placed into the shipper. Three individuals verify that the proper active product or placebo bottle, appropriately labeled, is available for assembly. Materials are reconciled and additional QA checks are made after the assembly is complete. Packaged material is transferred to a Finished Stock Warehouse for shipment to the appropriate investigator and all packaging documents are assembled and filed.

In the past, Burroughs Wellcome Co. has used small individually labeled bottles to package a single dose of oral medication in situations where patient compliance would otherwise be questioned. Although the objective was met, the packaging and labeling operations were labor intensive, and the final package was bulky. We are turning to blister packaging to provide a more efficient system and a compact unit-dose package.

One or several blister cards are designed to contain all medication required by one patient for a given time period. The medication and labeling are arranged so that day number and dosing time are easily recognized. However, double-blind clinical trials using placebo and positive-control drugs can be complex even with

blister packaging. As many as four tablets and/or capsules may be required per dose, especially for rising-dose studies, and dosing frequency may vary from one to five times a day. Additional variation in dosage form size and shape, study duration, and number of units required makes it difficult to standardize a blister packaging format.

We are using the Almedica unit-dose blister packaging system. Several variations and custom features are available in addition to the adaptable "universal" system described here. The universal blister card has four horizontal and seven vertical rows (28 blister cells) with adequate space for labeling. Only the rows required for a specific study are used; the unused portion is removed and discarded. To produce the universal blister cards, we stock the following items which are supplied by Almedica:

1. Special-weight computer paper, precut in the 4 x 7 configuration, with pretreated back for heat sealing
2. Preformed PVC blisters (each cell will hold up to two size #0 capsules)
3. Foil backing

A double-blind blister card is formed by the following major steps:

1. Label information is entered into the Almedica software package. This includes general directions, storage statements, and labeling of each blister cell for day and time of dose.
2. Fixed information is printed on the face of the blister card by computer.
3. Variable information is computer printed on adhesive labels.
4. Preformed blisters are manually filled with active product and heat sealed with foil.
5. Preformed blisters are filled with placebo and sealed.
6. Sealed blisters are assembled into the proper positions on the blister card face.

7. The blister card is formed by heat-sealing the back to the assembled face.

8. The blister card is cut into proper size and perforated to allow folding.

9. Each card is labeled with variable patient information.

This process can be performed and controlled entirely in-house and allows rapid turnaround and maximum control for a large variety of studies using a variety of dosage-form sizes. PRDL currently uses this system primarily when 1,000 or fewer blister cards are required for a specific study. If each card contains a weekly dose, a month's supply for up to 250 patients can be produced quite simply in-house.

If the dosage form is small, the cell of the "universal" system may be too large, and a special blister must be designed. This is not common for Phase I or II studies, where we routinely use size #1 or #0 capsules; a special design is more likely to be required for certain Phase III studies.

If more than 1000 cards are required for a specific study, we obtain from Almedica cut sheets preprinted with all fixed information. Also, individual blister strips can be automatically filled and sealed. PRDL does not have a blister forming and filling machine for CTM packaging, but may purchase one depending on future requirements. However, producing blister cards in lots of more than 1,000 still involves manual operation in assembly, heat sealing, and labeling with computer-generated variable information, because these steps make each blister card unique.

SUMMARY

The system for manufacturing clinical supplies at Burroughs Wellcome Co. is flexible enough to meet varying dosage-form and batch-size requirements, while providing controls that ensure product quality and integrity.