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DOSAGE FORMS FOR CLINICAL TRIALS

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INTRODUCTION

Both practitioner and student alike are (or should be) cognizant of the fact that the preparation of dosage forms for clinical trials (i.e., clinical supplies) enjoys an integral and necessary role in the cycle of drug development. In the pursuit of bringing new drug entities to market (or new delivery systems of established drugs) pharmaceutical companies must conduct clinical trials. In most companies, the clinical trial materials are prepared by the pharmaceutical R&D department. When the supplies are prepared, the Company has the responsibility to ensure that they are of the highest quality and that the GMP Regulations are adhered to. Such an obligation extends from the initial idea for a new drug entity, through the development of a manufacturing process, to the eventual clinical testing for establishing safety and efficacy.

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The FD&C Act prohibits introduction into interstate commerce of any adulterated drug. Section 501(a) defines a drug as being adulterated if the methods, facilities, or controls are not in conformity with current good manufacturing practices (i.e., current GMP Regulations, CFR 21, Part 211). In other words, any drugs (including investigational new drugs) which are not manufactured in conformity to CGMP Regulations are considered adulterated and subject to FDA sanctions. In fact, the FD&C Act in Section 505(d) indicates that a new drug application (NDA) may not be approved if "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity;". Thus, if an experimental drug product becomes contaminated, it will not only jeopardize the safety of the patient but can also be responsible for severe financial consequences. Clearly then, it becomes incumbent upon those responsible to ensure that sound scientific principles and good manufacturing practices are employed in the development sequence to assure product safety and integrity. This can only be achieved by a commitment to excellence requiring total dedication of first class equipment, facilities, documentation procedures and people.

In practice, clinical supplies manufacturing and packaging frequently become a microcosm of a fully fledged production facility—all the major elements are present--except the work is non-routine, and, since R&D is traditionally understaffed, scientists must share responsibilities leading to a dilemma in career goals. The other aspect in common is that both enterprises exist because of a profit making motive, and as a result, any

delay, no matter how small, becomes rather costly. Moreover a mistake too, may prove equally mortal. In fact, for many practitioners, the job can be considered highly stressful.

Why then should such dire comparisions be hinted at? Recently the design of clinical protocols has become increasingly more complex and the chance for human error in assembling such studies has risen exponentially. To complicate matters further, because of the Institutional Review Board process, clinical protocols are frequently changed at the last minute. As a result, delivery of repackaged finished goods therefore becomes inordinately rate limiting which unfairly places undue pressure on the clinical supplies team. The temptation to cut corners just to satisfy the needs of a clinical monitor encompasses risk-benefit decisions which are pervasive and uncalled for. Also, in the recent past, the nature of the new compounds (genetically engineered peptides are very potent and usually unstable), and the nature of the new dosage forms (transdermal patches need complicated lamination manufacturing processes) require sophisticated, non-traditional handling procedures. The usual restriction of not having sufficient time or materials prevails - with the result that there is a lack of historical data on which to set specifications. Furthermore the variety of clientele which the group services has expanded to include not only medical affairs, but also toxicology, registration and stability. As a result, there becomes an ample opportunity to commit mistakes which can lead to missed delivery dates (lost credibility within and outside the company), to non-compliance with CGMPs (an uncomfortable situation) and to acceptance of lower standards (quality is sacrificed). Consequently, the ambience of the clinical supplies team is clouded by attempting to operate

under the dictum of "not being rate limiting" as well as with the added restriction of not being allowed to make mistakes. Furthermore rewards are rarely lavished on those who meet clinical sschedules, however "appropriate" retribution is ever present if delays or mistakes occur.

Because of this hostile and unfriendly environment which has all the signs of a "no-win" situation, certain quality measures can be instituted to constantly upgrade the operation to ensure success--which in many cases becomes equivalent to mere survival. Intent of this paper is to discuss and highlight some common sense and business sense principles which have been (or are in the process of being) implemented at Squibb and at other corporations.

The rather extensive fragmentation of the clinical supplies function within all types of companies across the domestic and international pharmaceutical arena suggests that any effort to elaborate on a common thread must focus on bringing order out of chaos. Of all the companies represented in this audience today, probably no two define and pursue dosage forms for clinical trials in quite the same manner. A few generalities therefore may serve in developing a broad perspective.

Perhaps one might begin by thinking of the clinical supplies function in terms of its mission: "To design, manufacture, package, assemble and label an impeccable dosage form in a timely manner to permit an accurate assessment of efficacy and safety of the new drug candidate." This becomes a desirable but elusive goal especially when the constraint of being "timely" is imposed. What then are the desirable attributes of such a dosage form? Depending on the set of circumstances, these might include: (1) Appearance...Clearly the dosage form must be presented in such a way

that it looks good to the doctor prescribing it, to the nurse administering it and to the patient receiving it. (2) Performance...The dosage form must perform what it is purported to do--i.e., deliver its medication to the bloodstream in a bioavailable and reproducible way, in addition to maintaining its physical and chemical stability. (3) Economics...The equipment and ingredients used in the manufacture of the dosage form as well as the packaging and labelling components must be of reasonable cost. Correspondingly, the labor intensity of the job must not drive the costs up if an automated procedure can be adapted. This parameter's importance is proportional to the clinical uniqueness of the chemical entity being tested. (4) Durability...The dosage form package must be able to protect its contents to withstand the rigors of shipping and storage such that its chemical and physical integrity remain intact. (5) Purity...Clearly, the finished goods must comply with all the legal and regulatory requirements which imply freedom from adulteration and relate to patient safety.

In summary, every institution has a particular list of internal requirements and if it fails on any one of these, it is not of acceptable quality. Therefore, to administer successfully the preparation of clinical trial materials, one needs to concentrate on an entire span of demands. This places an enormous responsibility on the practioners, directly reflecting on their real and perceived professional competence.

OVERVIEW

From the Clinical Trial Materials Progression Chart (Figure 1), the sequential steps required for a drug to move from a new molecular discovery to clinical trials are described. After initial evaluation of the physicochemical properties (Physical Pharmacy Profile) the dosage design

CLINICAL TRIAL MATERIALS

PROGRESSION CHART

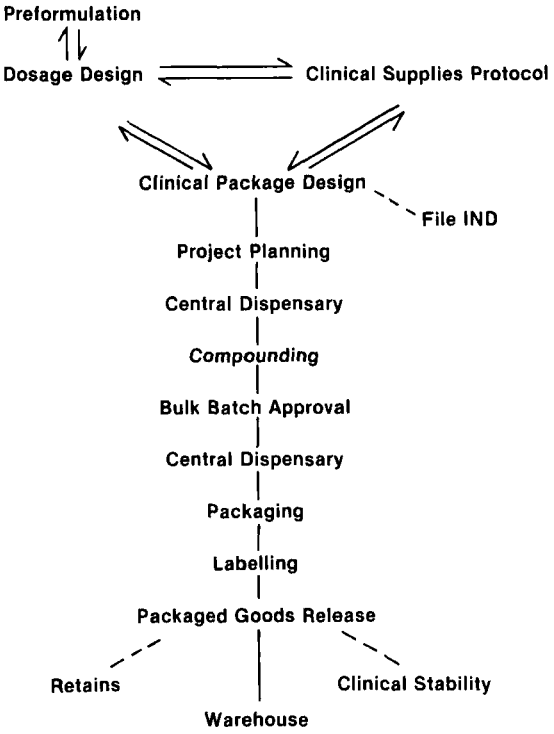


FIGURE 1

is conceptualized. The medical department decides on the nature of the clinical trial (blinded, open, placebo controlled, etc.), and then the pharmacy and medical departments decide jointly on the package design (blisters, foil, bottles, cap, cotton insert, etc.), and finally the clinical supplies protocol is issued. At this time the IND is filed. The project time chart is scheduled out. Materials are ordered from the central dispensary and these are portioned out (raw materials are weighed) and delivered on a shrink-wrapped pallet. The dosage forms are then compounded in the clinical supplies manufacturing suite and samples submitted to analytical

R&D for testing. Meanwhile, the sealed bulk batch is stored under quarantine until the results are transmitted (preferably electronically) back to the pharmacy for release. The packaging supplies and the bulk dosage forms in the amounts necessary for the job are requisitioned from the central dispensary and are assembled in an isolated packaging room. The correct number of labels is then printed via computer and applied either by machine or manually. The finished goods are then sampled and quarantined. After release, the samples are replaced (in the case of a blinded study) and the study boxed for shipment to the warehouse for further distribution to the field. Retains are catalogued and representative samples are placed on clinical stability to monitor the potency for the duration of the study. Each step in this sequence as well as key roles to be played by individual scientists can be elaborated upon as follows:

PREFORMULATION

When a lead compound in a promising new series is identified, there is a pressing need to place the drug in the clinic to profile its safety and efficacy without delay. Before that can occur, however, the requisite toxicology studies need to be conducted. Here, the physical pharmacist becomes involved in characterizing the physicochemical properties of the compound so that a formulation can be recommended to be employed in these studies. If a suspension is to be used for gavage, then the animals have to be dosed accurately (no settling), the formulation has to be chemically and physically stable, and the bioavailability has to be maximal (usually by micronization). Selection of the suspending agent should be made with the utmost care so that a special study doesn't also have to be run to look for toxic effects from the excipients. Usually at both ends of the dosing period, samples are analyzed to validate the study. Of course,

proper documentation is provided by the physical pharmacist to guide the toxicologist in preparing the doses. Should the preparation be so complicated that a pharmacist has to perform the compounding, then the amount of documentation/procedures become substantial, similar to that which will be described later in this presentation.

In the meantime, challenge stability studies are conducted to gauge shelf life and mechanism of degradation, and decomposition products are isolated and characterized to help validate analytical assays. If the drug exhibits unsuitable properties for preparing the desired dosage form (too hygroscopic for making tablets or too insoluble for a parenteral), then the drug candidate is returned to the discovery chemist to identify a more suitable salt or physical form or in most cases a new chemical entity in the same series.

In order to achieve success in this area, a good rapport has to be developed between discovery and toxicology personnel and the best way to do this is to employ highly trained, personable pharmacists who can conduct rigorous science. Scientific credibility within and outside the Company is an essential characteristic of scientists working in such a group. This investment in resources saves valuable time further down the line in preventing false starts which may prove very costly.

FORMULATION DESIGN

With a well written scientific report in hand, the formulation scientist has the proper background information to rationally design a formulation based on sound physicochemical principles.

Perhaps the biggest handicap at this stage is the paucity of material available for the design phase as well as the fact that the physical

properties of the raw material have a traditional habit of changing as refinements in the synthetic process are implemented. The other elusive fact that is never really given a firm answer, is the projected human dose. It becomes particularly difficult to design a dosage form when the percentage of the fill weight that the active occupies is variable.

As a result, the dosage form design must be robust enough to be able to accommodate these potential changes downfield. Optimizing bioavailability and stability, as well as establishing an in vivo-in vitro correlation with no extra material other than that required for clinical supplies is virtually impossible. Furthermore, there is an initial tendency to use the simplest formulation possible. However, on a larger scale, a new ingredient (such as a disintegrant or lubricant) may be needed to facilitate machine filling, and immediately questions are raised about the need to interject a bioavailability study to qualify the new formulation.

By using computer aided design techniques, it is possible to conduct optimization experiments on multi-ingredient formulations employing a modicum of representative raw material such that future changes are minimized. Should reformulation be unavoidable, then a whole new set of bioavailability and stability studies will need to be initiated. Ultimate responsibility for the commercial process also rests with the formulation scientist and the opportunity to practice his art on clinical supplies (using an independent practitioner) allows a unique opportunity for independent assessment of its feasibility in pilot production (trend analysis).

The requisite documentation chain also needs to be generated and this generally includes (a) composition identity, (b) master batch formula (per scale), (c) manufacturing instructions, (d) specifications, (e) reassay date and (f) storage conditions. Such documents are treated in a legal

manner and requisite signatures are obtained from the appropriate management personnel in analytical R&D and pharmaceutical R&D. They are stored under tight security in the documentation section. (Further elaboration of this cascade of documentation required is provided by Dr. Bettis in the second article of this series.)

Particular attention is paid in ensuring that any change in composition or process likely to cause a change in absorption profile of the drug is noted in the documentation and a numbering system which highlights such changes is enforced to gain a proper historical perspective. The need to interject a bioavailability study is generally catalyzed by a major change in the dissolution rate of the active ingredient from the dosage form. Of course, if the drug is particularly potent and is poorly and erratically absorbed, then extra care is employed. Clearly the object of the game is to have minimal changes.

CLINICAL PROTOCOL DESIGN

Here medical and pharmaceutical personnel jointly decide how best to present the dosage form to the patient to achieve optimal compliance. This function becomes more important as the complexity of the study increases. Shape, size, color of the active, placebo and competitive drug become primary points of discussion as well as the design of the package components. Moisture permeability of the packaging material needed to maintain product stability is also of major importance as is the question of using a child-resistant cap.

There are a number of clinical packaging categories of which the physician frequently has only a concept in mind of what scope the project should entail. These include (a) Open Study—where the products are

clearly labelled for the investigator and the patient, (b) Single Blind Study-- where the nature of the products is known only by the investigator and (c) Double Blind Study--where the products are coded both to the investigator and to the patient. The latter category predominates and usually involves a combination of active ingredients and placebo controls. The active portion may include positive controls using a competitor's drug. There are a number of scenarios available for this situation which involve either obtaining the marketed product and matching placebo from the competitor company, or perhaps their custom-made unlogoed matching pair. Sometimes, the competitor's powder blend or granulation can be acquired for in-house compression but this will require a new battery of analytical testing. An extreme situation would entail obtaining the competitor's drug and starting from scratch to match the in-house product. Of course the much discussed and controversial options of reprocessing the competitor's product or stuffing it into an opaque gelatin capsule are always available. If all else fails, a third-party blinding technique could be employed. Examples where this situation may prevail is in preparing clinical materials which are liquids, semi-solids, ophthalmics or lyophilized products.

A recent situation using a hypothetical clinical protocol design illustrates the value of a collaborative pharmacist-physician conference. Figure 2 illustrates the original concept design of 4 active blister cards each containing 3 tablets for morning and evening administration of either a placebo, beta-blocker, Ace-inhibitor or diuretic. To provide 6 matching tablets would be a formidable task in formulation especially if the tablets were to be of the same weight, shape, size and color. Furthermore, filling

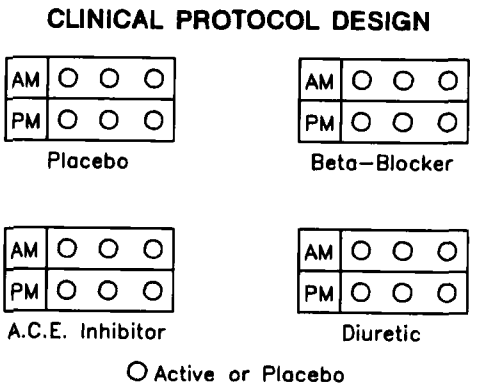


FIGURE 2

the blister cards would encounter severe logistical problems in preventing transposition of one round tablet into the empty cell of its neighbor. Figure 3 illustrates that proper advice and consultation can result in considerable labor savings and enhanced CGMP adherence without sacrifice of patient compliance. Here shape differences are taken advantage of such that transposition is virtually impossible. As a result only 3 sets of matching active/placebo pairs were actually needed.

Documentation ensuing from these negotiations includes:

1. Clinical Supplies Request - specifies number and potency
2. Packaging Identity Form - specifies materials and design
3. Master Packaging Formula - specifies codes and quantities
4. Actual Packaging Formula - specifies lot numbers and testing dates
5. Packaging Log Sheets - instructs how to assemble the package
6. Label Text - identifies exacting text for the labels and method of application. This generally includes a sealed disclosure label which permits the physician to identify a drug entity during dire circumstances.

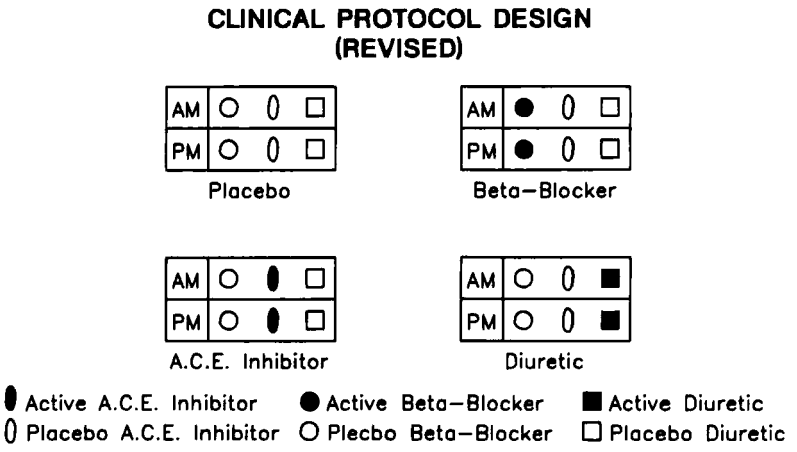


FIGURE 3

With these documents in hand, a critical review of the totality of the assignment can be deliberated by Quality Assurance, Quality Control and Drug Regulatory Affairs principals. Risk points during the mechanics of the assembly operation can be identified and a suitable sampling protocol can be designed which designates when, where, and how many samples are to be taken and analyzed. Since such testing is frequently destructive, a replacement strategy must also be included.

This exercise is particularly crucial to the success of the study—especially for blinded studies. It consumes considerable time but it is pivotal for the next step which is project planning.

PROJECT PLANNING

Major corporations typically endure a backlog of over 30 clinical supply requests on hand with several of these being processed concurrently. A suitable analogy might be Kennedy airport in a snowstorm with incoming airplanes being stacked up. Which one gets priority for the only runway in operation--the Boeing 747 containing 300 passengers with 10 minutes of

fuel remaining or the Cessna carrying 2 passengers with only 3 minutes of fuel left? As with clinical studies it depends upon which flight (study) you're on! The tenor of decision making in the context of clinical supplies area is of a similar nature. The juggling of resources has been a constant problem in the business world and fortunately there are several time-tested critical path analysis planning systems available which can structure projects so that one can foresee dead ends, wrong turns and contingencies. By incorporating such information as activity sequence, timing, resources, costs and deadlines into the system, a network of events is created which defines the projects. Interactive analysis then allows one to plan activities - those which are critical, which follow others and which are concurrent. A complete project schedule is then produced which schedules all the activities, their relationships and the dates they should occur. This schedule can show earliest and latest possible dates and the amount of float time available. "What if" questions can then be asked and the long-range ramifications of schedule changes can be evaluated in time to make all the necessary adjustments.

Missed dates of delivery can lead to losing patients and valuable investigators since customer satisfaction is inextricably interwoven with product quality, service and speed of delivery. This then becomes one of the criteria of performance by which the clinical supplies group is judged. The key to success is to publish a plan to keep the clientele informed and updated. The process requires nothing more than mostly well-coordinated hard work as well as polished interpersonal skills. Poor service can be related to poor management.

CENTRAL DISPENSARY

The functions of a Central Dispensary unit include:

1. Ordering, Shipping and Receiving (raw materials, packaging components and finished goods)
2. Maintaining a current inventory
3. Weighing
4. Dispensing and Record Keeping
5. Storage and Quarantine

Clearly here the key concept is complete control of any component connected with clinical trial materials. For weighing, special facilities are needed to keep hazardous materials segregated and to avoid cross contamination. These rooms should be centrally located and the floors, walls, and ceilings should be non-porous and be able to be easily cleaned. Also the electrical receptacles should be water and explosion proof. The air sweep pattern should be laminar if possible. The balances should be set out for certain ranges of sensitivity and preferably computer-interfaced to facilitate record keeping. It should go without saying that a strict schedule of maintenance and calibration needs to be adhered to. Weighing has frequently been implicated as the source of most manufacturing errors and therefore the idea of a specialized weighing function is to minimize mistakes and prevent adulteration. This requires dedication of procedures, facilities and people.

Of course the requisite SOPs for sanitation, status labeling, storage, sampling, retesting, receipt, labeling, safe-handling (sensitizing, addictive, toxic, unstable, and moisture-sensitive categories), retains, and identity testing apply. Exceptions for weighing fluffy materials, tares, split lots, etc., are also taken into account.

Particular enhancements of the computerized inventory control system include:

1. Always using in-date materials (stock rotation, timely and appropriate testing),
2. Reconciliation, Accountability, Traceability (audit trail, intended purpose, origin/source),
3. Consistency of records,
4. Monitored storage (Alarm system)

Once the order for materials has been filled, the components are sealed and labeled, then shrink-wrapped and palletized for disbursement to the compounding area.

COMPOUNDING

Compounding whether by sterile or non-sterile methodology should preferably be conducted in physically segregated areas from normal R&D or production facilities. The primary reasons for this are flexibility of scale, methods and scheduling. Again the risks of contamination are minimized. At Squibb, separate areas were constructed with limited access and dedicated air-handling systems. Principles usually applied to clean room technology and sterile suite construction were "borrowed" to achieve critical environmental requirements. To attain the required degree of cleanliness of sensitive areas, migration of particles carried by the air stream from less clean areas is prevented by directional airflow through controlled pressurization.

Some special features that were recently incorporated into the Squibb area included (a) using special finish walls, floors, ceilings and coving that were neither dust generators nor dust catchers - impervious,

durable, cleanable, non-porous, non-shedding and easily maintained; (b) using HEPA-filtered controlled positive pressure air with humidity and temperature control; (c) incorporating air-locks for personnel and equipment as well as air-shower protected gowning areas; (d) using one room designed as explosion-proof, specially equipped for extra air discharge during handling of solvent-based granulations; (e) building a separate, remote washing and sanitizing area as well as a marshalling area; (f) using air-trapped and capped drain systems; (g) employing clear labeling of pipework and (h) mounting television cameras for supervisory and safety considerations.

Equipment is of sufficient scale to allow for small or large quantities to be handled (from a few grams to 30 kg), but it is not necessarily dedicated to just clinical supplies alone. However it is cleanable and mobile. Limits for residues are set by consideration of toxicology profile and assay sensitivity. Results are recorded in the cleaning logs. Should a cleaning procedure need to be used repeatedly, then a protocol to validate the procedure based on solubility characteristics would be written up and followed. This saves time as the turnaround becomes quite long especially if the test is microbiological in nature. Procedurally the workers are required to don gowns and gloves and masks before entering the compounding room. Of course SOPs are followed for entering and leaving, qualifying the rooms for use, status tags for equipment, etc. Air flow patterns controlled by vents and dampers have also been validated when handling flammable solvents and for normal working conditions. Up to three products can be processed at the same time. For semi-solid preparations, microbiological contamination is of major concern and appro-

priate monitoring procedures are employed. Proper attention to detail of the documentation required during manufacture is a necessity.

BULK BATCH APPROVAL

After the supplies have been made, the requisite samples are taken by the Quality Control personnel and sent out for analysis. Results are transmitted back electronically and are automatically tabulated and compared with pre-existing R&D specifications. Any calculations such as means and standard deviations as well as flagging of outliers are also automatic. Approval of course is not based entirely on testing results but on other factors including adherence to CGMPs throughout the manufacturing process—for instance in-process testing and review of any deviations from the prescribed procedures. In the latter case, a formal assessment of its impact on product performance is made by the proper level of authority. Any unexplained discrepancies or failure to meet specifications are thoroughly investigated with consideration given to other batches which may be affected.

Of course the analytical methods employed must be validated for the corresponding batch designation—composition and manufacturing process. During analysis the bulk batch is sealed, labelled and stored under quarantine in the Central Dispensary.

PACKAGING

The principle of physical separation is invoked once again. Only one job is packaged in each room at a time and access is limited. Doors are lockable for security and integrity purposes. Packaging materials and bulk batch are requisitioned from the Central Dispensary in exacting amounts required for the job. Packaging and assembly are performed according to

the Master Packaging Formula and the corresponding approved packaging log sheets. Proper records are kept and measures to prevent product mix-up are taken. Equipment and rooms are of course cleaned between jobs. If possible when supplies are packaged for a major product NDA, rooms are dedicated for that product which minimizes the need for exhaustive cleaning.

LABELING

This function has the reputation in the industry for the most frequent cause of product hazard and product recall. Text for label is jointly written by the medical department and pharmaceutical R&D and approval is given by Drug Regulatory Affairs. To facilitate speed of approval (because the three departments are separated by considerable distances) the text is planned to be transmitted electronically such that labels cannot be printed by the computer without the proper authorization/protection codes. The validated computer system prints the labels twice over to guarantee precision of alignment. Precise numbers are printed to facilitate reconciliation and no storage is required since they are printed "on demand". Furthermore, a copy is stored on disk in the computer. Special unique numbering for blinding and randomization purposes can also be handled appropriately. Color, size and shape allow for extra flexibility.

Exactitude of labeling accountability is a must. The only weakness in this system is that the labels are applied manually (in most cases) and are therefore subject to human error. Identity checks are therefore required and final samples are taken by Quality Control personnel according to a preset statistically based sampling plan. Again a single product labeling line is employed.

PACKAGED GOODS APPROVAL

Final approval is based on the total process (reconciliation of yields, etc.) and requires signatures from proper higher levels of authority--such as Assistant Director or designee from both Quality Control (analytical R&D) and pharmaceutical R&D.

STORAGE AND SHIPPING

After the labelled goods are assembled and boxed, they are placed in shippers and cartoned to minimize deterioration, contamination, spillage and breakage. The consignment is labelled and shipped to the warehouse for further distribution. Here it is stored in an environmentally controlled secure area. To track temperature abuse during shipment in the field, the use of temperature sensitive labels should be considered. This will be particularly useful when perfectly adequate supplies of scarce material are returned from the field for potential use by another investigator.

RETAINS

Samples of bulk raw material, finished packs, and unusual excipients are stored at ambient temperature and kept usually for 7 years. They are kept in a secured area and cataloged for easy retrieval. Since these are essentially regulatory samples, withdrawals are discouraged and only allowed with very good reason. Files are kept on a computer. Usually twice the amount needed for a battery of release testing is retained. Also batch records are microfilmed and stored in a vault.

CLINICAL STABILITY

Historically, limited consideration was given to monitoring the stability of the clinical materials while they were in the field. The Company, however, is clearly responsible for their integrity during the clinical trial

and appropriate measures need to be taken. It is particularly important to prepare enough quantity as stability supplies might in fact constitute a high percentage of the batch. Representative samples are taken and stored at room temperature and 33°C for periodic testing. Assay results obtained for release are taken as zero time numbers. Reassay dates are assigned based on statistical treatment of data accumulated during preformulation and dosage design. To save resources, the 33° samples are assayed only. If no changes are observed, then the room temperature samples are disregarded. Extensions based on statistical kinetic analysis of accumulated data are granted by the principal formulator and the clinician is notified by letter. Critical quality parameters used to establish performance, safety and efficacy are usually monitored as the supplies age. These may include potency, dissolution rate, or color change of active versus placebo (in a double blind study). Clinical stability testing is clearly an evolutionary process. Conclusions reached at any one phase form the basis for designing testing programs at each subsequent phase. If the formula changes, or the method of manufacture changes, then this obviously calls for a new stability study.

SUMMARY AND CONCLUSIONS

These are the elements of preparing clinical trial materials and the chronology followed by the clinical supplies team. A critical aspect at this point is reconciling the differences or rationalizing the varying or conflicting viewpoints of managers comprising the clinical supplies team. It is essential to be consciously aware of the fact that the different managers who are all part of the exercise approach their tasks from different angles--because they find themselves measured by different yardsticks. For

instance the chemical process development chemist wants to get as much yield as possible for the lowest cost, no matter what physical properties may result. On the other hand, the formulator wants reproducible physical properties from start to finish, irrespective of the cost, just as long as his formulation runs smoothly all the time. Meanwhile, the process development chemist always believes his batch is of acceptable purity, yet the analytical chemist delights in finding and quantifying impurities. The medical monitor wants to use the commercial formulation right from the beginning so he won't have to interject a bioavailability study to qualify a new formulation, yet the development pharmacist may have no choice but to change excipients to facilitate machine filling at high speed or to enhance stability. Large scale trials may not be possible if the toxicologist has consumed all of the material in the beginning. On the other hand the packaging engineer wants a straight-forward container that can be filled on a high-speed line, yet the medical monitor wants an elegant blister pack that will enhance patient convenience and compliance.

The important issue here is to reconcile differences rationally and keep communications open. In such cases, success depends on the ability to make a compromise instead of running an undeclared war between the factions. Success also depends on managing resources across a broad range of disciplines and skilled trades. It can be compared to managing a 49 man roster on a football team in the NFL—each player has shared responsibilities—either a kick return specialist or a running back depending on the phase of the game. In like manner, a pharmaceutical scientist may design formulations one day and supervise manufacturing or packaging the next. Use of combined talents is the only way to meet the challenge and get the job done within normal constraints.

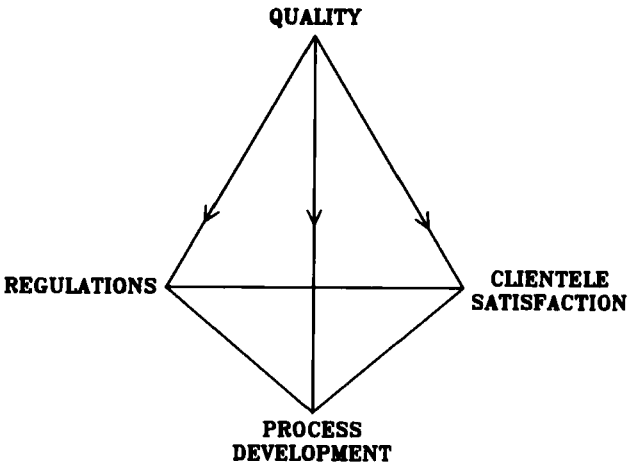
A word about people. In some corporations, the clinical supplies group has traditionally been the dumping ground for over-the-hill scientists. In the modern day environment, however, it is imperative to employ highly trained specialists to perform the work. Because the primary function is dispensing, it is incumbent on management to employ pharmacists who are the only ones properly and legally trained for this job, i.e., a 5-year baccalaureate degree and a state license constantly upgraded and kept current by continuing education credits. The key concept is to have a dedicated section who are knowledgeable in CGMPs, SOPs, computers, trend analyses and statistics, as well as manufacturing and packaging science, and who are personally committed to a standard of excellence in these areas and in keeping impeccable records. A GMP training program, besides being a requirement, is absolutely essential. It should include meaningful didactic work and discussion of case studies. Since the technology is rapidly changing, there is a pressing need to maintain current awareness. The architecture of the group should also be fabricated to include a research component for each employee. The areas of robotics, optical recognition systems, heat sensitive labels and new polymers are current areas for fruitful and active research.

As far as validation is concerned, it is certainly a requirement of the GMP regulations, 21 CFR part 211. This is basically because one has to provide suitable assurances of (a) safety and quality for the patient receiving the clinical supplies, and (b) identity, strength, purity, quality and safety of these drugs being reproducible from lot to lot comparable to a commercial dosage form. Now there are certain obligatory requirements from which no one can escape, viz. end-product testing such as sterility,

pyrogenicity, hygiene, potency, particulates, stability, reliability and accuracy of equipment, environmental air and water quality, purity and analytical methods, and data review and summary. However, because of the flexible nature of clinical supplies production, and the general lack of time and materials to conduct traditional validation experiments (autoclave loads, blending times, media fills, filtration bubble points, etc.) the concept simply is impractical in this case. What one has to do then, is to rely upon the modus operandi—the essence of this presentation today—i.e., the overall level of control and documentation exerted upon the procedures for carrying out the enterprise via a vis sound scientific principles and good management practices applied throughout the total process, as well as the degree of self-imposed auditing and peer inspection. As long as samples are taken intellegently along the way according to a carefully planned process flow diagram, failure investigations are reported and corrective action described, as well as the alluded-to documentation, existence of a "state of control" becomes fully defensible.

To accomplish the above...it becomes increasingly necessary to apply new levels of sophistication and new techniques to the execution of this function.

Over-riding all of these comments is the ultimate goal of research-based corporation—a steady stream of new products. To survive, a multitude of clinical studies must be ongoing and the supplies pipeline must be filled. No mistakes are permitted. A depiction of the delicate managerial balancing act required for this arena is shown in Figure 4. The pyramid illustrates the 3-way pull between Quality and the necessity to comply with GMPs, the necessity to develop a commercial product, and the



CLINICAL SUPPLIES MANAGERIAL SURVIVAL PYRAMID

FIGURE 4

pressing need to deliver the supplies on time. Clearly then, if management is truly committed to excellence, it makes eminent business sense to invest in this arena just as heavily as in the other critical parts of the corporation.

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