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DEVELOPMENT OF AN NDA - HOW DO WE GET THERE?

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The title of this conference is "Scientific and Strategic Planning from NDA back to the IND." The concept of the conference planners was to take a retrospective review of the development process from the time the NDA is submitted to the FDA back to the IND filing and determine what could have been done differently. As the keynote speaker, by definition, it is my responsibility to present the issues. Some of the issues include:

1) How can we reduce the development time and minimize cost without sacrificing the quality of the NDA submission?
2) What scientific approach and strategy should we use?

I am sure that the speakers who follow me will, in part, address these issues in their specific areas of expertise.

This conference is based on the assumption that the IND, for a solid dosage form has been filed with the regulatory agency and that we are now embarking on a program to obtain the data needed to file an NDA. It is at the time of the IND filing that the regulatory agency first becomes aware of your new chemical entity.

What I intend to do, is review with you the various components that comprise an NDA and attempt to identify specific areas where a different strategy or scientific approach might influence the NDA process.

Table I contains the contents of an IND.

TABLE I

CONTENTS OF THE IND APPLICATION

1. Form FDA 1571
2. Table of Contents
3. Introductory Statement
4. General Investigational Plan
5. Investigator's Brochure
6. Protocols
   a) Study Protocol(s)
   b) Investigator Data
   c) Facilities Data
   d) Institutional Review Board Data
7. Chemistry, Manufacturing, and Control Data
   a) Environmental Assessment or Claim for Exclusion
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information

TABLE II

CONTENTS OF THE NDA APPLICATION

1. Index
2. Summary
3. Chemistry, Manufacturing, and Control Section
4. a) Samples (Submit Only Upon FDA's Request)
   b) Methods Validation Package
   c) Labeling
      i. Draft Labeling
      ii. Final Printed Labeling
5. Non-clinical Pharmacology And Toxicology Section
6. Human Pharmacokinetics And Bioavailability Section
7. Microbiology Section
8. Clinical Data Section
9. Safety Update Section
10. Statistical Section
11. Case Report Tabulations
12. Case Report Forms
13. Patent Information On Any Patent Which Claims The Drug
14. A Patent Certification With Respect To Any Patent Which Claims the Drug
15. Other

TABLE III

Development And Reserach Functions Involved In Drug Development

Analytical Chemistry
Biochemistry
Biostatistics
Chemical Development
Chemotherapy
Data Processing Center
Drug Metabolism/Pharmacokinetics
Drug Regulatory Affairs
Medical Research
Organic Chemistry
Pathology/Toxicology
Pharmaceutical Research
Pharmacology

This is the information your company has submitted to the FDA.

Table II contains the contents of an NDA. This is the information we want to develop. Except for the clinical portion, most of this will be an expansion of the data base started in preparation of the IND. The approach to develop an NDA is based on my experience, and may not be identical for every pharmaceutical company. In most drug companies the development of a drug involves the expertise of many research and development functions as shown in Table III.

It is the responsibility of management to orchestrate the activities of these functions in order to optimize the development effort. This requires close project monitoring and coordination.

In some companies the coordination of projects is handled by development teams composed of members from the various research and development functions. These development teams are chaired by a member of the team, and the chairman may be changed as the compound moves through the various stages of development. In other companies, the coordination is handled through line management. Regardless of what system is used, the coordination of the projects is of the upmost importance.

The development of a drug is a long and costly process. The average time to obtain the data needed for an NDA is approximately four years after the IND has been submitted. The variation around this average can be large depending on how poorly or well the development process is planned and coordinated. Based on 1987 figures, the average research and development cost to develop a drug was 125 million dollars.

Many of the scientific programs were started prior to the filing of the IND and are continued up to the NDA submission. It is after the IND submission that the clinical program can be started in the U.S. The Phase I clinical study can start thirty days after the FDA has received the IND, provided the FDA does not inform you to hold shipment of the drug. The objective of the clinical investigators is to assess whether the drug substance is of value in the treatment or prophylaxis of a disease, keeping in mind the benefit to risk ratio. This involves determining the tolerance to the drug first in normal subjects then in the disease state.

TABLE IV

Phase I - Clinical Study

Rising Single Dose Tolerance With And Without Pharmacokinetics

Multiple Dose Tolerance With And Without Pharmacokinetics.

Clinical Laboratory Tests

Female Exclusion

Washout Period

24 Hour Surveillance

The Phase I clinical pharmacology studies include the initial introduction of the new drug substance to man. In most cases, normal volunteers are involved, except where contraindicated because of the potential toxicity, as with chemotherapeutic agents for the treatment of cancer. Table IV contains a list of the parameters associated with this type of study.

The Phase I studies are usually conducted within a hospital setting. These studies are concerned with tolerance and pharmacokinetics and the effect of the drug on target organ systems. Dose-range studies conducted during this phase also provide information on the maximum tolerated dose. This type of study involves administering various doses, starting with a very low dose and proceeding cautiously up to a maximum tolerated dose. The pharmacokinetic information gained from these studies could aid the toxicologist in determining dosing frequency and in select-

ing an animal species, for his chronic toxicity studies, that metabolizes the drug substances in the same way as man.

The analytical chemist also becomes involved in regard to developing assay methods for the drug substance in blood, urine, and body tissues. These methods are needed for studying drug absorption, distribution, metabolism, and excretion.

The formulation usually used in Phase I and the early Phase II studies is what I term a "Clinical Pharmacology Formulation" versus what will eventually be developed as the "Commercial Formulation."

As mentioned before, this is the first time the drug is introduced to a human; therefore the investigator will start with a very low dose and gradually increase it until the maximal tolerated dose is obtained. The difference between the lowest and highest doses used could be extremely wide since the initial dose is usually based on a fraction of the minimal symptomatic dose in the most sensitive animal species from the toxicology studies. The maximal tolerated dose could be a large multiple of the starting dose. Therefore, it is usually a waste of resources and time to attempt to finalize a formulation before the drug has been demonstrated to be effective and an optimum dose has been defined. It would be preferable to have a simple solution, suspension, or a lactose mix in a capsule where the dose can be easily changed. This simple type of formulation can be used unless there is evidence from preclinical studies that the drug solution or the drug substance administered as a suspension is poorly absorbed.

If a clinical pharmacologic model exists for drug activity, then the Phase I clinical study in normal volunteers can also be used to determine drug activity. For instance,

if one is evaluating an antihistamine, you could induce a histamine wheal in the skin to determine antihistamine activity. Antiserotonin and antibradykinin activity could be similarly evaluated. Citric acid induced cough has been used for early evaluation of antitussives, and the vasoconstrictor skin test has been used for topical steroids. The use of a biochemical marker in normals is another parameter that can be used. An example of this is the effect of compounds on glucose and insulin levels when evaluating an antidiabetic agent or the effect of compounds on blood platelet monoamine oxidase activity when evaluating inhibitors.

Therefore, if one could devise a pharmacologic test in the clinic, it could be possible to obtain an early indication of the activity of the compound. These studies could also provide information regarding onset and duration of drug action. Positive results from these types of studies would provide an impetus to invest more time and resources early in the development program. The financial risk of initiating long-term toxicity studies at an earlier stage of development would be minimized.

Phase II clinical investigations are intended to include early controlled clinical trials designed to demonstrate efficacy and relative safety in patients. Usually, the early studies are performed in closely monitored patients. Some of the parameters associated with this phase are contained in Table V. Early Phase II studies should be pilot in nature. It will save considerable development time later if dose response curves following single and multiple dose can be established now. I can't over emphasize how important it is to establish an effective dose range early

TABLE V

Phase II - Clinical Study

Research Institute - Specialists
Open And Controlled Clinical Trials
Multiclinical Studies
Clinical Laboratory Tests
Biostatistics
Comparative Clinical Trials

in the program. This type of information would also help the formulator in establishing what dosage strength to develop in finalizing the commercial formulation.

After initial positive results from the early Phase II studies, one can decide to escalate the clinical program. In the early part of Phase II, it is best to focus on one clinical condition until efficacy and safety are established.

In setting up clinical trials, it has been my experience that these usually take twice as long as was contracted for with the investigator. The reason is that patient entry is much slower than promised. This is a result of investigators promising the same patient population to different companies. Therefore, in order to expedite this phase, one can decide to start twice the number of studies needed and pool the data at the time an adequate number of case report forms are in house. This will depend on the resources available and the philosophy of the Medical Department.

It is also in Phase II that the Data Processing and Biostatistics Groups should become actively involved in helping to plan the clinical program so as to minimize patient load without compromising the development time. Their early involvement will also be of help when the data have to be analyzed.

The development of many drugs are discontinued at the end of the early Phase II studies because of side effects or lack of evidence of efficacy. Available animal laboratory tests are incapable of detecting certain adverse effects that occur in man. These include epigastric distress, headache, tinnitus, and urticaria. Some blood dyscrasias such as agranulocytosis are not detected until a large number of subjects have been exposed to the compound. When any of the above side effects occur in a large percentage of the subjects at therapeutic levels the development of the compound usually ceases.

If the compound survives the above obstacles, Pharmacy Research should begin efforts toward developing the solid dose form that could be commercialized. We are assuming that all preformulation work had been initiated when the compound was identified as a clinical candidate. Formulation development will proceed from the laboratory bench, through pilot plant equipment, and eventually into manufacturing. Much of the clinical trial material will be made in the pilot plant.

In the case of a multinational company, it is very important at this early stage to consider excipients, flavors, and colors that are available or acceptable in other countries if your company desires to move toward a global formulation. It is also important to know the manufacturing equipment in use at the various manufacturing sites in regard to transferring the process at a later date.

Dissolution methods are developed at this time for the solid dose forms as a process control tool, not as a predictor of bioavailability. In regard to solid dose forms, an attempt should be made to use the same granulation for all dose strengths. This reduces the number of clinical bioavailability studies and eventually manufacturing inventory. However, this does increase packaging problems when conducting double-blinded clinical trials.

It is important to start stability studies as early as possible, particularly in packaging material and container shapes that will be used for commercial purposes. Unlike other areas in development, one cannot reduce the time it takes to obtain one, two, or five years stability data. Although this is not the primary data to be used to establish outdates, it can be used as supplemental data in supporting a statistically derived estimate on the expiration-dating period. Also included in the stability program should be a study of the effects of temperature fluctuation for the shipping and storage conditions that may be encountered in distribution. This should include cycling through temperature conditions that simulate distribution conditions.

The process for deciding the shape, color and what is to be printed or debossed on a solid dosage form is extremely important in saving time and mental strain for the formulator. We have instituted a system whereby this decision is based on an agreement by the formulator, research management, and representatives from Manufacturing and Marketing. This recommendation is then approved by the President of the company. In some companies, this could be approved by a business management team, provided the members of the team are at a decision making level in their respective areas.

In the past, a product manager would make one decision and, as we progressed through the development process, the

TABLE VI

Toxicity Studies - Chronic

General Toxicity - Target Organ Studies	
Reproductive Studies	
Segment I -	Fertility And General Reproductive Pperformance
Segment II -	Teratological Studies
Segment III -	Perinatal And Postnatal Studies
Carcinogenesis Studies	
Irritation Studies	
Sensitivity Studies	

product manager would be changed and the new manager would want a different color and tablet shape. These types of changes could result in analytical methods being revised and in starting new stability studies, thus causing a delay in the development project.

Chronic toxicity studies is another area where the development time cannot be markedly reduced. There is no way of obtaining one or two year toxicity information in six months. Table VI contains some of the studies conducted during this phase. The duration of toxicology studies will depend on the length of treatment needed in the clinic or the class of drug being studied. Interim sacrifice periods should be built into these studies to allow for multiple dosing in the clinic during early Phase II since, in many

clinical conditions, at least one to two months treatment may be needed before efficacy can be determined. It is only after the completion of teratology studies that women of child bearing age should be entered into the clinical evaluation program. A number of compounds fall by the wayside because of toxic effects in animals, particularly in the area of teratology and carcinogenesis.

It is during the conduct of the Phase II clinical studies and prior to starting the Phase III studies that the formulation intended for marketing should be developed. It would be wise to determine the bioavailability/bioequivalence of any new formulation in a pilot bioavailability study prior to initiating any extensive clinical study. It is essential, if at all possible, that all pivotal clinical studies be conducted with the intended commercial product. This is also true for the drug substance. If Chemical Development desires to develop an economical, efficient, practical and safe process, it should be developed, if possible, at this time. By knowing the physical properties of the drug substance to be made available at the commercial level, the formulator can better finialize the process needed to scale up the solid dose form. Both formulation and process of the drug product can have an effect on bioavailability.

Analytical Chemistry must finalize the test methods to assure the identity, strength, quality, and purity of the drug substance and product. They must also finalize the specifications needed to assure batch-to-batch uniformity for both drug substance and product.

I am convinced that the development process can be greatly enhanced if the coordination of Phase III is controlled by a committee consisting of decision makers who

TABLE VII

Phase III - Clinical Study

Expanded Drug Exposure
Specialists And General Practitioners
Women, Pediatrics And Geriatrics
Combination Studies

meet on a set schedule throughout the year and specifically review the development status of a particular compound. Everyone should be held accountable for adhering to the development time line, particularly those responsible for the clinical operating plan which has the greatest tendency to slip.

Phase III clinical studies are the expanded controlled and uncontrolled trials (Table VII).
For initiation of Phase III all three segments of the animal reproductive studies should have been completed.

During this clinical phase, studies with drugs commonly used in the treatment of a disease will be conducted to determine drug interactions. For certain types of drugs, one may want to consider fixed drug combinations.

The formulator and the clinical department begin to consider other routes of drug administration (Table VIII). Fortunately, the human body does not have more orifices than we currently have or the formulator would possibly be faced with additional formulation work than is contained in Table

TABLE VIII

ROUTES OF DRUG ADMINISTRATION

Oral	Parenteral
Sublingual	Intravenous
Buccal	Intra-arterial
Topical	Intracardiac
Intraocular	Intraspinal
Intranasal	Intraosseous
Aural	Intra-articular
Intrarespiratory	Intradermal
Rectal	Subcutaneous
Vaginal	Intramuscular
Urethral	
Transdermal	

IX. However, now is the time to consider developing various formulations if the clinical situation and market warrants them.

In some companies, the methods developed in the Analytical Department are transferred to the Quality Control group prior to manufacturing the validation batches. This provides them the time to become familiar with the methods and develop automated procedures where needed to handle assaying the various dosage strengths in the various sizes and types of packaging.

Pharmacy Research will begin to prepare small production batches on production equipment. This would also be the

TABLE IX

Dosage Forms

Tablets	Ointments
Capsules	Creams
Solutions	Pastes
Syrups	Plasters
Elixirs	Aerosols
Suspensions	Lotions
Magmas	Sachets
Gels	Sprays
Powders	Inhalants
Troches/Lozenges	Suppositories
Patches	Chewing Gum

approach that Chemical Development would use for the drug substance. In process controls are established for the manufacturing process for both the drug substance and the dosage form. Following this phase, three validation production batches of each dosage strength are made.

In developing the commercial formulation, one should consider making several large scale batches prior to preparing the three validation batches. This experience would provide you with the confidence that the process and formulation are correct and do not require any modifications.

Samples of capsules or tablets should be selected from one of these validation batches for the definitive bioavailability study. Based on the above manufacturing experience,

TABLE X

Product Name

Nomenclature Committee
U.S. Adopted Name Council (USAN)
World Health Organization (WHO)
International Nonproprietary Name (INN)
Trademark

they should be representative of the various validation batches so that the dissolution rates and product specifications that are developed will encompass this batch as well as the previous batches.

It is at this point that the product process is transferred from Research to Manufacturing. Slight modifications in the process may be necessary as more experience is obtained with subsequent batches.

When a compound is first submitted for study it is assigned a chemical name and code number (Table X).

If the compound is active and recommended for clinical evaluation the company nomenclature committee will recommend a nonproprietary name, generally referred to in the U.S. as a generic name. This name must then be approved by the USAN (U.S. Adopted Name Council) which is a group composed of representatives from the AMA, USP, APhA and FDA. In addition, for global use, the name must also be approved by WHO and is assigned an INN (international nonproprietary) name. The

members of the WHO committee on Nonproprietary Names are drawn primarily from representatives of the national nomenclature agencies. The Trademark name is one that is registered with the U.S. Patent Office.

Product packaging is usually a joint decision between Research, Manufacturing, and Marketing. Marketing is concerned with the presentation to the physician and pharmacist. Manufacturing is concerned with these as well as bulk packaging. Research is concerned with all packaging in regard to product stability. Changes in packaging design and composition, particularly with polymers, could have an effect on product integrity.

Finally, the Drug Regulatory Affairs Department will prepare sample labeling to be used with the product. This includes package inserts, labels on the bottle, and any other material which is supplied to the physician. Labeling is approved by the Medical Department for accuracy of content and must be consistent with the supporting data.

The company Drug Regulatory Affairs Department should designate a person to be the contact with the FDA. This person should make the routine administrative contacts. In addition, the actual scientists involved with a compound should interact with the FDA scientist(s) regarding scientific questions. However, these contacts should be handled through the DRA department.

After the human pharmacologic and clinical studies previously described have been completed, and the manufacturer is convinced that the new drug is safe and effective, a New Drug Application (NDA) with supporting data and proposed labeling is submitted to show that the drug is safe and will have the claimed therapeutic effect when used as prescribed in the proposed labeling.

And thus we have completed our journey from IND to NDA and now await the review process within the FDA. Preliminary periodic visits with the reviewing division scientists during the development program may help expedite the reviewing process and reduce unnecessary testing. A dialogue with the FDA should be on-going during the entire review time up to the FDA approval of the New Drug Application.

I hope that I have given you an overview of the development process and have identified how this process can be expedited.

REFERENCES

1. E.A. Swinyard, in "Remington Pharmaceutical Sciences" 17th Edition, Mack Publishing Company, Easton, Pennsylvania (1985) p.1357.

2. B. Spilker, "Multinational Drug Companies - Issues in Drug Discovery and Development," Raven Press, New York (1989).

3. F.D.C.Reports, January 9, 1989, p. 4.