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ORGANIZING TECHNOLOGY TRANSFER FROM RESEARCH TO PRODUCTION

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ABSTRACT

An overview of issues to be considered when organizing the transfer of technology from the research arena to the production environment will be presented. The discussion will focus on the coordination and implementation of a transfer program for a product with emphasis being given to those factors peculiar to the pharmaceutical industry. The success of any program is highly dependent on the effectiveness of the communication preceding its implementation. Therefore, the preparation and distribution of a complete document

summarizing raw material and equipment requirements, manufacturing and packaging processes, process validation parameters, quality control procedures, as well as a detailed plan of action outlining expected results and time frames, must be disseminated prior to the scale-up experience. Input from the marketing and manufacturing centers must also be integrated into the plan to ensure that the right product is developed at the right price within the desired time frame. An outline encompassing these critical aspects of a transfer program will be presented.

INTRODUCTION

Recently, more attention has been placed on stream-lining the time it takes to bring a product to market. In high technology areas, the element of time, combined with the associated costs of manpower and physical resources, frequently results in very expensive ventures. The pharmaceutical and cosmetic industries are no exception. Planning for process commercialization is one area where tangible rewards can be realized. The successful transfer of a project to a production site from the research arena does not happen on its own. Organizing the transfer of a technology or new product from research to production

may be one of the most perplexing problems that a development scientist,engineer, or marketer may encounter during their career. This presentation will provide some insight into what issues should be considered during the transfer program and offer a sequence of events toward completing the task.

To rationalize the reasons why planning your future efforts are necessary, one must consider the development process.While very simplistic in its scope, the development process may be represented by this first figure (Figure 1) prepared by Brian Rushton of Air Products and Chemicals ,Inc.[1]. It shows that the major decision point in the development pipeline is that point where the idea or process is advanced from a purely research oriented program to that targeted toward commercialization. Generally, the cost of product development rises dramatically during the pilot scale-up and initial production batch efforts.In other words, the critical path for success is dependent on the completion of the technology transfer to the production site at a livable cost.

Three major issues must be addressed to implement an effective transfer. Namely, a plan must be devised to organize the people and process steps involved. Once prepared, the plan must be communicated to the involved

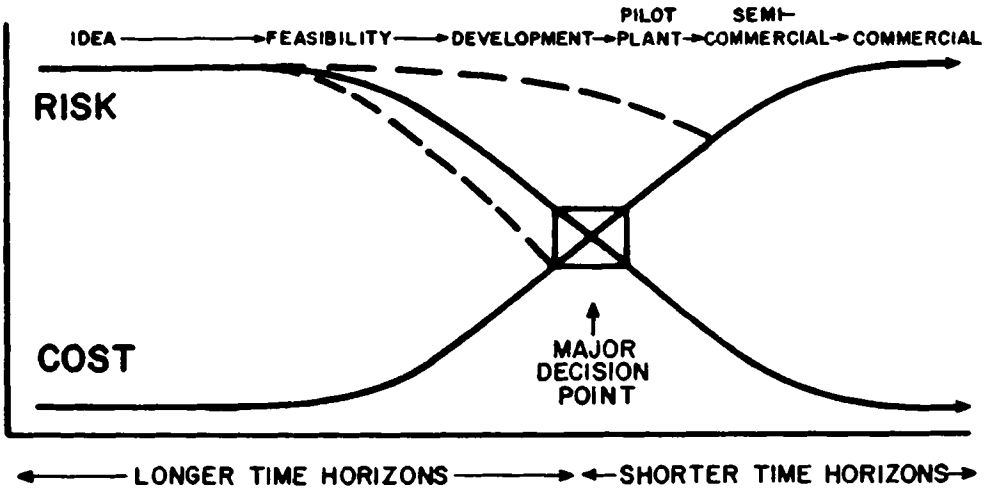

FIGURE 1 -- THE INNOVATION PIPELINE

parties in research, at the corporate level and at the production site. The success of any program is highly dependent on the effectiveness of the communication preceding its implementation. Therefore, identifying the parties involved in the development process is an important issue to be considered.

PERSONNEL

Let us first discuss the people involved in the transfer program. As it has been said, knowing who the actors are makes the play more enjoyable.So it is here. Informing the proper personnel of their involvement, desired contributions, and responsibilities up front

helps to identify potential problem areas which may hinder the accomplishment of the task at hand.

From the research and development group, a Project Leader is the focus of the communication pattern. It is the responsibility of this individual to coordinate the assembly of the necessary information to support the product's advancement for process development. Information from the Product Development area would be gathered from the formulator, analytical and microbiology testing groups,as well as the packaging development unit. A safety evaluation from the Toxicology group should be completed prior to a scale-up effort. Reviews should be also solicited from the Patent Department and Drug Regulatory Affairs units to insure that proper legal protection has been secured and that an agreement as to how much of what information is needed to either submit for a drug approval or introduce the cosmetic to the market place. The goal here is to collect the proper amount and kind of data necessary to support the prerequisite filings, either internal or external to the company.

From the Corporate offices it is common to involve personnel from the production planning unit, engineering group, new product coordination section as well as marketing as each of these divisions have a

vested interest in the success of the venture. The effort to keep them informed becomes a critical accomplishment toward the final acceptance of the product by the corporation. Therefore, any time taken with them to explain the steps involved in the transfer program is time well spent.

At the manufacturing site , there are a number of individuals whose cooperation must be gained to insure the timely and efficient completion of this transfer effort.The plant manager,technical director, production planning group, manufacturing area supervisor,quality control and quality assurance units,plant engineering, packaging, and transportation supervisors must be informed as to their responsibilities. Manpower training must also be considered if the technology is new to this site. Last but not least, do not overlook the contributions that the line mechanics and chemical operators can make to the program. Remember they perform the necessary functions day in and day out. Their insight and practical experience are an invaluable resource which should not be overlooked.

The success of the transfer is dependent on the ability of the Project Leader to motivate people to work with you toward a mutually beneficial goal; that is, introducing a new product which, hopefully, will

create jobs and profits for the company. It is of the utmost importance to never forget that when you are presenting the worth of the project all around your company, what you are striving to do is to express yourself, rather than to impress others.

PRE-TRANSFER CONSIDERATIONS

Prior to the advancement of any product for plant scale-up trials, several assumptions must be accepted. First, the Marketing division should have examined the proposed product prototypes and agreed that the product meets their needs. Second, the intended commercial package configuration (color, size, shape, composition,etc.) should have been selected.While it is not uncommon to package portions of the first scale-up batch in a variety of packages, it is incumbent upon the Project Leader to eliminate any unnecessary packages to minimize the dilution of effort. Third, any constraints, such as cost or time, must be identified so that they may be given due consideration.

TRANSFER PROGRAM

Any development program should be reduced to a written form.Figure 2 summarizes such as development program. A outline or check-list for the program must

PROJECT TRANSFER CHECK LIST

Activity	Completion Dates Target	Actual
1. Formulation selected		
2. Site for trials established		
3. Planning meeting scheduled		
a. Manufacturing Monographs		
b. Raw Materials		
c. Packaging Monographs		
d. Packaging Components		
e. Testing Monographs		
f. Process Validation Protocols		
4. Date of plant trial established		
a. Manufacturing		
b. Packaging		
c. On-site Review of Experience		
d. Shipment to R&D Center		
5. Date of shipment delivery		
a. Confirmation of Results		
b. Stability Initiation		
c. Product Evaluation - Safety		
- Efficacy		
6. Post production review meeting		
7. Assembly of final monographs		
a. Manufacturing		
b. Packaging		
c. Testing		
d. Stability		
e. Material Safety Data Sheet		
f. Shelf-Life Projection		
g. Bibliography		
8. Review of final monograph		
a. R&D		
b. Manufacturing		
c. Quality Control (Testing)		
d. Regulatory Affairs		
e. Corporate		
9. Issue product monograph		
10. First Commercial Batch		

FIGURE 2 -- PROJECT TRANSFER CHECK LIST

be compiled to ensure the appropriate consideration has been given to relevant issues. This also helps to insure that all parties are approaching the task from the same perspective and priority. A manufacturing site must be designated and the appropriate personnel notified as to their involvement. Assembly of the collected necessary information must be disseminated to the involved parties. At a minimum, copies of the proposed formula and manufacturing directions should be distributed so as to allow sufficient time for review and comments to be generated. A planning review session should be convened with representatives from the Research, Corporate, and Manufacturing sites in attendance. Selection of the time and location of this meeting should be such to encourage maximum participation.

The meeting should be chaired by the Project Leader. It is his or her responsibility to determine the relevant issues to be discussed, that an agenda for the meeting is distributed, and that minutes of the meeting are taken for later issuance.It is important that any concerns which arise during this meeting are noted and addressed as the purpose of this gathering is to draw from the experience of the participants in identifying potential problem areas in the program.The tone of this session should be one of a team and not

one of autocratic rule.Motivation, communication and cooperation must be stressed in the voice and actions of the Project Leader. This is the first step to accomplishing the prime program objective : The timely and informed transfer of a new product from the research arena to the production site.

The following areas should be discussed at the planning meeting:

a. Formula
b. Raw Materials
c. Manufacturing Equipment
d. Manufacturing Precautions
e. Manufacturing Directions
f. Packaging
g. Process Validation
h. Quality Control and Quality Assurance
i. Re-work Procedures
j. Transportation

Each area should be reviewed to ensure that critical issues have been addressed. A discussion of these elements may include some of the following thoughts.

Formula

As the base upon which all effort is centered, understanding the formula, its derivation and its constraints is the first prerequisite to any development program. The feasibility of the formula may be established by reviewing the ingredients of the composition and then explaining their function in the formula. It would be appropriate to review the claims and physical characteristics of the product while passing around a sample so that the participants appreciate what the product is to accomplish.

Comments about the pre-stability and finished product stability profiles should be presented as an overview of the new product's chemical stability. This will reinforce the formula's anticipated shelf life and ability to withstand the "process shocks" normally encountered during production scale-ups.

The toxicity of the finished product should be discussed. This information insures a decision regarding handling of the formula has been made based on generated data and/or experience. A draft or tentative Material Safety Data sheet may be one avenue to disseminate this information.

Review of any constraints such as specific ingredients or sources, cost of goods or manufacturing equipment should be made clear. This aspect helps to explain why given actions or directions were followed. Constraints must be considered when formula optimization is undertaken. Optimizing formulas, may, in some instances, be best addressed in the production environment as batch size and manufacturing equipment have been shown to render viable laboratory and small scale formulas virtually inoperative. The experience gained during the manufacture of laboratory and scale up batches is invaluable and should be shared with the participants, especially the production staff.

Raw Materials

Sources of raw materials, especially those critical to a new product's functionality, should be identified. Availability and costs should be ascertained to aid in the planning process. Testing monographs including methods to ascertain a lot's chemical and, if necessary, microbiological integrity should be provided to the selected manufacturing site in advance so that the methods may be applied to the incoming supplies. Handling of materials including storage, disposal and employee precautions should be

documented, especially for new or potentially hazardous materials.

Manufacturing Equipment

The availability, size and surfaces or composition of the required equipment needs to be specifically identified so that the scale up effort may be representative of a production run. A preliminary compatibility screen of contact surfaces should be completed where appropriate prior to the selection of scale up equipment. The location of the equipment to other needs such as services or the filling area may be a factor in the selection of equipment. A cleaning validation study should be conducted on the equipment used for this batch to ensure no residue remains and that the equipment is suitable for production use once again.

Alternate equipment may be considered and used. However, experience will dictate as to its suitability.

Manufacturing Precautions

While pretty much self explanatory, any concerns regarding the manipulating of equipment or product by employees should be voiced at this time. This is

especially important if the areas of concern are environmental, such as particulate contamination or sterility, or atmospheric, such as a product's oxygen sensitivity.

Manufacturing Directions

Directions should be clear and concise. Flexible generic descriptions (should be utilized were possible). For example, pass the emulsion through a suitable colloid mill such as an Eppenbach mill at a setting of 0.005 inches is preferred to a description referencing a specific piece of equipment. While process validation testing may be necessary for any particular piece of equipment, generic descriptions simplify the regulatory filings by allowing flexibility in allowable equipment.

Directions should be realistic. Remember that any instructions must be scale oriented. Specific parameters may be necessary for manufacturing areas. For example cooling or heating times are typically equipment dependent. Cooling 1 kg in the laboratory in 15 min may take 4 hours for a 40,000 kg batch in the plant.

Based on the experience gained during the pilot scale up effort, a process flow chart should be constructed. A process flow chart helps to identify steps and issues in need of process validation review. Also, the timing of activities toward the scheduling of manpower needs, such as for in-process testing, generally are more apparent when viewed in context with the total process.

Process optimization parameters as identified during the pilot scale up effort should be monitored during the production scale-up batch. In this way, appropriate recommendations based on experience may be integrated into future batches. Many optimization experiments may be efficiently incorporated into the process validation program.

Packaging

The description, specifications and test methods for any package to be processed should be available to the plant prior to the production scale-up. Unit functionality and fit should be included as a practical use test in any specification. The plant equipment to be utilized in packaging this batch needs to be evaluated for its feasibility, speed, if it is critical, and contact surface compatibility.

Preliminary evaluations on surface compatibility, as discussed previously should suffice as an early indication of packaging equipment suitability. Finally, the cleaning of the packaging equipment should be checked prior to the equipment being used for other products.

The availability of, or lead time to secure, the necessary packaging components frequently places stress on the project time line. Package costs and possible alternative packaging could be evaluated with bulk produced from this batch. Therefore, a course of action to minimize project failure due to an unsatisfactory package may be appropriate.

Directions for filling the batch including fill tolerances and precautions such as aseptic handling or nitrogen gassing should be reviewed to state the requirements for success up front. As a part of this production scale-up effort, it may be desirable to evaluate the product's bulk stability in the storage tank in order to establish limits on the length of time a batch may be held prior to filling. Storage container compatibility may be a crucial issue here and deserve appropriate attention.

Finally, the personnel involved in packaging of the product should be instructed about any safety and handling issues which might affect them or compromise the product's integrity.

Process Validation

Each class of products needs specific issues to be addressed. In general, process steps which may be variable such as mixing times and temperatures, need to be validated. Many articles have been written regarding the validation of processes affecting pharmaceutical products. Protocols to evaluate those parameters which may affect a product's integrity should be agreed upon by both the R&D and production staff. During the preparation and packaging of the pilot production batch, generation of data toward improving the efficiency of these processes as well as minimizing batch to batch variations is very important as this information will serve as documentation to support the new product's commercial feasibility.

Quality Control and Quality Assurance

One of the purposes of the pilot production batch is to introduce the manufacturing site's functional

areas; manufacturing, packaging, and control, to the new product in its entirety. Therefore, in addition to the manufacturing and packaging issues previously discussed, the release of raw materials and packaging components, as well as in-process, bulk, and finish product testing should be completed at the site as if this were a commercial batch. In many organizations, the pilot production batch does, in fact, become the first batch offered for sale.

Formula issues to be discussed are those concerning the in-process testing, bulk release prior to filling and finished product specifications. These limits are proposed based on the experience gained with the smaller laboratory and scale-up batches. Essentially any comments or concerns regarding the test methods and specifications should be aired at this time. Reagents and equipment to complete the required testing must be available at the plant. A contact at the R&D analytical laboratory should be established so that explanations to questions or aberrant values may be expeditiously secured.

Communication of requirements of time and manpower to the Quality Control Department is a critical issue that must not be overlooked. It is their prompt

attention to your analysis needs that helps keep the pilot production batch process moving forward.

Sampling must be scheduled for release and for stability testing using a statistically valid sampling program, where appropriate. This is especially important for samples to be used for stability studies. This way the chosen samples are documented to be representative of the entire batch.

Batch documentation, is also an important factor to be considered. Preparation of master batch records in accordance with plant SOP's should be followed by an approval of the document by the sponsoring division, usually the process development staff of the R&D unit. Upon completion, a review of the batch records by the Quality Assurance group ensures compliance to GMP's and that all necessary modifications to the manufacturing records are properly explained and documented.

Scheduling Date for Manufacturing Trial

When the date for the trial is being established, time constraints must be considered along with the availability of raw materials, packaging components, plant time, and the required personnel. Coordination of

the people and supplies is the responsibility of the project leader. An ability to lead and to negotiate another individual's priorities helps to bring the trials to completion on schedule.

Lastly, arrangements for transporting raw materials, if necessary, and filled product must be set up to insure the scale-up effort is completed on schedule and that stability studies are initiated expeditiously.

Complete the Manufacturing Trial

In review, the activities to be completed at the manufacturing site are:

a. release of raw materials and packaging components
b. manufacture and packaging of the trial batch
c. generation of data from in-process, bulk, and finished product samples
d. process validation, batch record, and on-site experience
   reviews
e. shipment of finished product to the research facility

Finally, an exit interview with involved plant personnel offers a mechanism for their comments to be aired. Their efforts should be acknowledged and their input seriously considered and incorporated into the manufacturing document where appropriate. Any differences which cannot be resolved at this time should be noted and studied further. The art of listening and diplomacy must be employed as this forum must be one of cooperation and not one of confrontation.

At this meeting a discussion about possible re-work procedures may be appropriate. The ability to recover materials, especially expensive drug actives, is desirable. Early identification of steps where re-work may be possible, allows for procedures to be tested and verified and in place should they be needed. Logistics and economics, as always, will dictate whether a re-work will be implemented.

POST PRODUCTION ACTIVITIES AND EVALUATION

Once the plant experience has been concluded, confirmatory analyses on duplicate samples for in-process, bulk release and finished product, previously tested at the plant site, should be completed at the

R&D center. In this way,the proposed methods are challenged to yield similar results in the hands of different analysts in different locations.Discrepancies in values generated at this point must be investigated and resolved.

Samples should be placed into the stability testing system as per the organization's policies.Samples may be also submitted, if necessary, for efficacy and or toxicity testing.

Finally a report must be prepared and issued expeditiously summarizing the experience, reviewing each area's involvement, and proposing, if necessary, changes in the process or control methods. Timely and factual communication of project progress to the other Corporate areas not directly involved in the scale-up, such as the marketing unit, aids in the commitment of resources.By fostering informed decision making through directed written communication , the time required to plan or complete those activities to bring the product to market is minimized and the resource usage optimized.

A formal Post Production Trial Review meeting should be scheduled and held with invited

representatives from the R&D, Corporate and Manufacturing centers. Plans to commercialize the product, or to submit documentation for government approval if this is the next step in the development scheme, are outlined contingent upon the successful completion of a defined stability program. Agreement as to the suitability of all the factors involved in the preparation of the product should be the result of this meeting with a substantiating document in the form of meeting minutes or a signed"statement of concurrence" being generated and distributed.

A product monograph of all pertinent sections to support the product's introduction, is assembled, reviewed, and disseminated to the appropriate parties as per the organization's policies.

The transfer of the project is considered complete when commercial batches of product are produced solely under the control of the manufacturing site without problems.

SUMMARY

This presentation has reviewed issues to be considered when organizing the transfer of technology

from the research arena to the production environment. Critical areas affecting the manufacture, packaging and quality of pharmaceutical products have been discussed in relationship to their impact on the transfer process. The necessity of the communication of a plan with input from the research, corporate and manufacturing centers was emphasized. The success of the program is highly dependent on the communication and cooperation shared throughout the transfer process.

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REFERENCES

1. B. M. Rushton, Research Management, 29, 22 (1986).