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MODERN PHARMACEUTICAL DEVELOPMENT

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Abstract: An analysis and discussion of the role of development in the pharmaceutical industry in terms of products and processes; pilot plant facilities and Good Manufacturing Practices; in-process controls and quality parameters, and the interface between Research and Development and Production. Examples of the organizational form of development groups in four countries are presented and interpreted.

The nature of research problems in the pharmaceutical industry involves an intermix of chemical, physical and biological principles which has over the past few decades led to the adoption by most research-oriented companies of a procedural pattern varying only slightly from one organization to another. New drugs continue to be born as synthetic chemicals or as plant or animal extractives; pass through the screening operations of microbiologists, pharmacologists and toxicologists; then through the formulation trials of research pharmacists, and finally into clinical investigation for the determination of safety and efficacy in man.

Application of the principles of physical chemistry to pharmaceutical materials, now known as physical pharmacy, has contributed greatly to the rationalization of pharmacy research by reducing the level of empiricism associated with the formulation of dosage forms. The recent flood of experimental and pedagogic interest in biopharmaceutics, serving as a cathartic reminder of the influence of physico-chemical properties on biological response, has to some extent brought back into research focus the previously obscured vision of

the patient as the significant element in the entire chain of events.

Eventually and, of course, hopefully, pharmaceutical preparations escape from the confines of laboratories and move up the ladder into full-scale manufacturing operations. When this stage is reached the problems involved take on a character requiring the adoption of a planning and operating philosophy associated with an organizational apparatus capable of coping with technological problems and governmental regulations related to the introduction of pharmaceutical preparations.

DEFINITION & CURRENT STATUS OF PHARMACEUTICAL DEVELOPMENT

Pharmaceutical development can be defined as that phase of overall pharmaceutical research and development which is concerned with the investigation, organization and initiation of the full-scale production of a pharmaceutical dosage form. Unfortunately, unlike chemical development with its career-oriented chemical engineers, separate university degrees and a large and important body of textbooks, journals and professional organizations, pharmaceutical development in spite of its obvious importance remains an illegitimate and unhappy orphan in the large, brotherly family of pharmaceutical scientists and technologists.

Although the expression "pharmaceutical engineering" is seen occasionally in the catalogues of some schools of pharmacy, there is little evidence that the same companies in the pharmaceutical industry which manufacture medicinal substances, and have operated chemical pilot plants for decades, have seriously considered the merits of establishing pharmaceutical engineering groups. It is clearly the particular blend of training in chemistry and engineering that provides the basis for the application of skills, sufficiently distinct from those of the synthetic chemist or mechanical engineer, which explains the successful existance of a separate profession; chemical engineering. The number of individuals possessing academic degrees in both pharmacy and engineering is so small that their influence can be considered to be negligible. Specialized journals in pharmaceutical

development equivalent to any of the excellent periodicals associated with food or chemical engineering are nonexistent although individual papers of high quality have begun to appear in pharmacy journals during the past five years.

Would it be correct to state that the low level of pharmaceutical development as a recognized area of specialization is due to the simplicity of the operations involved in the manufacturing of the various dosage forms of drugs? Hardly, since one would imagine that by this time the vast biopharmaceutic literature and world-wide concern with manufacturing practices would have convinced even the most persistant believers in the art of pharmacy that such a point of view is retrogressive and dangerous. The direct relationship between the quality and therapeutic activity of a drug preparation and the manufacturing process is now too obvious to overlook without serious risk.

The proposition that there is no shortage of excellent pharmaceutical development under way or that pharmaceutical manufacturing has reached an unsurpassable peak of technological perfection which remains hidden as an economically advantageous stratagem is rather anemic and untenable. It is so difficult to hide advances in pharmaceutical technology from public view that almost all advanced companies no longer deceive themselves by the erection of highly porous walls of so-called trade secrets. As we shall see later, certain quite specific evidence of technological deficiencies become apparent from an analysis of pharmaceutical products recalled from the market either voluntarily or upon government demand.

This is not to say that pharmaceutical product development and technology have been completely quiescent nor are examples of significant progress lacking. However, in as sensitive an area as drug development, production, control and distribution it is apparent that a level of performance lower than the best attainable on a scientific and technological basis at any particular time is just not going to be acceptable. To meet such a challenge pharmaceutical scientists must identify the basic reasons for deviations from quality standards and find the means for preventing them.

The crude interpretation of process development as a means of making a larger batch of a product than the one previously prepared needs to be discarded. Trial and error judgement involving minor changes in components, equipment or operating conditions represents an empirical approach which can not attain the desired objective. Only a development program involving a critical analysis of the process; controlled experimentation covering the basic physical principles and parameters, and repeated process simulation related to the specific variables will provide the conditions for reaching and maintaining an acceptable level of product quality.

THE PILOT PLANT

The presence of a few machines with higher capacity than those generally found in the laboratory does not qualify for the designation "pilot plant". Stated most simply, a pilot plant is an area containing or having room for process equipment and essential utilities, supported by instrumentation necessary for the precise evaluation of all variables associated with a process under investigation. Provision for the evaluation of intermediates or the end product itself can be made in the pilot plant or in adjacent laboratories.

In an organization involved in the development of numerous dosage forms the range of equipment utilized and its association with specific environmental control requirements may necessitate the establishment of several pilot plants. Special construction features, as is the case with sterile products, may be essential for sound developmental investigation. The quality requirements of pharmaceutical preparations are directly related to the dosage form and the development pharmacist must always keep in mind the precise manner by which the product will be administered. Unlike their colleagues in chemical development who strive to obtain a process yielding an intermediate rather than an end product, the pharmaceutical development group aims for a process which will provide the patient with the actual material used in the treatment of his illness. The identity

and purity of a medicinal chemical represent its primary quality parameters whereas dosage forms must, in addition to the chemical requirement, meet specified physical and biological standards.

Meeting such standards is frequently dependent upon the design of the process equipment and the operating conditions during manufacturing. With properly organized studies formulations can be checked in the pilot plant for acceptability in large scale production. The pilot plant is the most suitable location for determining the advantages of modifying existing production equipment or operating environment, and the most practical area for the critical evaluation of new process equipment.

Whereas the solution of problems in particle size reduction, mixing, drying and filtration lie in the province of both chemical and pharmaceutical development groups, processes such as granulation, compression, coating, sterilization and emulsification most often concern development pharmacists.

In general there is bound to be more variation in the layout and equipment of pharmaceutical pilot plants than is the case with chemical development. Both the range of preparations involved and the magnitude of the production operations determine the physical requirements in the design of such facilities. While the proposal that pilot plant design and equipment should be similar in principle to that existing in the production department appears to be meritorious, justifiable criticism has been directed against this approach as restrictive of constructive change and tending to support utilization of obsolescent processes and equipment.

Examples of modern pilot plant facilities used for dosage form development in a large, international pharmaceutical company are shown in two photographs. Figure 1 illustrates part of a sealed, explosion-proof area in the tablet section designed for the study of the fluidized bed principle as a technique for drying granules, applying medicated or nonmedicated substances to particles or granules, and applying coatings to compressed tablets. The ease of setting

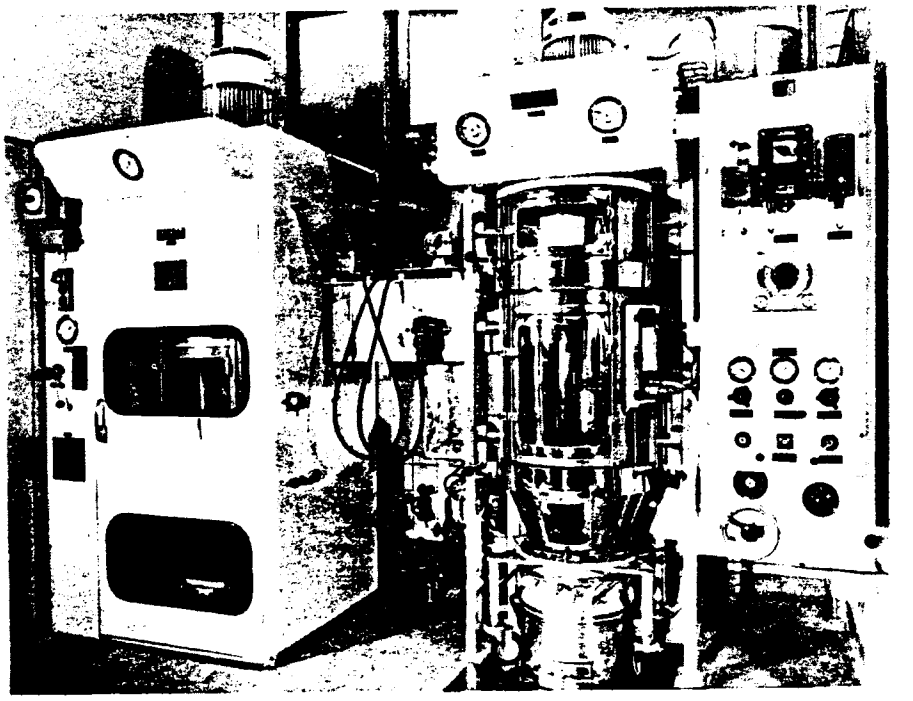

FIGURE 1

Fluidized Bed Pilot Plant (courtesy Sandoz Limited)

and controlling all physical operating parameters within narrow limits; the closed and therefor protected system, and various safety features provide the precision and flexibility essential for the study of process dynamics.

Figure 2 shows part of the semi-solids pilot plant with its specially designed, highly-instrumented equipment for the preparation of creams and lotions. Fully-jacketed, stainless steel vessels; counter-rotational, variable-speed stirrers, and vacuum or pressure connections simplify the solution of problems in the scale-up of emulsified dosage form systems.

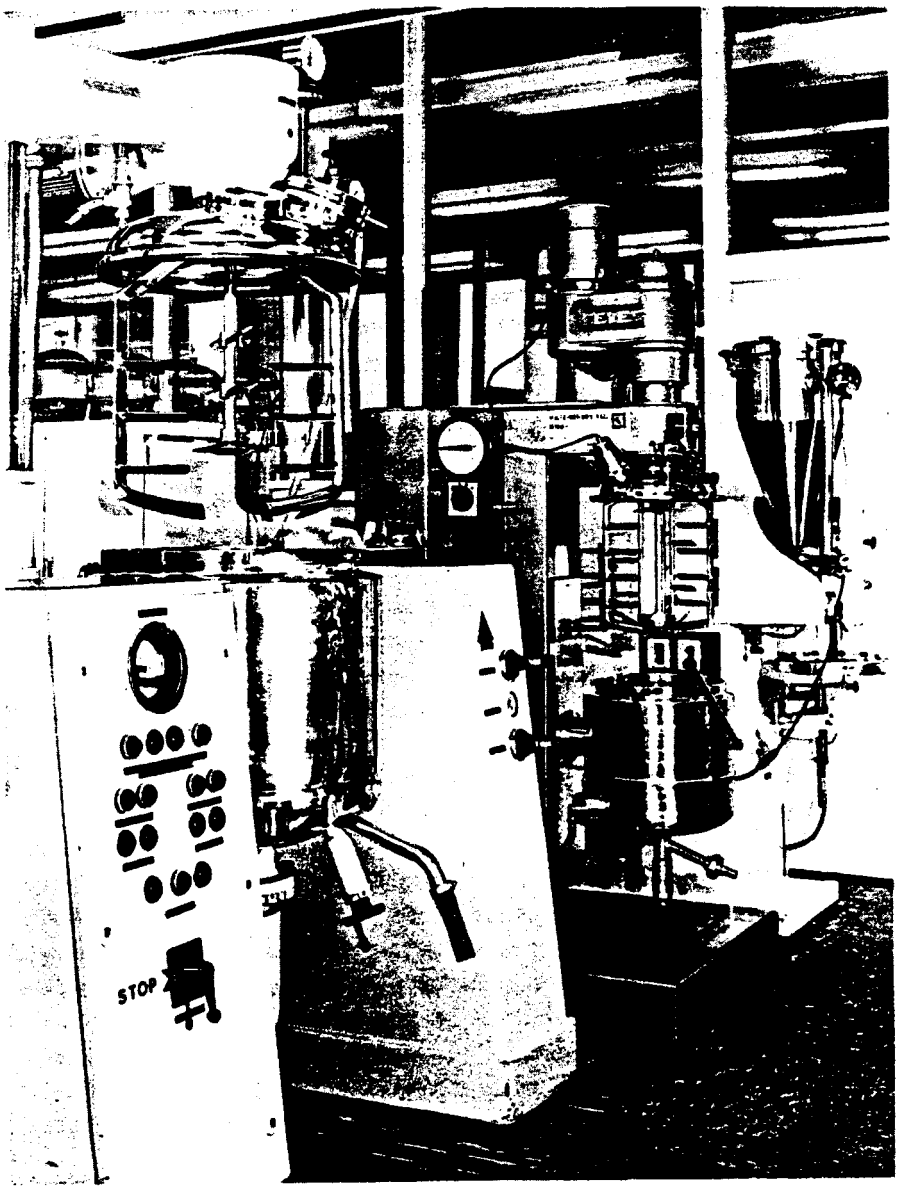

FIGURE 2

Semi-Solids Pilot Plant (courtesy Sandoz Limited)

QUALITY STANDARDS AND DEVELOPMENT

The rapid expansion of the world market for pharmaceutical preparations coupled with advances in technology represents a challenge to efficient, large-scale production. in this context it becomes obvious that the simple application of advanced engineering principles without intensive investigation of drug product quality requirements is not acceptable. Conformance with the dosage form design utilized during the investigational period is necessitated by scientific principle and regulatory force. Modern pharmaceutical product development requires a multi-disciplinary approach effectively organized for the attainment of measurable objectives. Not only must the final product meet relatively narrow physical, chemical and biological test limits but under the rapidly expanding Good Manufacturing Practices Codes, the production environment itself is subject to external control regardless of end product quality.

During the past three decades and particularly during the past 10 years Production Departments have begun to recognize that they could not meet their responsibilities without increased technological support both quantitatively and qualitatively. For certain products, continuous processes are now feasible; rapid expansion in control engineering has provided new means of automatic, in-process controls; production machines with higher capacity are readily available; new techniques such as film and compression coating, micro-encapsulation, fluid energy milling and others offer opportunities for product improvement; efficient environmental control equipment to limit microbial and nonmicrobial contamination can be installed; a variety of new excipients for almost all dosage forms has altered dependence upon materials with definite limitations, and finally, there has been a rapid rise in quality standards in pharmacopoeias and government regulations.

As a consequence, the pressure to modernize facilities; replace obsolescent equipment; introduce in-process controls; remove operator variability by automation of processes, and

improve old formulations has steadily risen. Just how to resolve the complex problems raised by these accelerating demands in terms of personnel and organization currently challenges the managements of most pharmaceutical companies.

ORGANIZATION OF DEVELOPMENT

The U.S. National Science Foundation defines basic research as "original investigations for the advancement of scientific knowledge that do not have specific commercial objectives, although such investigations may be in fields of present or potential interest to the reporting company". Of the 684 million dollars spent by Pharmaceutical Manufacturers Association member companies for research and development activities in 1971 approximately 14 percent, or 96 million dollars, was devoted to basic research with most of this work done in company laboratories.

The rest of this large expenditure went to so-called "applied research" with a somewhat more obvious return on investment coming into focus. In actuality there is little, if any, difference between basic or applied research insofar as the requirements of logical thought and experimental methodology are concerned. The organized effort to recognize and demonstrate facts is the normal research way of life in academic, governmental and industrial laboratories.

The structural form of organization and the types of personnel employed vary considerably and may have a bearing on the productivity of the research program. This variability is particularly visible in pharmaceutical development groups as will be demonstrated later with actual examples.

It is interesting to note that regardless of the size of the Research and Development budget there is a 1 to 1 relationship scientists and technicians plus supporting staff, i.e., literature, clinical, statistical and other services, in the U.S. pharmaceutical industry. This is clearly demonstrated in Figure 3 which shows the 1969 manpower distribution in Research and Development according to budgeted research expenditures. Although precise figures are not available, the ratio of scientists to technicians is

R&D Budget	Total R&D Staff	Scientific & Professional	Technicians & Supporting	Scientists per 100 R&D Staff
>20M*	10,005	5,115	4,890	51.1
10-20M	5,650	3,010	2,640	53.3
5-10M	2,285	1,045	1,240	45.7
1-5 M	1,750	910	840	52.0
<1M	540	265	275	49.1
TOTAL...	20,230	10,345	9,885	51.1

*M=Millions of Dollars

FIGURE 3

U.S. Manpower by R&D Budget Group
and Scientist-Support Personnel Ratio, 1969

far lower- possibly as much as 3 times lower- in continental Europe.

An analysis in depth would be required to determine whether this difference in staff composition has an important bearing on the efficiency of the research and development operation. My personal impression is that indeed it does and in favor of the U.S. staffing system but in the absence of a systematic analysis of research productivity this is difficult to prove.

GOOD MANUFACTURING PRACTICES AND DEVELOPMENT

Over 10 years have elapsed since the subject of Good Manufacturing Practices became a potent area of concern in government and industry circles in the United States. More recently the subject has aroused so much global interest that the International Pharmaceutical Manufacturers Association sponsored an international symposium on Good Manufacturing Practices in Geneva. In addition to the regulations promulgated by the U.S. Food and Drug Administration, other countries, organizations and groups have published texts covering their ideas of Good Manufacturing Practices. A reasonable explanation for regulatory interest in manufacturing operations lies in the variability of the quality of pharmaceutical products as evidenced by occasional deficiencies on the part of individual manufacturers and gross inadequacies on the part of others.

In reviewing the reasons for the recall of prescription drugs in the United States and Switzerland it quickly becomes apparent that a considerable number of violations actually arose from deficiencies in manufacturing practices as described in the regulations. The most important of these can be ascribed to inadequate air control (particulate matter), contaminated raw materials or intermediates (pathogens such as Salmonella), water supply or treatment (bacteria or pyrogens), potency variations (weighing errors or non-homogeneity), and accountability (label control). About 30 to 40 percent of the recalls arose from deficiencies in product or process development. Examples of these familiar to product development pharmacists are disintegration time, suspension breakdown, crystal formation, subpotency due to instability, inappropriate containers and misbranded products. Whether these deficencies occur in manufacturing or in development it is quite clear that their prevention lies in improved technology in formulation, plant design, equipment or process control.

It would indeed be extremely shortsighted for development pharmacists to adopt the position that Good Manufacturing Practices is something that only their colleagues in the production department should worry about. Changes leading to increased safety and efficacy of pharmaceutical preparations as they move through the sequence of production operations are brought about through the application of experimentally tested and proven concepts. Simpler, more rational formulations; unit rather than sequential operations; closed rather than open operating systems; nonreactive equipment surfaces, and automated, self-controlling processes are examples of advances which serve to consistently elevate the standrads of manufacturing practice. Some of these technological improvements reduce or even eliminate the potential for human error while others are reliable monitors of predetermined quality specifications.

From many recent publications and presentations at scientific meetings it is becoming quite evident that research and development pharmacists are becoming more cognizant of their potential for establishing, at least in part,

the environment in which Good Manufacturing Practices can flourish. Such projects as the automatic separation of metal particles from solid dosage forms, automatic weight correcting attachments for tablet presses, spray-vacuum unit operations for granulations, fluidized bed granulating and coating systems, automated tablet coating, clean room technology, automatic inspection systems for parenterals, in-line statistical sampling and testing, and many others are examples capable of inspiring similar efforts by others. In collaboration with production pharmacists and engineers, development pharmacists can participate in studies of optimal air flow velocity and direction, equipment shielding, particulate matter control, air sampling techniques, effective equipment cleaning and maintenance programs and segregation systems for contamination control.

IN-PROCESS CONTROL

In-process control, as employed until quite recently in pharmaceutical production, involved the measurement of a suitable parameter to determine whether or not the product during a selected, intermediate stage was or was not exceeding specified tolerances. The process could be stopped until the results of the test were known or, more frequently, was allowed to continue. For example, it has not been customary to stop tablet presses while an operator would weigh samples or determine disintegration times. With high speed, double rotary presses large numbers of tablets would be produced before the operator learned that the process was out of control.

Many process control systems, such as automated tablet coating, operate on the basis of time sequence steps but these are not truly automatic in that they lack a feedback system. The latter requires signals related to one property of the material being processed; for example, pH, viscosity, temperature, turbidity, unit weight, etc., as a means of holding on to predetermined product parameters. The necessity for in-process controls, automatic or otherwise, arises from variations or disturbances generated by components,

equipment or personnel. Correction of these variable disturbances in the shortest possible time is the objective of efficient, automated process control.

Delays in correction, or time lags. arise from three properties in process systems; namely, capacitance (or the ability to store energy, materials or electricity), resistance (or the property of restraining transfer), and transport time (or the delay caused by the time needed to carry forward a change from one point in a system to another). Knowledge of these properties in specific terms permits the development of a rational control scheme based upon process dynamics. In general, precise derivation of the controlling factors requires appropriate experimental and mathematical treatment. Only then does it become possible to effect the essential compromise between the desired product quality and the cost of the control system.

For any pharmaceutical manufacturing process maximum consideration must be given to the influence of the process itself upon the invisible as well as the visible properties of the product. Having been intimately associated with the step-by-step development of a pharmaceutical preparation from gestation to commercial introduction, the research and development pharmacists should be in an excellent position to identify the parameters which must be carefully monitored during the manufacturing process. Their proposals relative to process controls, if based upon experimental evidence and cognizant of the overall requirements of production technology, would be welcomed.

The advantages of automated process controls lie in the establishment of greater uniformity of end product. The record indicates that much of the criticism of the industry in producing a homogeneous level of finished products is justified. Up to now, failures in almost all instances have been based upon physical or chemical non-homogeneity. As biopharmaceutic methodology improves it is not improbable that biological non-homogeneity may be added to the list. The shift in Food and Drug Administration requirements from batch to dosage unit integrity reflects the importance of controlling

the physical, chemical and biological homogeneity during the entire manufacturing and packaging operation.

THE INTERFACE BETWEEN RESEARCH AND PRODUCTION

Most experienced research administrators agree that the development function is the technological bridge between research and production. Like bridges which link one shore to another, development people face both research and production. Since it is difficult to demonstrate that the interests of both are receiving equal attention a source of conflict automatically arises. How is this problem handled in different companies and in different countries? Is it best for the development group to be a part of the Production Department or of the Research Department? Should the development laboratories and pilot plants be a part of the facilities of the Research Department or is it advantageous to locate them within or adjacent to the manufacturing area?

The famous Bell Telephone Laboratories in New Jersey struggled with these problems and reached the conclusion that it was bad to have both an organizational; i.e., administrative, barrier and a space barrier between development and production. When both barriers exist simultaneously communication becomes too difficult and problems arise in the transfer of new scientific developments into new technology. For this reason the Bell Laboratories development group was moved into laboratories on the premises of the Western Electric Company, a manufacturing group. Organizationally the development staff are a part of Research and Development but physically they are linked to Production.

As a means of illustrating the wide variety of attitudes and organizational patterns for product development in the pharmaceutical industry let us now take a look at a number of companies with excellent research reputations in the U.S.A. and Europe.

As early as 1953 one U.S. company set up a pharmaceutical group under the title "Pharmaceutical Technical Service" as a division of the Pharmaceutical Production Department.

In 1971 the staff consisted of 4 chemical engineers, 2 pharmacists, 1 chemist, 1 biologist and 1 bacteriologist. Most of these individuals are former production line or staff personnel- an indication of the orientation of the group. Their responsibilities include projects involving cost reduction, trouble shooting, new product introduction, new equipment and technical consulting.

To maintain original product design, close liaison with Product Development and Quality Control is needed during process improvement and reformulation. Trouble shooting is a basic responsibility requiring immediate investigation (top priority!), analysis, determination of cause and recommendation for action where the problem is technical in nature.

Initially this group was not to have a laboratory but was to use the Product Development laboratories or more often, small scale production equipment. The latter proved to be inadequate and new equipment had to be purchased in order to provide flexibility for the increasing volume of pilot work. After 18 years of experience this group recognizes the existence of a split, organizational personality by listing the advantages of locating Pharmaceutical Engineering as follows:

In Research

1. Avoids duplication of pilot laboratory equipment.
2. Better control of scale-up of new products since there is no transfer of technical responsibilities.
3. Better conformance to original design in process improvement and reformulation work.

In Production

1. Ready access to production scale equipment.
2. Better communication with production regarding technical difficulties, equipment needs, etc.
3. Better technical service to production with respect to production difficulties.

In another U.S. company we can see an example of change resulting from growth and expansion of research activity. For 20 years Pharmacy Research and Development functioned as a division of the R&D Department with consistent expansion

of staff and facilities. A few years ago several of the R&D Divisions were separated from a new Research Department and organized into a Development and Control Department as shown in Figure 4.

Of particular interest in this case are the facilities of the Pharmacy Research and Development Division which although adjacent to the Pharmaceutical Production building includes unusual design features and equipment. Such features are based upon the assigned areas of responsibility of the division as listed below:

1. Establishment of those physico-chemical properties of drug substances and dosage forms which will influence their uniformity, stability, and biological availability.

2. Development of the final formula and full-scale manufacturing process for all forms of administration of new drugs.

3. The improvement of existing formulas and processes in terms of quality or cost on the basis of scientific investigation.

4. The evaluation of new raw materials; i.e., excipients, solvents, preservatives, etc., with potential value in pharmaceutical formulation.

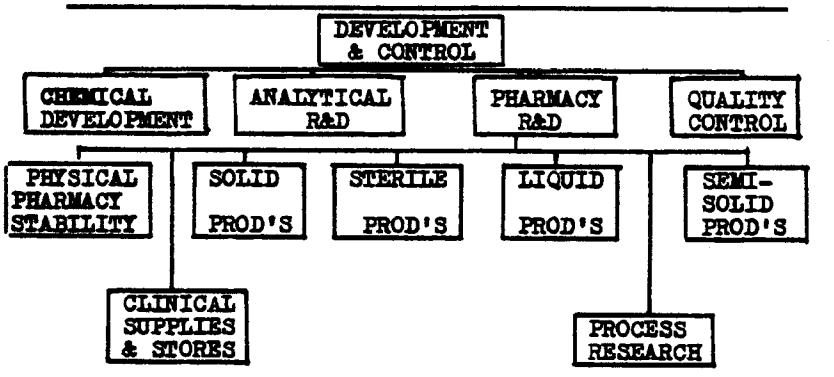

FIGURE 4

5. The preparation, packaging, and control of new drugs during the entire period of clinical investigation.

6. The scientific investigation of the stability and recommended storage conditions for all new products.

7. The scientific investigation of the merits and faults of new equipment preliminary to routine use in pharmaceutical production.

8. The investigation of the suitability of proposed packaging materials and containers.

The Process Research group in the division is responsible for scale-up, equipment evaluation and process aspects of trouble shooting. All projects, basic or applied, are organized at a level critical enough to be acceptable for publication in reputable scientific journals. This requirement not only represents a challenge to quality performance but encourages the acquisition and retention of creative staff.

Until a few years ago the Pharmacy Research and Development division in another U.S. company assigned to the task of developing new product formulations and associated processes was also responsible for technical support of manufacturing operations. In this company, however, the conclusion was reached that under such an organizational plan manufacturing support received a lower priority in comparison to the excitement and glamour of new product development. The decision was therefor reached to set up a new technical group within the Production Department by combining an existing Packaging Development Division with a new Pharmaceutical Manufacturing Development Division (see Figure 5) made up primarily of pharmacists and technicians.

For new drug preparations, projects are transferred from Research as soon as the New Drug Application has been submitted to the Food and Drug Administration. From this stage on the Pharmaceutical Manufacturing Development Division prepares all clinical supplies until formal approval of the New Drug Application and the initiation of commercial production.

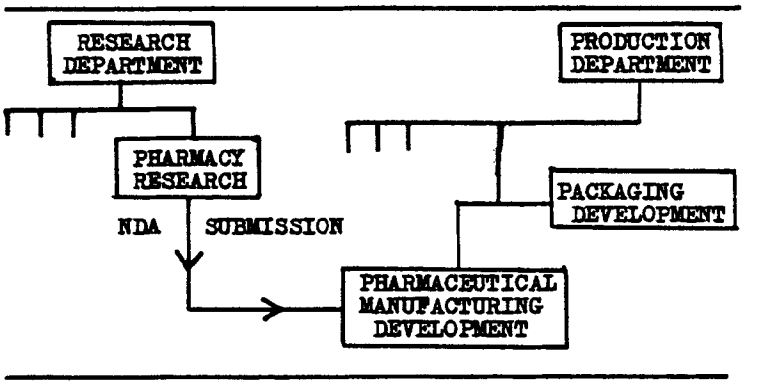

FIGURE 5

For scale-up the Division employs regular production equipment at variable batch sizes with Quality Control supplying analytical test results. The emphasis upon production support can be seen in the following list describing the scope of activities of the Pharmaceutical Manufacturing Division:

1. COMMERCIAL PRODUCTS
   a. Problems associated with manufacture of current products.
   b. Revision of current products when necessary to improve their quality and/or produce them more economically.
   c. Preparation of supplies for clinical testing of revised products.
   d. Effect smooth transfer of research items to full-scale production.
   e. Package changes for current products.
   f. Compatibility inquiries regarding current products.
   g. Raw material changes.
2. PROCESSES USED IN PRODUCTION
   a. Problems associated with current processes.
   b. Evaluation and recommendations concerning technology.
   c. Assistance with transition to new processes.

3. PRODUCTION EQUIPMENT
   a. Evaluation and recommendations on modification of existing equipment or purchase of new equipment.
   b. Assistance with transition to use of new equipment.
4. MONITORING SERVICE
   a, Check on environmental conditions in Production areas.
   b. Examine the various water systems used by Production.

Among the processes investigated by the Division and either already used by Production or still under study are automated enteric coating, automatic weight control, dust measurement and control, and automated disposable syringe assembly, filling and sealing. Although directly allied to the Production Department the Pharmaceutical Manufacturing Development group has no direct responsibility with reference to Good Manufacturing Practices.

Another U.S. company also decided to change its organizational plan but did so in an opposite direction. Previously, the Research Department was responsible for formulation and initial scale-up, at which point the Production Department took over and continued developmental studies until an acceptable process was achieved. This situation was considered to be unsatisfactory for the following reasons:

1. Production people are not as strongly motivated as their research colleagues in putting out a new product- admittedly an exceedingly complex function today- so that the production of established products is frequently assigned a higher priority level.

2. The individual most familiar with the formula; that is. the one who originated it, is no longer involved in adapting the composition to the process; a new group looking at the formula for the first time is responsible for adapting it without sufficient background.

3. Research people may be less critical in formulating a product when they know that the final details of the formulation will be decided by another group in the Production Department.

4. Research loses control of the time schedule for introducing a new product when another department takes over and creates a new schedule based upon their operating capacity.

5. The initial stability data may become meaningless in the event of significant changes during scale-up.

As a consequence of the risks of interrupted developmental continuity this company changed its organizational pattern so that the Research and Development Department carries on formulation and process research right through the initiation of routine production (see Figure 6).

Research remains directly involved with Production for at least five consecutive batches. Trouble shooting is carried out by the research personnel who originally developed the product assisted by chemical engineers within the group and, when necessary, by plant engineers.

In a large German company pharmaceutical development is the responsibility of the Pharmaceutical Technology Division which reports to the Research Department (see Figure 7). On the basis of a departmental network scheme, the planning, costing, coordination and control of product development are integrated with the total research program. Technical operations in Pharmaceutical Technology are carried out be three laboratory groups; solids, liquids and veterinary products. These groups work from the earliest basic formulation tests through the scale-up stages and on to the transfer of the operation to the Production Department. This approach is

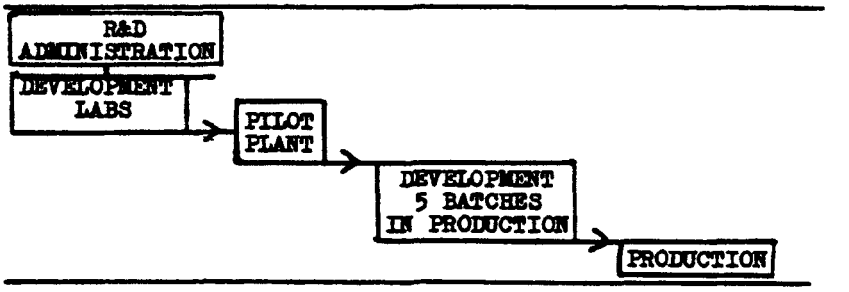

FIGURE 6

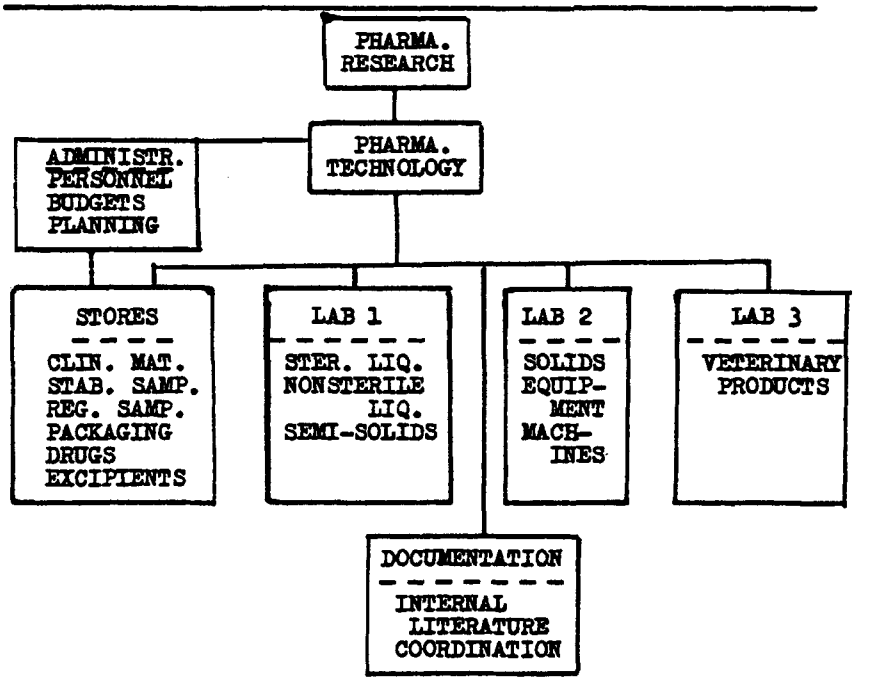

FIGURE 7

based upon the philosophy that "the expert who carries through the first formulation trials with a drug should be responsible for this drug right to its introduction into production since he is most familiar with the substance and its respective dosage forms and will therefor reach his goal in a straightforward way". The Pharmaceutical Technology Division undertakes comprehensive stability testing and controls its formulations continuously with drug release or in vivo effectiveness determinations.

At the present time scale-up by development staff is handled on their own equipment (up to 250 liter vessels and 100 kilogram mixers) or, for larger batches, in the Production Department. All high speed rotary tablet presses are

located in Production but close proximity enables such machines to be moved to Development when convenient. Construction of a planned, new building would necessitate a review and possible alteration of this policy. Up to the present time, trouble shooting remains a responsibility of the Production Department.

In a very large American company the organization of Pharmaceutical Development has changed frequently over the years depending upon the strengths and weaknesses of people involved at any particular time. Internally this situation has been interpreted as evidence that the organization was flexible and could still function effectively. Apparently this implies a shift in responsibility and function between and within various individuals and groups in research, development and production as deficiencies and capabilities are recognized. Until a few years ago a Director of Product Development supervised a pharmacy research group and four pilot plants. It was the responsibility of the pilot plants to prepare all clinical trial material, scale-up new formulas to production size, participate in process development programs and provide technical assistance to Production.

Following a reorganization five years ago (see Figure 8) the four Pilot Plant groups were reassembled into two groups with one retaining the responsibility for clinical trial materials and the development of new formulations received from Pharmacy Research. The second group, reporting to the Production Department, provides rechnical services, product improvement of marketed preparations and process development. Experience thus far indicates that the new form of organization has resulted in a stronger committment to maintaining and improving the quality of marketed products and closer collaboration between Production, Technical Service and Quality Control. It is recognized, however, that the R&D Pilot Plant group primarily faces Research and, although directly responsible for scale-ip of new formulas, has failed to involve the Production Operating Unit early enough in many instances. As a result, too many formulas

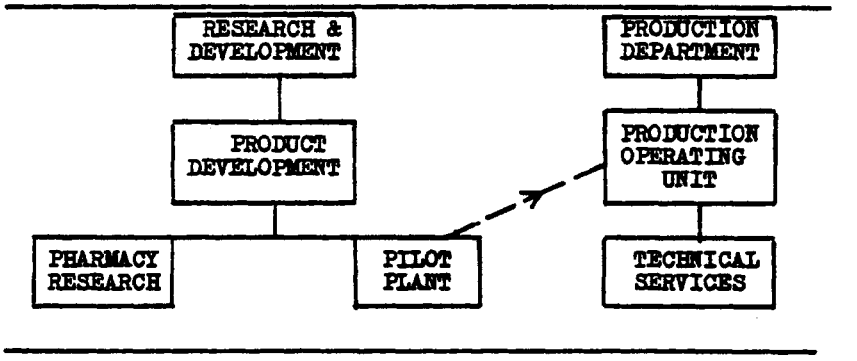

FIGURE 8

are reaching Production which subsequently require modification by Technical Services.

Examples of projects initiated to reduce operating costs or improve product quality include the development of high speed capsule filling, polishing and sorting equipment, combined granulator-dryer for tablet production, and automated coating. Similar types of projects involving sterile products, liquids and semi-solids are currently under way.

The problem of where to locate a pilot plant which is administratively a part of the Research and Development Department has been resolved by one U.S. company in the following manner. As can be seen from the organization chart (see Figure 9) there are four sections in this division, all reporting to the Director of Pharmacy Research and Development. The reasons given for including the Pilot Plant Section within the Research Department are the following:

1. The entire scientific and technical history of the evolution of the product is more readily available than it would be to a group reporting to Production, Control or Engineering.

2. A Pilot Plant group reporting to Production would be more prone to provide "Band-Aid"; i.e., superficial treatment in case of a problem rather than seek its eradication.

As with the Bell Telephone laboratories the decision was made to locate the Pilot Plant within the production

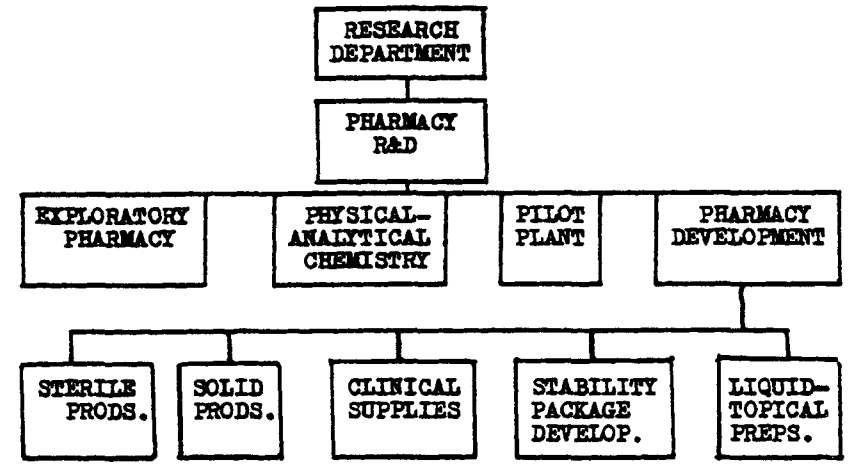

FIGURE 9

area. The objective of establishing a close physical link between Research and Production has apparently succeeded. As stated by one production supervisor: "The development pharmacist is one of us; not a visitor who comes with pomp and ceremony without the production staff knowing what he did or how successfully he did it".

To succeed in bridging the gap with Development, Production must be psychologically as well as technologically involved and this can only achieved with individuals they know and meet on a day-to-day basis. It is clear that in this technologically advanced pharmaceutical company the bridge role of Development is recognized and the same solution found as was the case with the Bell Laboratories.

In one of the large Swiss companies a Development Department is unique in having a Biopharmaceutics Division as a separate organisational component closely associated with product development.

This approach (see Figure 10) attempts to unify the development effort from the point of view of chemical,

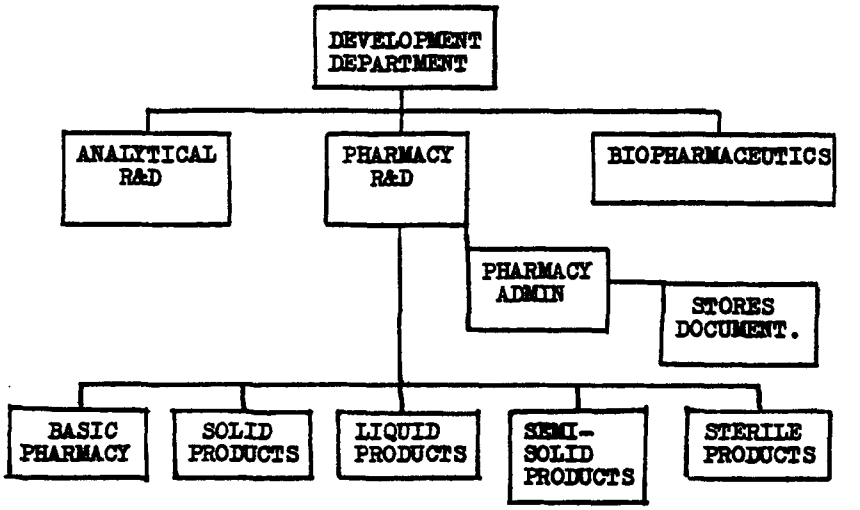

FIGURE 10

physical and biological requirements. Collaborative planning, experimentation and evaluation are obviously facilitated in such an arrangement. Transfer of processes to the Production Department involves bridging an administrative gap and efforts are under way to establish an appropriate mechanism to accomplish this, perhaps including the construction of shared pilot plant facilities. If effective, biopharmaceutic problems resulting from processing should be kept under control.

A search of the literature reveals a dearth of information concerning pharmaceutical development activities in the Scandinavian countries. This does not mean that this phase of pharmaceutical research and development has been ignored or neglected. It may simply reflect a policy position based upon proprietary interests or a decision to emphasize other aspects of drug research.

In one company in Sweden (see Figure 11) the Pharmacy Research and Development Division is a unit of the Research and Development Department with responsibilities in formulation and processing. Since Production is located at a distance from these laboratories considerable attention is directed towards pilot plant problems and the proper development of manufacturing processes. In accordance with the nature of the product line major activities, particularly in scale-up, are concentrated on tablets. Pilot plant batches range in size up to 500,000 tablets, preferably scheduled during an early stage of product development so that a relationship between large scale production and clinical efficacy can be demonstrated.

Transfer to Production is made smoother by the presence of a production technologist during the pilot plant stage of development and conversely, a development pharmacist participates in the preparation of the first full scale manufacturing batches. Only after the successful production of five batches is the recommended process considered to be acceptable, and full responsibility turned over to the Production Department.

All trouble shooting activities must be approved by the Pharmacy R&D Division. At the present time automation of

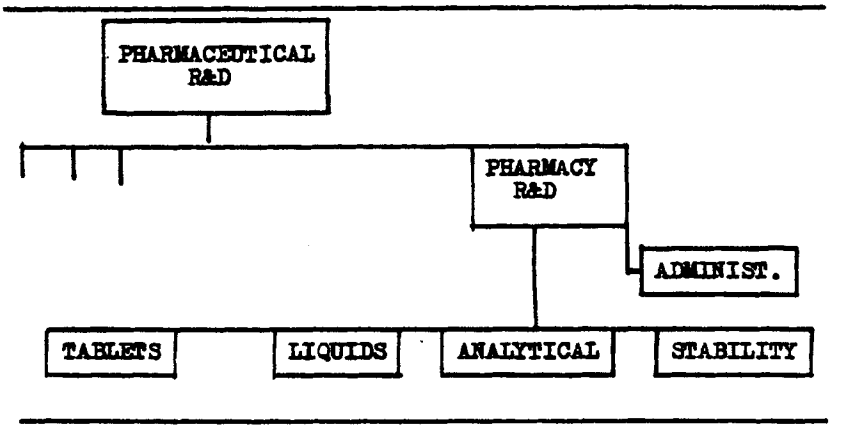

FIGURE 11

production processes is extremely limited and only conventional, non-automatic, in-process controls are used.

Pharmaceutical companies involved in international distribution face development problems of far greater complexity than those operating solely on a national scale. Universal formulas and processes turn out to be more fantasy than reality. Changes in governmental regulations, availability of raw materials and containers, technological capabilities, environmental conditions, and others contribute to the magnification of the normal scientific and technological difficulties. Either the acquisition of home staff capable of coping with the problems of international development is a necessity or small but effective development laboratories, closely linked with the central development group, must be established in the affiliates.

CONCLUSION

It is fairly obvious from the information presented that there exists widespread variability in the attitudes toward pharmaceutical development and the organizational forms for this function in the pharmaceutical industry. In spite of its increasing importance and the relevance of dosage form design, an acceptable and uniform philosophy of organization has not yet emerged. The reasons for this situation are varied but probably the most important one is the failure to break away decisively from the residue of an over-casual attitude toeards pharmaceutical formulation and processing. As in many other aspects of pharmacy the chains of tradition are difficult to break.

However, much discussion and experimentation is now under way and the intensive research activity in basic pharmaceutics, industrial pharmaceutical technology and biopharmaceutics will undoubtedly stimulate action with reference to the proper role of development. When clearly defined and properly organized, advances in scale-up practices, in-process controls, unit operations, process automation, and product uniformity can be expected to rapidly accelerate.