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THE IMPORTANCE OF INTERDISCIPLINARY COOPERATION IN PHARMACEUTICAL PRODUCTION TROUBLE SHOOTING

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A description of the complexities involved in trouble shooting of pharmaceutical products is presented. Also discussed are several organizational structures that can serve as effective cover for trouble shooting personnel. Several examples of trouble shooting situations are used to illustrate the importance of cooperative interdepartmental interactions.

INTRODUCTION

The economic health of a pharmaceutical company is dependent to a great measure on the smooth coordinated efforts within and between its component divisions, departments, and sections. The people who constitute the line organization and/or committee functions are responsible for the existance, growth or failure of the company. Part of this overall effort is the responsibility for the development, and quality control of safe, effective and stable drug products produced in the most efficient and effective manner.

From the conception of a new product and through its development, planning, and coordination; cooperation and patience are essential in bringing the product to market. The effectiveness and efficiency by which each department contributes to the master development plan is dependent to a great extent on the cooperative efforts of its personnel.

Intracompany departmental coordination and cooperation is very important in the "trouble shooting" function of pharmaceutical processing. In some instances, few if any structured or unstructured efforts exist. This paper will restrict the discussion to trouble shooting in the manufacturing phase of pharmaceutical products.

Time after time, in any number of companies, production problems crop up which create situations nothing short of chaos. The ensuing panic brings into play various numbers of people scurrying about in several departments with little or no coordination. Each person or group usually ends up speculating what they thought was the cause of the problem, followed by usually futile attempts to resolve the problem and often times blaming each other for the cause.

In these situations, the primary cause of the problem many times is never really entirely defined. Instead, a number of minor causes are touched upon, or someone puts forth a pet theory which must be considered because of certain egotistical traits in that person. Much to the dismay of the people involved, the problem often reoccurs when the heretofore undefined and still uncontrolled conditions again develop. The result? The entire sequence is repeated, and more time and money are wasted.

All of us realize that most production problems must be solved within the shortest time possible. Cold facts dictate this; i.e., no product, no sales. It is a fact that a temporary production stoppage may mean potential loss of future sales, particularly if these items are back ordered and whole-salers are buying from competitors to fill their orders, and it becomes very critical should stoppage occur during a new product introduction. The expense and possible loss in prestige of a recall for one or several unsatisfactory product lots is also a fact.

Who does trouble shooting involve? In many cases it involves people working together as a team, and at other times it may involve an individual seeking the cooperation of people in a number of different departments.

What does trouble shooting involve? Literally, "find the trouble and shoot it down". It may be the recognition of the need for a minor machine adjustment or procedure change, or it may involve a complex problem analysis requiring considerable time and effort from several disciplines before completion.

TROUBLE SHOOTING PROCEDURE

Trouble shooting requires cutting across company lines to expedite the solution of a problem. However simple or complex the problem may be, trouble shooting has certain steps which should be considered and sequentially followed. These are seen in Table I.

TABLE I

Basic Steps Involved In Trouble Shooting

DETECTION
CONFIRMATION
FEEDBACK
PROBLEM EVALUATION
DECISION
IMPLEMENTATION
RESULTS EVALUATION

Recognition of a problem may occur from many sources such as (a) an observation by an operator about something unusual in his particular stage of the process: (b) the noting of an unsatisfactory product quality attribute or trends toward an upper or lower test limit of a product by quality control; and (c) although we do not like to see things carried to the market, a problem may be recognized by the dispensing pharmacist, the consumer or maybe even the FDA during a routine check.

Once a problem has been detected and/or recognized, confirmation of the problem is made by the trouble shooting individual or group. This may involve merely the observation of a process, performance of laboratory tests, or the checking of the product appearance on the pharmacists' shelves. The point here is to make certain the apparent problem is not an isolated case.

Having detected and confirmed the problem, efficient feedback must now occur between the point of detection and the problem solving mechanism. Again, this may be as simple as a conversation between a production operator and the supervisor, or it may entail information passed down through several departments and disciplines in the line organization. In the latter case, people acknowledging the original observation should write down all pertinent facts.

Evaluation of the problem is the next important step. The seriousness of the problem must be ascertained: Does it jeopardize the consumer in any way? Does it alter product elegance? Does it threaten shut down of the operation until changes can be made? Is the answer obvious? These and many other points must be considered.

Possible problem areas are explored. Is it a manufacturing problem? Has it happened before, if so, what were the causes then? Do the same causes exist now?

At this point, the situation is carefully evaluated and a decision is made on the course of action to be taken in investigating all possible causes of the problem. The type of testing, the disciplines required, the number of people required, the assigning of priorities, and the approximate length of time required to accomplish the task are also necessary at this point.

Implementation must be coordinated such that minimum time lapses to bring the project to completion. Work is conducted in accordance with its priority, and in cases where considerable time and effort is involved, status reports and reviews are essential, particularly when current work indicates a change in approach or work priority.

Experimental work is conducted, data is collected and tabulated when necessary, and each cause and effect checked. Corrections in the process are made in accordance with results. Evaluation of results should be done statistically when an appreciable amount of data must be interpreted.

To many people, these basic steps may appear to be a very time consuming procedure in shooting down a problem. One can be assured that this approach and interdisciplinary interaction is basic to problem solving. The time and effort spent in executing these steps is basically dependent upon two factors:

1. The number and cooperation of people involved.
2. The complexity of the problem

The first factor (number of people involved) in most cases is the largest contributor to the time required to solve a problem, particularly when poor project leadership is encountered. The "number of people involved" may also contribute considerably to the complexity of the problem itself.

ORGANIZATION, INTERACTION AND RESPONSIBILITY

To illustrate this, consider three trouble shooting organizational possibilities as shown in Table II.

TABLE II

Three Trouble Shooting Organizational Possibilities

Individual

Carries out on an individual basis almost all phases of trouble shooting

Coordinator - Team

Coordinates efforts of people in different departments appointed to work on a particular problem

Trouble Shooting Group

Headed by a group leader, the group's sole responsibility is solving production problems.

The existence of any of the three possibilities in a company will more than likely be dictated by the company economics, the need for a trouble shooting program, and the size and number of operations carried out within the company.

To be more specific, the following discussion compares each with regard to its organizational structure, resulting interaction, and responsibilities.

Table III compares the three organizational possibilities.

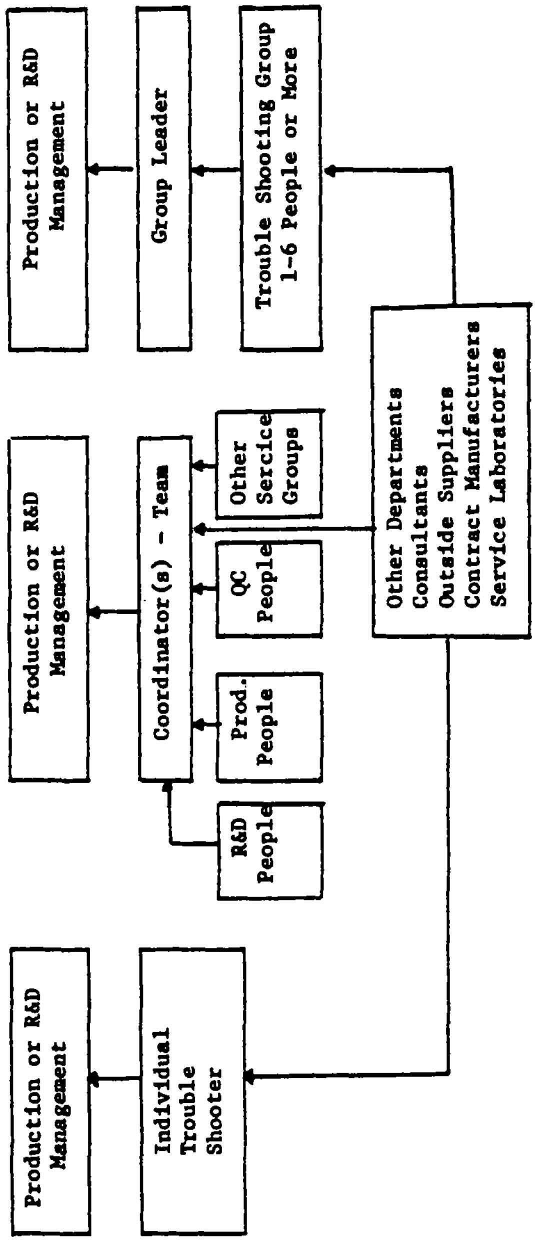
Operations common to each setup include reporting to production or research and development management, depending upon which department assumes the trouble shooting responsibility, and contact with other departments, suppliers, etc.

The simplest possibility is the individual who may or may not be hired specifically for trouble shooting; i.e., he may have responsibilities in either research and development or production in addition to trouble shooting. This person should have experience in trouble shooting, production, research and evelopment and quality control if possible. The disadvantage in this setup is the limitation as to the number of problems the individual can give adequate attention to, while the advantage is the simplicity of the setup with regard to interactions. Fig. 1 is a schematic representing the possible interactions (lines) between the individual, various departments and management.

Next, the coordinator-team approach involves a person or persons given the responsibility to direct and coordinate trouble shooting efforts in solving one or a number of problems. Specific people from the various diciplines needed in investigating and solving a particular problem are assigned to report to the coordinator. Although these people are responsible to their respective department heads in the line organization, trouble shooting priority assignments worked out cooperatively between management, the coordinator, and the respective department heads allow these specialists

TABLE III

ORGANIZATION



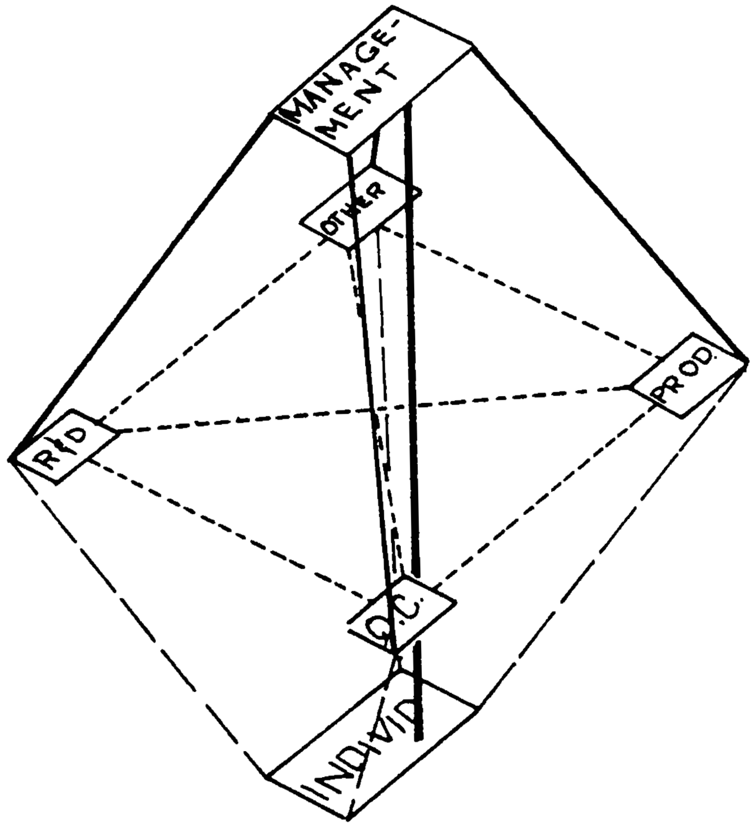


Fig. 1 INDIVIDUAL TROUBLE SHOOTER INTERACTIONS

to report directly to the coordinator. The coordinator(s) may or may not have responsibilities other than trouble shooting work, and their backgrounds should be the same as described for the individual approach. The major disadvantage in this approach is the number of people involved in the assigning of priorities, while the major advantage is the ability of a coordinator to handle more problems than the individual and possibly problems of more complexity. Because the coordinator-team approach enlists the help of more people than does the individual setup, more than double the number of interactions between people and departments are possible as schematically represented in Fig. 2.

The third approach is the trouble shooting group which includes a group leader and 1 to 6 people or more if

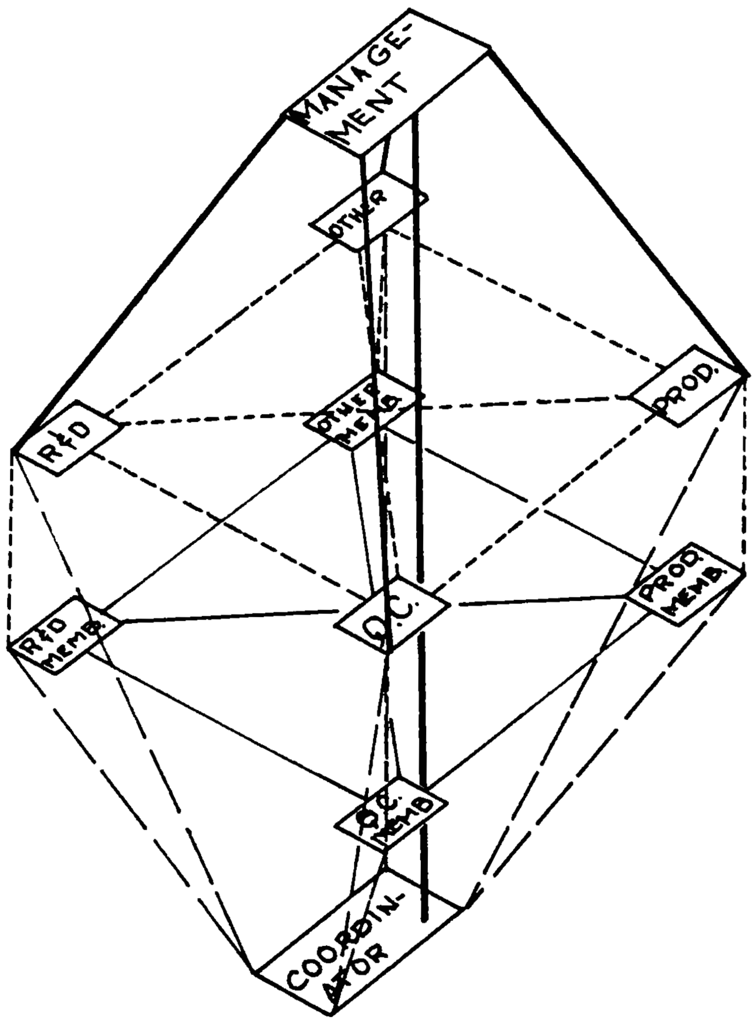


Fig. 2 COORDINATOR TROUBLE SHOOTING INTERACTIONS

necessary. In this setup, the group leader and the people in the group are hired specifically for trouble shooting work. The group leader is an experienced trouble shooter and his people may be scientists and/or technicians with varied research and development, production and quality control backgrounds. It would be desirable for each person to have some trouble shooting experience.

The major disadvantage with this setup is possibly economics, while the advantage in the group is found in the number and types of problems it can handle along with efficient priority assignments and use to time. The trouble shooting group presents the greatest number of possible interactions between people and departments, as seen in Fig. 3, because each member of the group has the potential of interacting with all other departments as well as with all members within the group itself. This large number of interactions is also brought about, in part, through additional responsibilities the trouble shooting group assumes as seen in Table IV.

Table IV compares the responsibilities of the three trouble shooting organizational possibilities discussed. The trouble shooting group concept has greater flexibility in time and priority and the potential of handling all the types of trouble shooting, while the concept of the individual trouble shooter has the least flexibility with regard to time and priority.

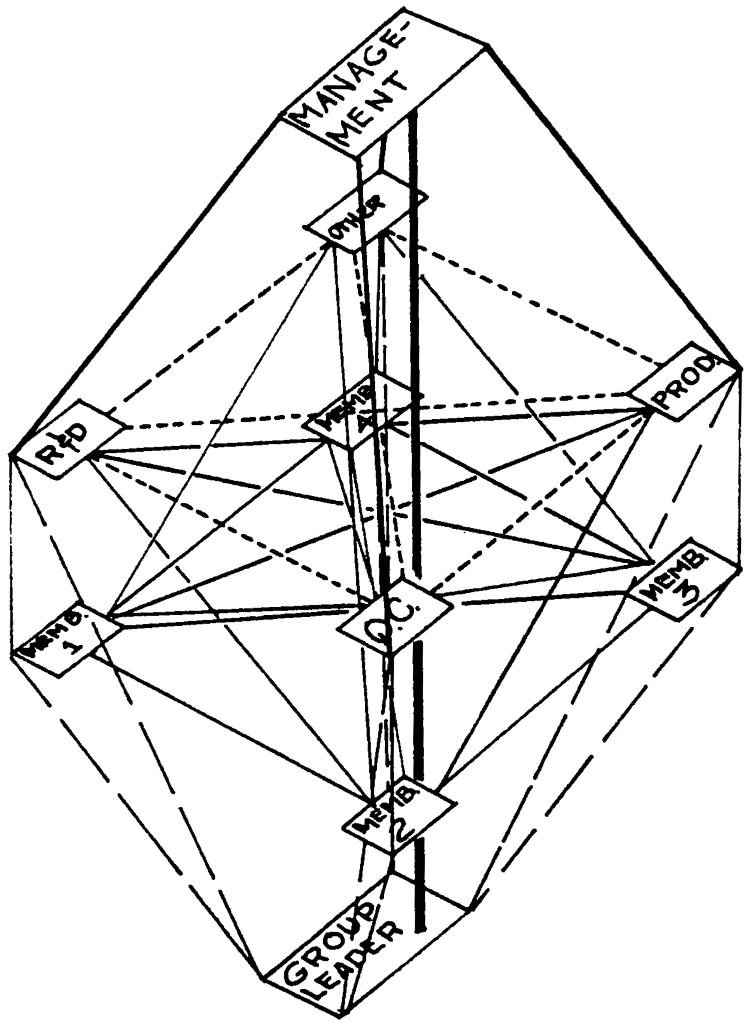


Fig. 3 TROUBLE SHOOTING GROUP INTERACTIONS

Examples of each type of trouble shooting presented in Table IV would include:

1. Tablet capping, sticking to punches or poor granulation flow as problems needing immediate attention.
2. Punch and die wear and stability problems would require surveillance and study over long periods of time.

Table IV

Type of Trouble Shooting Responsibility

Type of Trouble Shooting	Individual	Coordinator(s) *	Trouble Shooting Group
1. Prod. problems needing immediate attention	X	X	X
2. Prod. problems requiring surveillance & study over long periods of time		X	X
3. Seeking out and correcting potential trouble areas before they become problems		X	X
4. Optimizing production processes			X
5. Evaluation of new equipment			X
6. Evaluation of new raw materials.			X

* Will depend if people are hired only for trouble shooting

3. A process yielding product which show tendencies to the upper or lower physical and/or chemical specification limits would be a prime example of a potential problem that could be studied and corrected before rejections of lots out of specifications would have to be made.
4. Optimizing production processes projects must always be underway in an effort to economize and improve product quality.
5. The evaluation of new equipment is akin to number 4 above and must be undertaken not only to update or

improve older processes but also to plan and carry out new processes.

6. At this point in time the evaluation of new raw materials for new formulas or for replacement in current formulations is extremely important because of the raw material shortages which have been felt throughout the entire chemical industry.

Bearing in mind the organizational possibilities, the types of trouble shooting, and the possible interactions generated by each setup, one can begin to realize why the time consumed in solving many problems is more "people dependent" than "complexity of problem dependent".

TROUBLE SHOOTING EXAMPLES

A sample situation can be cited illustrating poor cooperative interaction between departments of a company whereby a particular product already in production was suspected of having a stability problem. It was also known that at times the analytical results were known to vary to a certain degree. In order to confirm the existance of the problem, it had to be shown that the change in assay values taking place over a period of time were either originating from variables in the analytical method, or were product dependent and statistically significant. This required a statistical design eliminating the bias from the analytical method, and a considerable amount of analytical work to provide data for the analysis.

The response from analytical personnel was hostile because their methods and techniques were being questioned, and they claimed they did not have the time or personnel to accomplish the proposed task. The arguement was that the assay method was straight forward, and no significant assay variability could take place. The counter-arguement pointed out that the study was merely a means of determining what part, if any, analytical variability contributed to the apparent change in assay results.

Needless to say, the dispute was finally solved by management intercession. Analytical ran the study which showed the assay method to be good, and that changes in assay with time were real and were significant. The most damaging part of this in-fighting was not necessarily the time lost here, but the feelings of resentment within the departments involved that lingered for a considerable length of time after the incidence. Egos were damaged and it made working relationships uncomfortable for a time.

In contrast to this situation, an example of cooperative interaction was encountered some time ago at a company when quality assurance and production noticed a small percentage of tablets of a particular product coming off the machine which appeared to be capping and sometimes splitting 2/3 of the way up the tablet.

Since the product had recently been changed from a wet granulation procedure to a direct compression formula, an investigation by both research and development and production was made, and the existance of the problem was confirmed. A coordinator from the research and development staff was picked to check out the possible causes of the problem because of his familiarity with the product. Evaluation of the problem indicated three possible causes: improper particle size of raw materials, improper lubrication, and worn tooling on the tablet machines. A joint decision was made to investigate all three possibilities.

Particle size analysis of raw materials was rechecked by quality control, while research and development investigated the lubrication factor.

Tooling in the tablet machine was not checked immediately because it was only 1/3 through its life expectancy. However, production set up a second machine with other tooling and the tablets compressed on this machine were satisfactory: no capping and no splitting.

The original machine was broken down by production while research and development used photographic techniques to show wear on the dies. Gauging the inside diameter of the dies confirmed the photomicrographic findings.

Results of the lubrication tests and particle size analysis were all negative. The answer appeared to be worn dies. The question was then raised by the entire team as to why the dies only lasted 1/3 of the time they usually last for this product.

A correlation was then made with the changeover from a wet granulation procedure to direct compression. It became evident that the direct compression formula was far more abrasive than the formula made using the wet granulation technique. Score marks on the dies indicated this.

In view of the results, the coordinator recommended that the tooling be checked on a more frequent basis for this product.

In this particular case, cooperative interaction was taking place between management, the coordinator, quality control, research and development and production. The work time required excluding the report writing was a little under two days. Production down time was about 1 1/2 days.

Excellent cooperation, assigning of priorities and implementation solved this problem quickly. The key phrase - cooperation between each of the disciplines involved.

Another example started with a definite change in tablet friability with a particular product. No problems had been seen previously with this product until quality assurance and production noticed that tablet friability was slightly higher than usual with three successive lots of tablets. The statistics department ran a statistical analysis on the friability data which indicated that a significant change had taken place. A check with the production operators revealed nothing unusual, and again a coordinator from research and development familiar with the product was selected.

An evaluation of the problem by the coordinator, research and development, production and quality control narrowed down the possible causes to a change in the binding properties of the granulation.

Production checked the raw material lot numbers and found three changes in raw material lots in these three troublesome tablet batches. Research and development and quality control checked physical specifications on these three raw materials and found one of the three to be larger in particle size when compared to previous lots, Table V.
A recheck of the particle size data made by quality control and research and development confirmed the original finding.

It was also noted that this particular raw material would not compress in the form of larger crystals, but acted as a binder when in smaller particle size form.

Table V

RAW MATERIAL PARTICLE SIZE DIFFERENCE

MESH SIZE	ACCEPTABLE MATERIAL	UNACCEPTABLE MATERIAL
60	6.7%	7.4%
60 - 80	11.5%	33.6%
80 - 100	13.5%	18.3%
100 - 200	38.6%	29.4%
$<$ 200	29.8%	8.3%

Contact with the supplier revealed this particular lot of raw material was not whithin the suppliers particle size specifications when it was shipped, and quality control did not use particle size as a basis of accepting or rejecting this material at that time.

The coordinator recommended a particle size specification placed on this raw material to prevent further occurances of this problem. Quality control in cooperation with research and development drew up specifications for this raw material.

Again, cooperation between management, the various departments, and in this case an outside supplier were instrumental in checking out cause and effect, implementing the course of action and arriving at a sound solution to the problem.

In conclusion, it becomes evident that the success of trouble shooting pharmaceutical products is almost totally dependent on interdisciplinary cooperation.