ABSTRACT

Title of Thesis: Process Hazard Review for Drug Development

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The development of drugs has become increasingly complex, requiring the use of a wide variety of pharmaceutical actives and isolated intermediates, a majority of which are not always completely characterized with respect to their hazard potential. This can present a source of potential exposure to those who handle these substances during initial drug development, manufacturing of the drug active and ultimately the finished pharamaceutical product. It is, therefore, essential that safety and health information be documented and communicated during the entire drug development process.

The need for application of process hazard review techniques to the development of new drug materials is becoming increasingly more evident. Developing trends in health and safety legislation, along with changes in the technical aspects of accident control, now make utilization of process hazard review programs in the pharmaceutical industry a necessary element in preventing employee injury and health hazards during drug development. Often little time is devoted to formal safety reviews during the research and development (scale-up) stages where valuable safety data is likely to be generated. Therefore, it is desirable to implement and use it to control potential hazards.

The primary aim of this paper is to provide a practical resource for safety personnel which stresses the importance of conducting

process reviews at all stages of drug development. It will provide a process review format for recording new safety and health data as it is generated to assist in the prevention of accident/injury and capital loss. The paper is also intended to promote the use of safety reviews in drug development, and to help the safety professional become more involved in the transfer of safety and health information during that process.

PROCESS HAZARD REVIEW FOR DRUG DEVELOPMENT

by
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CHAPTER I

INTRODUCTION TO PROCESS HAZARDS REVIEW

Background

All new projects embody some element of change, but in the pharmaceutical industry, the degree of change experienced in new drug product development is often considerable. It is important to recognize that the amount of established experience expressed in policies or written guidelines is limited by the extent of existing knowledge and can only be beneficial to the extent to which it applies to new products, new plant equipment and new methods of operation involved in new product development. In recent years, it has become more readily apparent that although written hazard evaluation procedures are extremely valuable, it is also particularly important to supplement them with an imaginative anticipation of hazards when new products are initiated and developed.

Process hazard analysis in the pharmaceutical industry, however, is generally not as well established as in the chemical industry. A rigid regulatory environment established by the Food and Drug Administration to guarantee drug purity and efficacy have provided a good measure of safety and health protection for workers handling drug materials and process equipment. However, a great deal of effort is put into the development of a new drug prior to its authorization for commercial manufacture, and it is during these stages of development that the process can undergo frequent and significant changes. Change

in the discovery and pilot plant stages is usually a dynamic and exciting time, but seldom routine or without potential hazard. Therefore, safety and evaluation of hazards should receive equally important consideration at the initial and intermediate stages of development as in the production or manufacturing phase.

The principal objectives of using hazard evaluation in new drug development is to provide an efficient and safe process for the manufacturing of a drug product. As a result, a considerable amount of very detailed safety information can be obtained and designed into the final production process if a hazard review is properly conducted during the previous stages.

Ideally, all process hazards are identified during design and construction and controls are incorporated prior to start up. A single process change may not introduce a hazard, but a series of changes can easily introduce serious hazards. These changes include increased production, equipment modification, corrosion, erosion, changes in temperatures, raw material changes, higher pressures and new catalysts.

With insurance, compensation, and replacement costs rising, and with federal and local laws focusing attention on safety, health and environment, keeping process incidents and overall risk to a minimum is a prime business requirement. The use of hazard reviews will also help to counter risk trends where there is major expansion in the use of flammable and unstable chemicals, chemical processes that require higher operating temperatures and pressures, increased handling of hazardous chemicals and mechanical processes which reduce the number of available personnel to handle emergencies.

A paper on process hazards by Trevor Klatz notes the following:

> "The traditional method of identifying hazards, in use from the dawn of technology until the present day, was to build the plant and see what happened"[1]

He uses an old adage to emphasize the obsolescence of this type of thinking, "every dog is allowed one bite..."; until the dog bites someone, we can say that we did not know it would. This was not a bad method when the size of an incident was limited, but it is no longer satisfactory now that we keep "...dogs that may kill many people at one bite".[2]

When then did the more formalized method of identifying hazards begin in the first place? It begins as systems safety in the military sector during the late 1950s and early 1960s in weapons development programs. It was developed in response to a need which recognized that the destructive power of weapons and their delivery systems were rapidly increasing and that the problem of safety of the whole system could not be solved by mere life testing of the component. Studying the interworking of the system elements was required to make sure the component failures or unexpected system events would not cause catastrophic results. "Western Electric Company and Bell Laboratory's development of analysis techniques, using B`oolean algebra, and the Boeing Company development of fault tree analysis, in connection with their Minute Man missile contract, began the development of system safety techniques. From this evolved a specific standard for system weapons systems, including missiles and submarines, which have proceeded to safety requirements now identified in the Armed Forces as

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[1] Klatz, Trevor A., "Eliminating Potential Process Hazards", Chemical Engineering, April 1, 1985, p. 40.

[2] Ibid

MIL Std.882A. This standard has the purpose of providing a uniform requirement and criteria for a system safety program."[3]

"The development of this standard focused the necessary alterations to safety of weapons systems and, as a result, development of major operational readiness without a major incident. To reach this point, however, numerous analysis techniques were developed. Among them were : preliminary hazard analysis, sub-system analysis, failure mode and effect analysis, criticality analysis, energy analysis, interface analysis and flow analysis".[4]

Additional techniques were developed by the Nuclear Regulatory Commission (NRC) to evaluate the safety of nuclear power systems. The NRC development called probablistic risk analysis is more complex than the military approach, according to Mr. J. Capps. This is due to the fact that they do not take the approach that hazards "can be eliminated" or that they are controlled to be "as safe as possible".[5] Because they are dealing with a large complex hazard control system with essentially fixed elements, decisions are based on levels of continuing risk and their acceptability. This is not the case in drug development where processes undergo dynamic change constantly.

Following the industrial revolution, equipment began to grow progressively more complex, involving the use of greater and greater amounts of energy, and increased potentials for accidents, injuries and

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[3] Rogers, William F., Introduction to Systems Safety Engineering, New York: John Wiley and Sons, Inc. 1971.

[4] Capps, James H., "Systems Safety for Plant Safety Specialists", Professional Safety, June 1984, p. 22.

[5] Ibid.

damage. Accident prevention failed to keep pace with technological growth so the number of mishaps increased tremendously with passing years. Corrective action was taken only after a particularly severe accident occurred or through the continued efforts of an outstandingly determined and energetic crusader. These efforts can be traced to legislation for industrial safety, mine safety, railroad safety, marine safety, and traffic safety. Unfortunately, adverse attitudes towards accident prevention also raised roadblocks in the effort to improve safety. There appears to be an inborn human behavior which resists devices and procedures by which individuals can safeguard themselves or others. The reluctance or resistance can take various forms such as:

- o opposition to change
- o opposition to additional effort or cost of implementing a safeguard
- o "macho" pride in completing an activity without benefit of suitable protection

Indeed, human error has usually been considered as the primary cause of accidents. Almost every mishap can be traced ultimately to personnel error, even though humans have prevented accidents by taking corrective and timely action when equipment malfunctions. Man generally is superb in adverse situations and cannot be surpassed in ability to overcome unforseen conditions and problems. But in today's computerized world, systems (that could generate an accident or intercede to prevent one) are being operated without benefit of a human present. Unmanned systems, therefore, still presented a problem when failures occurred or emergencies developed and it became readily apparent that many safety problems could be solved only by good design.

The principle of a Process Hazards Review is based on this concept which is an effective approach to avoiding, reducing or eliminating hazards and dangers during design and development.

The costs of accidents have been a big factor in establishing priorities for the health and safety of individuals. Loss experiences in the military and non-military sectors have provided the initial impetus for systems reviews, however, a new awareness was created for the recognition of hazards in the 1970s with the creation of OSHA and the Occupational Health and Safety Standards and the Environmental Protection Agency's regulations which define toxic and hazardous substances control and disposal.

Process Safety and Legislation

The impact of safety legislation, as well as the general awareness of society, has created a new sense of responsibility and awareness among professional personnel such as chemists, chemical engineers, environmental engineers, industrial hygienists, occupational health nurses and physicians, and safety professionals at all levels. In addition, the need to ensure process safety as a means of preventing public disasters has also become all too apparent in the office of today's top corporate officers.

In the last decade alone in the chemical industry, there have been several major disasters which have produced large loss of life, economic loss and an erosion of public confidence. These disasters have shown that major problems are not confined to geographical borders. A few examples selected from recent experiences illustrate

the concern that the real value of safety in the manufacturing industry has yet to be fully recognized.

"On July 10, 1976, in Seveso, a town of 17,000 population in Northern Italy, the safety-valve stack (pressure relief) of a reactor for making trichlorophenol (TCP) released, forming a cloud which spread over the town and surroundings. The fallout contained the TCP with an impurity of dioxin (dioxin is more toxic than TCP). Evacuation of the area was required followed by decontamination and treatment of 500 persons. No recognized treatment is available for dioxin poisoning."[6]

"A temporary bypass, intended to keep operations continuing during repairs, ruptured, causing a cyclohexane vapor cloud to be released into the air, which then ignited: 28 were killed and 36 injured inside the work site, and 53 recorded casualties occurred outside the works. The loss was estimated at approximately 100 million" [dollars].[7]

The Seveso, Italy disaster led to legislation which was to provide common industry and common market members, states regulations for the prevention of major accidents and the limitation of their consequences.

More recently, however, a poison gas release at a Union Carbide plant in India during December of 1984 could well be the worst chemical exposure disaster in history. Approximately 2000 people were killed along with perhaps 200,000 cases of exposure in Bhopal and nearby towns. Months later, in a similar plant located at Institute, West Virginia, 135 people were injured when a chemical leaked from a

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6 Fawcett, Howard H. and William S. Wood, Safety and Accident Prevention in Chemical Operations, Second Edition, Wiley Inter-Science, 1982, p.9

7. Ibid

Legislation of the 1980s has begun to provide a watchful eye as an initial step to improving safety in large plant operations. OSHA's Hazard Communication Law and state "Right-To-Know" laws will require manufacturers of hazardous materials to label, and provide written safety data on hazardous materials handled and produced at their locations to employees and municipal agencies. Appropriate training of employees is also required.

Faced with the growing regulatory pressure and battered by continued bad publicity, companies are now beginning to take a fresh look at hazards. Intensive efforts are being directed in areas such as:

- Setting up review of all chemicals used to find out how many are toxic and how effective the safeguards are.
- Additional training for employees to help them better understand plant processes.
- Review of cost cutting policies which may lead to the purchase of substandard equipment.
- Changes in maintenance procedures.
- Installation of computer equipment to organize records and control processes.
- Increased usage of outside consultants to conduct independent inspections.
- The stepping up of safety reviews. Increasing their frequency and intensity.
- Writing emergency plans to provide explicit procedures on how to deal with potential hazards.
- Reducing storage of hazardous materials on site.

The objective of the pharmaceutical and chemical manufacturing companies is now moving towards providing manufacturing processes which are efficient and safe. The types of safety reviews necessary to properly evaluate process hazards will vary by industry depending upon the type of business conducted. Although the technologies in the pharmaceutical and chemical industries are very similar and overlap to a large degree, process operations and handling of hazardous materials can vary greatly.

Chemical and Pharmaceutical Industry Process Differences

One particular factor that makes the pharmaceutical industry unique regarding process safety is the basic fact that the end products manufactured have a biological or physiological effect - they are medicinal chemicals. Not only does the final product have physiological activity, but generally, intermediate precursors in the complex production chain also have activity. Many are potent drugs which have human medicinal dosage levels measured in milligrams and as such, small quantites can produce serious consequences if not handled properly.

Some of the uniqueness in the pharmaceutical industry can be traced to the differences in the quantities of production. The typical chemical industry plant will produce large continuous quantities of basic chemicals, plastics, resins, etc., and the processes are likely being handled in bulk systems by highly trained personnel skilled in handling a relatively small variety of chemicals. These operations will, for the most part, remain unchanged from day to day and the

operators will handle and carry out the same process procedures that have been followed for many months or years.

In the typical pharmaceutical plant, however, the situation is quite different. Pharmaceutical plants are generally small batch producers rather than a large volume continuous producer of its products. The variety of products produced can be very broad involving a wide range of chemical processes. Because small batch operations can be nonrepetitive, the problems associated with running them can be more serious. A batch run today may be a year's inventory. By the time the product is produced again, few operators remember all the special precautions that may be required in running the process safely and, in fact, may not be aware of process changes which may have taken place in the interim.

Process Safety and Future Technology

An even more serious concern lies ahead for the pharmaceutical industry in exploring the frontier of biotechnology. In fact, as the pharmaceutical industry moves to producing products with efficacy at microgram dosages, to products that are biological in nature and to products that effect the most basic of genetic and cellular functions process reviews will have to focus increasingly more on individual safety.[8] While guidelines for recombinant DNA research have been specified by the National Institute of Health, additional guidelines

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[8] Cooper, Theodore, M.D., Ph.D., "The Corporate Impacts of Occupational Health and Safety Programs", Pharmaceutical Manufacturers Fourth Annual Conference on Occupational Health and Safety, Sept. 10, 1985, p. 14.

for biohazards may still be needed. The burden may fall on industry to provide process control measures to ensure employee and public safety. The potential effects of biohazards, if not controlled from the beginning, may be significant and only reinforce the need to conduct more frequent and sophisticated reviews of new pharmaceutical materials.

It becomes obvious then that to increase the margin of safety in complex operations such as pharmaceutical processes, a company should consider a hazards review approach to safety - in effect a "walk-through" process to identify all potential faults that could cause an accident and/or possibly a chain of negative events.

Some Current Process Review Program Methods and Definitions

There are a variety of safety review methods available to help identify hazards. The theoretical techniques most commonly used include procedures such as fault tree analysis, the Dow fire and explosion index, failure mode analysis, event trees, Hazard and Operability Study (HAZOP) and Techniques for Human Error Prediction (THERP). A common disadvantage of these techniques is that they require a great deal of time and effort by specialists in various areas if the results are to be meaningful and reasonable. Clearly, there is no quick and easy method for conducting these kinds of studies and though they may appear overwhelming at times, process hazard reviews are worthwhile if they prevent serious accidents, property loss, and public disasters.

The challenge in the pharmaceutical process industry today,

however, is to provide a sufficiently flexible process review protocol that will encourage the use of safety reviews at all levels of the new drug development process and one that will speed drug development by preventing not only accidents but providing answers to safety questions that will be asked later.

Many of the major chemical and pharmaceutical companies today use systematic and formalized approaches for evaluating new (and in many cases, old) processes and hazardous materials attendant to their manufacture. The degrees of concern over need in establishing a chemical process hazard review protocol has often been dictated by the unplanned incident which results in a large loss. It is the recognition and control, or elimination of unplanned incidents, to which the process hazard review must address itself. A more specific definition of a process review is provided by Mr. J. Hoffman of Parke Davis who states:[9]

> "... the phrase Chemical Process Hazard Review has widely varying meanings. To the professional safety engineer, it connotes a broadly based review of a chemical process which, when conducted properly, would provide assurances that a process can be conducted "safely"; safe for scientists in the laboratory, the technicians in the pilot plant and the chemical operators in the manufacturing plant. Chemical engineers, destined to design both the process and equipment, may depend on such a review to provide the details necessary to design the process "safely". Environmental engineers and control specialists consider a review process as a means for estimating risk to environmental exposure (air, water and ground) and a source of data to develop compliance information. Management needs the assurance from both line managers and staff functions that the process can be conducted and, the hazards associated with the process in its entirety, are identified to the extent that appropriate risk/benefit decisions can be made. An appropriate Chemical Process Hazard Review can and should meet all of these needs."

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[9] Hoffman, John M. and Daniel C. Moser, Chemical Process Hazard Review, ASC Symposium Series 274, American Chemical Society, 1985, p.1.

Taking Mr. Hoffman's definition, and descriptions from other sources, a Process Hazard Review, can be defined as an intensive examination, from both the theorectical and practical standpoints, of a designated process for exposures to personnel and property. A process Hazard Review also stresses early identification of potential safety and health hazards and elimination or control through development of adequate preventative measures.

Emphasis should be placed on areas such as:

- health effects and exposures due to materials handling and transfer operations.
- regulatory compliance requirements.
- suitability of operating procedures.
- suitability of fire and explosion control devices, equipment design, materials of construction.

In addition, a review should be distinct from, and in addition to, prestart-up, equipment acceptance, or area inspections. It should also be separate from investigations prompted by accidents or unusual incidents and periodic reviews performed for the purpose of updating procedures.

A Process Hazard Review (PHR) should be initiated for all programs requiring or involving:

- The use of highly toxic or hazardous material including, but not limited to, recognized carcinogens, mutagens, highly reactive compounds and teratogens, explosives, radioactive compounds, biological agents and drug actives.
- The use of process equipment in which significant pressures are developed (e.g. >100 psi).
- Radiation sources - ionizing and non-ionizing.
- All new capital projects - development of new products and/or

technology and proposed long term R&D efforts.

- o Changes in existing operations (i.e. increased pressures, temperature, changes in raw materials, introduction of new organism strains, etc.).
- o Changes in staffing of major operations.
- o Large scale material transfer and manual operations.

Organization of a Process Review

The need to check process design for errors has been recognized for some time but has traditionally been done on an individual basis. This method, however, is not as likely to detect potential hazards concerned with the interaction of a number of functions or specializations. In order to anticipate whether the experimental design or process will operate as intended under all possible circumstances, the combined skills of a group of experts is required. Therefore, in order to effectively conduct process reviews, a committee should be established. A Process Hazard Review Committee is needed to insure that the process has been thoroughly examined, the destructive potential of identified hazards has been assessed and that sound engineering judgement has been provided in formulating appropriate control measures.

In fulfilling its responsibilities, the committee must direct its efforts toward identifying hazards associated with processes that could cause explosion, fire, release of large quantities of toxic materials, serious injury, and inappropriate exposure to chemicals. The committee must also evaluate the magnitude of the hazards for probable area involvement, number of personnel affected, potential property loss and

frequency of occurrence. Finally, the committee must develop practical recommendations to eliminate or control hazards.

Composition and Responsibilities of the Process Review Committee

The effectiveness of the review depends on the skills, knowledge and effort of the process hazard review committee members. Therefore, the committee chairman should be in a management position sufficient to command the resources needed to successfully accomplish the review. At the minimum, the review committee should be composed of permanent and rotatable personnel. The non-permanent personnel would be rotated depending on the process being studied. Corporate Safety and Industrial Hygiene and Environmental groups should participate in all committee meetings to provide advise on the use of personal protective equipment, fire protection equipment, emergency facilities and new approaches to safety management. Typically, a Process Review Committee would consist of the following type of personnel in addition to Safety and Industrial Hygiene.[10]

- process engineer - usually the chemical engineer who drew up the flowsheet is involved when an actual potential hazard is identified. He suggests methods for minimizing or eliminating such a hazard.
- plant supervisor - responsible for operation, has scientific or chemical engineering background.

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[10] DuPont, Process Hazards Management, Manual prepared by Finishes and Fabricated Products Department, E.I. duPont deNemours & Co., Fourth Edition, copyright 1984, page 3.

- process investigation manager - responsible for investigating technical problems and for transferring laboratory results to plant-scale operations.
- independent team leader - job is to ensure that the committee follows procedure. Needs to be skilled in guiding a group of people and must pay meticulous attention to detail.

Depending on the nature of the process, other individuals that could contribute and should be invited to the review process are on an "as needed" basis are:

- instrumentation design engineer - because modern chemical processes contain sophisticated control and monitoring systems.
- research chemist - If new chemistry is involved and/or chemist works with the project, he provides a basic reactive sequence summary, offers his opinion on specific operations, chemical components, and prepares formalized process directions.
- operations foreperson - knows what actually happens rather than what is supposed to happen.
- operator - actually performs the work and can provide real workplace input.
- mechanic intimately familiar with the operation - has handled mechanical maintenance and should be familiar with the many faults that can occur.

When needed, other individuals with specialized knowledge or skills can also be called in on a consultation basis. Objectivity of the committee is the key toward completing a successful review in which all identified or suspected hazards have been included in a documented format regardless of anticipated acceptance or rejection. As a result,

the work of future review committees covering the subject area may be significantly reduced.

Occasionally, there will be more than one process that will require review. In a case where more than one process is involved, an initial priority list should be established. After experience is gained, management will be able to develop a review frequency and/or priority schedule with little trouble. It is important that management initially identify the process to be reviewed because committee selection is dependent on the process to be reviewed.

Following identification of the process to be reviewed, a committee chairman should be selected and instructed as to his/her responsibilities. Committee chairman candidates should include either the supervisor of the area in which the process under review is located, or the supervisor responsible for the process. When selected, the chairman should be instructed as to:

- o purpose and procedures involved in conducting a review
- o selection of the appropriate method of analysis
- o available material covering the process (such as past reports of the process).

The committee members should then be chosen based on a demonstrated knowledge of the process and preferably a recognized expert in some aspect of the operation to be studied.

After the committee membership has been fully organized, an organizational meeting should be held to:

- o Acquaint members with the studies, objective and procedures to be followed.
- o Assign each member a specific portion (or portions) of the

process to review.

- o Establish a timetable for meetings and deadlines for completing tasks.
- o Develop specific questions and checklists as needed.
- o Provide a process information update with data covering:
  - Process Chemistry (exothermicity, reaction rates, cooling rates, side reactions, effects of contaminants, temperatures, pressure, etc.).
  - Process material hazards (toxicity, reactivity, flammability, compatability, infectivity, radioactivity, physical properties, etc.)
  - Examine process flow diagram or experimental design narrative and/or outline.
  - Review equipment descriptions (materials of construction, operating temperature range, pressure ratings, capacity, instrumentation, safety devices supplied, etc.).
  - Review operating instructions - including safety, health and environmental needs.
  - Review emergency shutdown procedures.

Following the initial organizational meeting, the committee should then conduct a field review. During the field review, operator practices and equipment suitability and location can be evaluated. Information obtained from the field review will supplement information covered during the committee meeting and help to provide objectivity and practicality to committee recommendations.

As the information is gathered, a determination must be made by the committee as to what method of analysis will be used to evaluate the

process. There are three commonly used methods known as What if?, Failure Mode and Effect, and Fault Tree Analysis. Checklists and a technique developed in the 1970s called Hazop are also used.[11] A brief description of each to show the basic differences among the methods is given at this time, however, each technique is discussed in more detail in the next chapter.

Common Process Review Techniques

1. What if? - Most Common Method

- o This method is generally applied to those relatively uncomplicated processes that can be reviewed from raw materials to final product.
- o Review members formulate and answer What if? questions at each handling point in a process step to evaluate the effects of components failure or procedural errors in the process.

2. Failure Mode and Effect Analysis (FMEA)

- o Used when a specific item of equipment, such as reactor, is to be studied?
- o Committee would assess the effects of component failures and the occurrence of certain specified events or errors in the

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[11] Gibson, S.B. and A. Shafaghi, "Hazard and Operatiblity Study, A Flexible Technique for Process System Safety and Reliability Analysis", Chemical Process Hazard Review, ASC Symposium Series 274, American Chemical Society, 1985, p. 34

process.

- Used for determining the possible causes of a preselected undesired event.

3. Fault Tree Analysis (FTA)

- Committee would analyze the sequence of subevents and the combinations of causes that could result in the undesired event.

4. Checklist

- Provides a more organized approach to processes which are slightly complex.
- Uses lists of words and phrases that will stimulate questions concerning the subject.

5. Hazard and Operability (HAZOP) Study

- Designed to anticipate hazardous problems in areas of novelty and new technology where past experience was limited.
- Every part of the process is examined to discover how deviations from intended design can occur and how these deviations can cause hazards.

Upon selection of the method of analysis and ultimate evaluation of findings and observations, the committee should develop recommendations. After each committee member has identified all

potential hazards associated with the portion of the process he/she has studied, the committee should meet to define and evaluate the identified hazards, make recommendations to remedy problems and set priorities for correction of deficiencies.

Following the development of recommendations, the committee should issue a report summarizing its findings including existing or potential hazards identified and recommendations for follow-up or corrective measures. Target dates for completion of recommendations should also be included in the report. Copies of the report should be issued to all committee members and appropriate levels of management to help ensure that process safety needs will be met satisfactorily.

Deciding on an Analysis Method

The most difficult decision, of course, is what method of analysis should be used. Since process operations will vary from the exploratory stages, on through development and into manufacturing, the approach to identifying and controlling hazards through process reviews must be flexible, but organized. Organized and systematic process hazard reviews are particularly needed as a tool to increase process reliability and to meet today's regulatory demands. The two can clash in radically different environments such as research and manufacturing, thereby discouraging use of the process hazards review system in less structured environments such as research.

The following table provides some suggestions in the selection of types of review which resulted from thinking and decision making by DuPont Experimental Station scientists who conducted an evaluation of

the complexity of a process as it relates to the scale of the process operation. The PHR selection method is used in an ascending order of intensity, the "What if?", the Checklist, the Failure Mode and Effect, and the Fault Tree.[12]

TABLE 1 PHR SELECTION METHOD

	Batch Process		Continuous Process	
Scale	Lab/SW	Service	Lab/SW	Service
Exploratory Research	What if?	What If?	What if?	What if?
Research Scale-Up	What if?	What if?	What if?	Checklist
Process Development	Checklist	Checklist	Checklist	FM & E
Start-Up/Shutdown	FM & E	FM & E	FM & E	FTA
Freestanding Equipment	What if? or Checklist		What if? or Checklist	

SW = Semi-works

As can be seen from the table, in batch operations, the "What if?" method is most commonly used with the checklist and failure mode and effect method is used in larger, more complex operations.

The use of and need for the various types of methods in conducting process hazard reviews during the major phases of new drug development as noted previously is explored in the next chapter.

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[12] Hoffman, Mary J., "Hazard Review in a Chemical Research Environment", Chemical Process Hazard Review, ASC Symposium series 874, American Chemical Safety, 1985, p. 11.

CHAPTER II

PROCESS HAZARD ANALYSIS TECHNIQUES

The following sections discuss some of the more common analysis methods available to a Process Review Team and the appropriateness for a given process environment.

Methods of Analysis - General

As noted previously, there are three commonly used methods for reviewing process hazards:

- o What if: (Checklist)
- o Failure Mode and Effect Analysis (FMEA)
- o Fault Tree Analysis (FTA)

Each method differs in how thoroughly it analyzes hazards. The procedures used in the first two methods, however, are similar because:

1. The failure of each system or component is assumed.
2. The consequences of the failure are assessed.
3. The seriousness and frequency of the consequences are estimated.

Other techniques such as Hazard and Operability Study (HAZOP) and Management Oversight and Risk Tree (MORT) analysis were developed in contrast to the traditional methods because they are simple, creative, flexible, and increase the tools available for improving process safety and reliability.

What If?

The "What if?" evaluation is performed by inspecting equipment as installed in the field. Of course, this cannot be done for designs or even for a plant under construction until reasonably close to start-up. The method's lack of structure and the absence of well defined procedures limits its thoroughness. A modified What If? (checklist) should, therefore, be utilized for evaluation of design.

The Checklist method provides a more organized approach.[13] This is accomplished by the use of lists of words or phrases that would stimulate questions concerning the subject. For example, the phrase "Personal Protection" should lead to questions relating to the adequacy of ventilation and to the toxicity of the chemicals which are used. Checklists should be applicable to the site or department for which it is written.

For the "What if" technique to be effective, each segment of the process under study must be challenged by qualified committee members who ask "What if?" questions at each handling or processing step. When employed in a systematic manner involving an exchange of information among members of the committee, this method of analysis can be very productive in identifying and correcting serious process hazards.

An advantage of the "What if" (Checklist) method is that it includes reminders to use in-house services like the Library Literature Search, Analytical Services, Computer Applications and Health and Safety Staff department resources.

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[13] DuPont, Safety and Fire Protection Guidelines, Section 6.4, "Process Hazard Reviews", July, 1981.

The "What If?" method, if employed systematically, can also be very productive in identifying and correcting serious process hazards. It's success, however, is dependent upon the degree of participation and exchange of information among members of the committee.

Examples of typical questions asked during a "What if?" analysis and a What if? Process Review Procedure flowchart are included on the next two pages. A simple acid delivery system in which the What If? technique is used to identify potential hazards is also provided as an example.[14]

What If? Method: Acid System Example

Process Description

The process is a batch operation (see Figure 2) consisting of a measuring tank that is filled to a predetermined level through a fill valve (4) and a pump (9). The quantity of acid is determined by an operator's observing the rise of liquid in the sight glass and closing the fill valve (4) when he has the proper amount in the tank. The tank is vented to the atmosphere through a dryer (3) containing a desiccant to prevent moisture from being admitted to the tank as its contents are emptied into the process downstream.

All the components of the process under review are included in the sketch on the following pages. This process does not include the supply tank and equipment downstream from the outlet valve (5).

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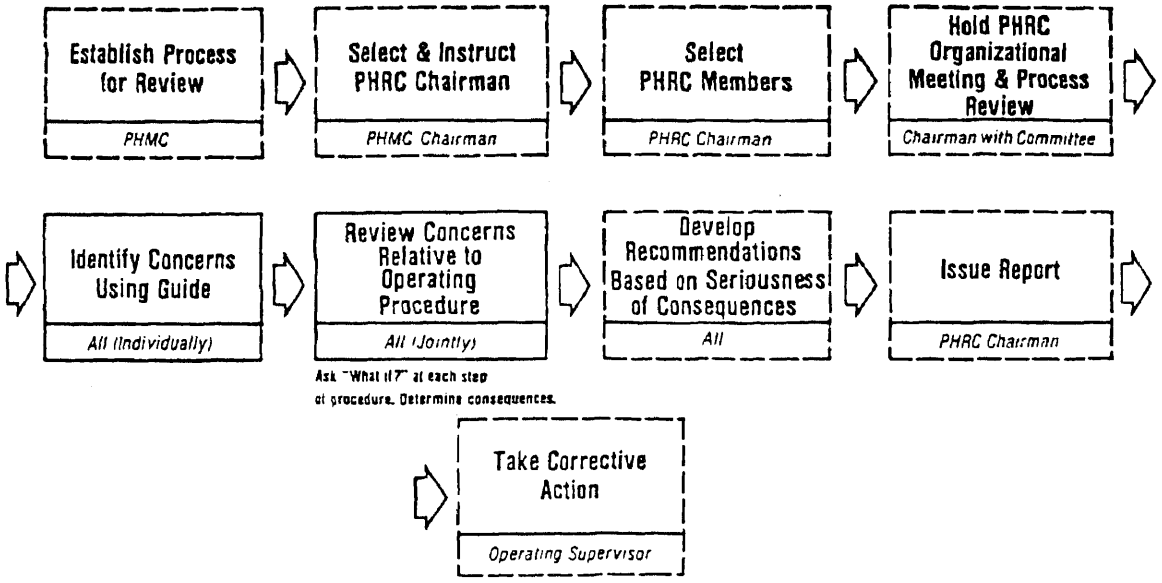
[14] DuPont, Process Hazards Management, E.I. duPont de Nemours and Company (Inc.), fourth edition, revised 1984, section 5.5 - 5.11.

PROCESS HAZARDS REVIEW PROCEDURE:
WHAT IF? METHOD*

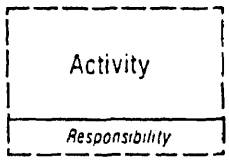


Abbreviations:

PHMC = Process Hazards Management Committee

PHRC = Process Hazards Review Committee

Symbols:



* Dashed boxes indicate general procedure
Solid boxes are specific to the What If? Method

Figure 1

DuPont; Process Hazards Management Manual, Fourth Edition, 1984, Section 5.5

ACID SYSTEM

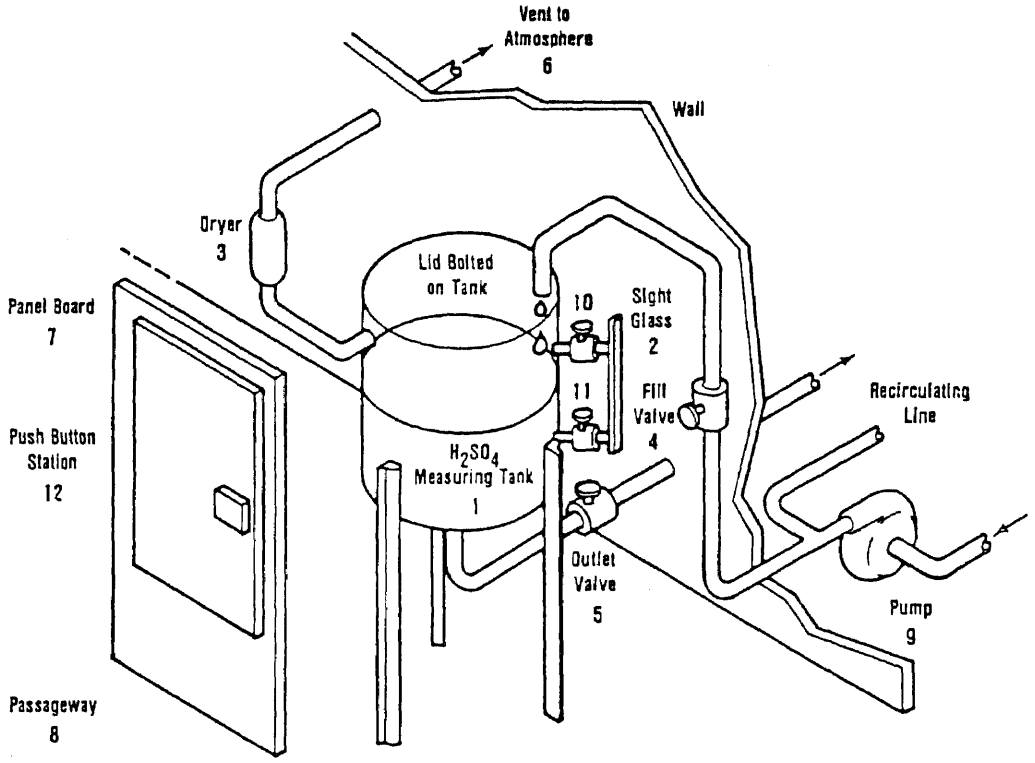


Figure 2

DuPont; Process Hazards Management Manual, Fourth Edition 1984, Section 5.8

Operating Procedures

Step

1. Ensure that the outlet valve (5) is closed.

2. Open the fill valve (4).

3. Start the pump (9).

4. Observe the sight glass (2) for liquid rise.

5. Throttle the fill valve (4) closed as the level of the liquid approaches the full mark. Close the fill valve when the tank is full.

6. Stop the pump (9).

What If? Method -- Typical Questions and Answers

Question - What If:	Answer
the sight glass (2) ruptures?	- *Liquid would spill onto the floor and flow to the nearest drain. No spill containment is provided. - The pump (9) would be shut off.
the dryer (3) plugs	- There may be an acid fume condition in the room from the venting of fumes around the tank lid seal. There probably is an industrial hygiene problem.
the valve (11) plugs or is closed?	- There would be no indication of the acid level. - The pump (9) would be shut off. This would be no problem.
the valve (10) plugs or is closed?	- *There would be a false (low) tank level indication resulting in acid overflow through the vent and/or acid spill from the loose-fitting lid.
the fill valve (4) fails to seat?	- The operator would recognize the condition and shut off the pump (9). This would be no problem.
the pump (9) fails to stop?	- It would recirculate again through the valve (4) and would not be a problem.
the operator fails to observe acid level?	- *The acid would overflow through the vent and/or spill from the loose-fitting lid.

*Items for which corrective action should be considered.

What If? Method -- Typical Questions and Answers (continued)

Question - What If:	Answer
the acid contaminates the dryer (3)	- * The dryer medium would eventually form a mass and plug the vent.
the dryer (3) and the valve (10) both plug?	- * A serious spray would result at the lid, which is the weakest point in the system.
a spray occurs from the top of the tank?	- * Any employee in the vicinity could be sprayed.
a leak occurs at the measuring tank?	- * The spill would not be contained. - The operator would have to wear protective equipment to enter the area and close the valves.

*Items for which corrective action should be considered.

Failure Mode and Effect Analysis (FMEA)

Use of FMEA

The Failure Mode and Effect Analysis (FMEA) method can be utilized to evaluate all aspects of a particular operation or investigate and determine the destructive potential of each individual hazard and that of interacting hazards. It is equipment-focused and, as such, the users may not give proper emphasis to:

- o omissions or errors in operating procedures.
- o Incorrect operational sequences in batch operations.
- o The possibility of operator errors.

Hazards associated with the above aspects of a process may need to be studied separately.

FMEA is recommended for analysis of small segments of a process having a high hazard potential, such as a reactor or distillation column, in contrast to an entire production operation or an operating building. A portion of the process that is reasonably independent of other systems, but is not too complex to analyze efficiently should be selected.

Application of FMEA

While this method may not place emphasis on operating procedure errors or omissions, or the possibility of operator errors, it does assess the consequences of component failure and its effect on the entire system. The value of the entire analysis depends on the

availability of a sketch outlining the components of the selected system. A sketch should be made available to committee members as early as possible. The success of the analysis depends on the accuracy of the sketch and that the system be shown as it presently exists. The sketch should be a line diagram of the process which breaks down the process into subsystems if necessary, making it easier to study all modes of operation.

Failure or Error Mode

There are many ways in which a system component can fail, such as a valve which is jammed closed or a power failure. Each possible mode of failure including any potential operator error that might cause a component to fail should be documented. Although some components can fail and have little effect on the overall system, it is possible that a failed component may affect the overall system very seriously.

A practical illustration of how the FMEA technique can be applied would be in an example analysis of a simple pressure tank system (Figure 3)[15]. The illustration shows a pressure tank which is assumed to contain a very critical material such as one which is subject to ignition or extremely hazardous to personnel. The pressure tank is assumed to have a pump with piping back to the reservoir or source of supply, pump motor and series of relays and reset switches which will govern the activation of the pump motor. These relays in turn are activated by pressure relief switches which sense pressure in the tank

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[15] Celanese Chemical Company, Inc., Corpus Christi Technical Center, Process Safety Review Manual.

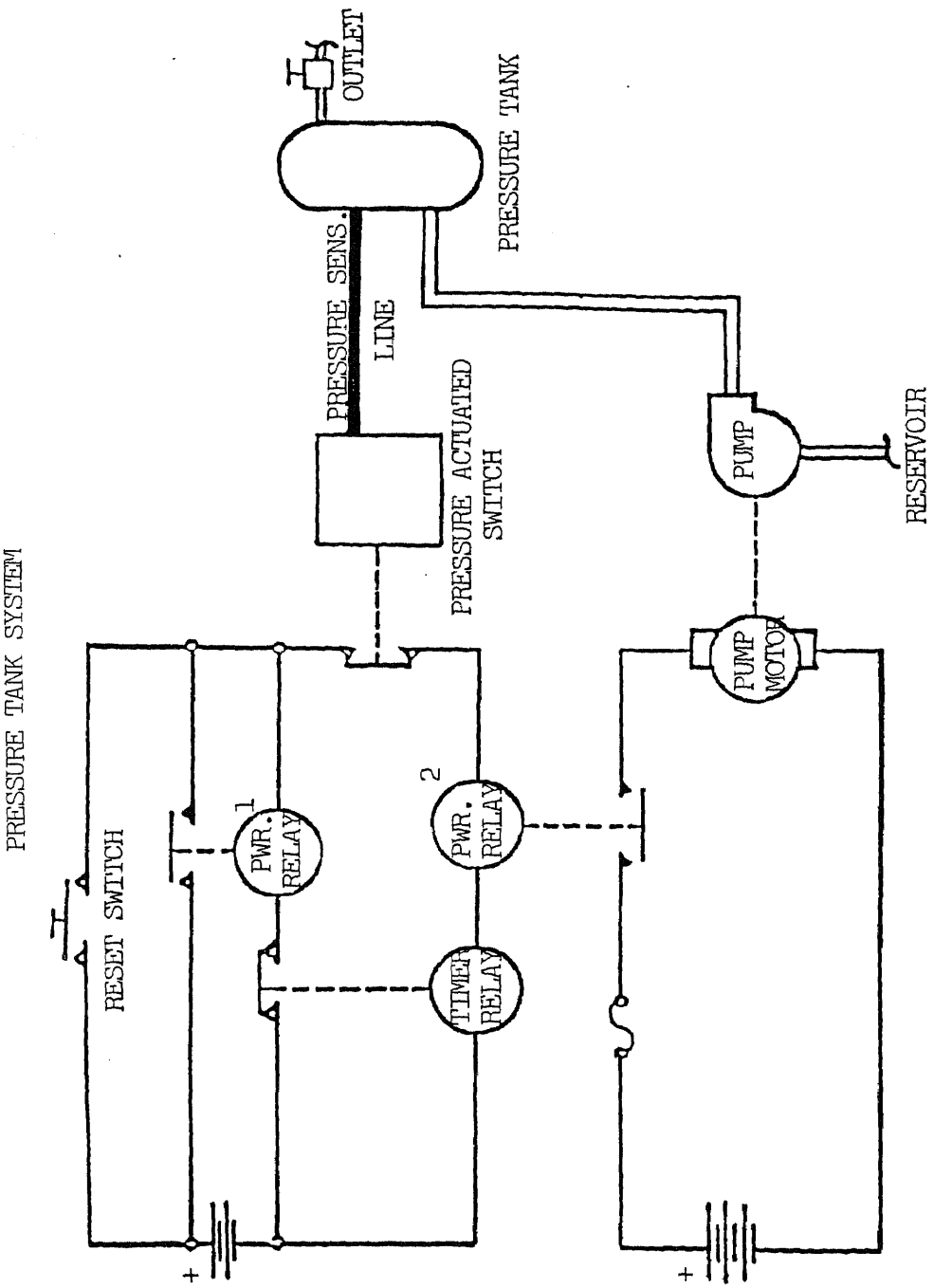

Figure 3

Celanese; Process Hazard Review Manual, page 2

or adjacent lines.

A preliminary analysis has been completed and it has been determined that due to the criticality of the contents of the tank and the probability of tank failure, there is sufficient need to do further safety analysis using the FMEA method.

Using the Failure Mode and Effect method, we should take into account every possible way in which each of the system components could fail and what would be required to minimize the probability of such failures. Although there may be many things that could cause failure, the two basic causes would be that the tank failed under design environment or it failed from excess internal pressure due to continuous pump operation. Of course, the causes of these failures could be a failure of a weld, failure at a seam or just metal fatigue. It would be very difficult to determine the causes without extensive testing, and depending upon the criticality of the end undesired event, a degree of testing and reliability research commensurate with the risks involved would be needed. However, for the moment, if the possible failing of the tank under design environment conditions is set aside and accidental or unexpected rupture is considered, in this case, it would be that the tank failed from excessive internal pressure due to continuous pump operation. There may be many others but for the moment one facet of it should be concentrated on and carried through.

Initially, the human factor must be considered. Someone could have failed to press the right button; someone could have failed to shut off the motor or allowed the motor to overrun. From a mechanical standpoint, there could be a continuous pump motor operation due to failure of a relay contact to open after cycle. If this occurred, the

motor would continue to run. If we examine the illustration, it is possible that the power was not removed from relay number two coil or that relay number two contacts failed in the closed position. If these possibilities are traced out, not only the potential causes can be determined, but also where in the system the necessary safety devices can be put that will cause the system to either deactivate completely or at the very least to fail in a safe mode.

What about other saving methods, such as relief valves, relays in parallel, etc? Once the failure modes have been properly identified, a number of methods and lock-out type devices can be employed to reduce the risk of error.

Probability of Process Failure and FMEA

The probability of failure of a process can be determined by estimating the approximate frequency of failure in terms of failures per hour. For a batch process, it is the number of failures per batch. Since there are approximately 10,000 operating hours in a year (10^4 hours/year), one failure per year would correspond to a probability of 10^{-4} per hour. If 10,000 batches were made in a year, one failure per year would correspond to a probability of 10^{-4} failures per batch.[16]

Failure rates can be expressed in failures per hour when the failure is detected promptly (within one hour). When the failure is for a longer period, the time to failure must be determined. For

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[16] DuPont, Process Hazards Management, E.I. duPont deNemours and Company (Inc.), fourth edition, revised 1984, section 6.3.
components that are inspected or tested regularly, the failure rate can

be assumed to be one-half the interval between inspections or tests. Failure rates can be acquired from several sources such as:

1. Plant maintenance records.
2. Estimates made by knowledgeable operating or maintenance personnel.
3. Failure rate data developed from other resources such as the example Failure Probability Graph (Figure 4) and Decision Tree (Figure 5) developed by du Pont.

Failure data from outside sources, however, should be used with extreme caution because it may have been developed from an experience base much different from the industry and environment being evaluated.

Due to the need for detailed records and the amount of time required for an accurate calculation, a suggested expression of the probability of failure as noted by du Pont, Inc. is given in table 2 below.[17]

Table 2 Probability of Failure

Category	Degree of Probability	Approximate Probability of Failure
A	Extremely likely	10^{-1}
B	Likely	10^{-2}
C	Reasonably likely	10^{-3}
D	Unlikely	10^{-4}
E	Remote	10^{-5}
F	Extremely remote	10^{-6}

[17] DuPont, Process Hazards Management, E.I. duPont deNemours and Company Inc., fourth edition, revised 1984, Section 6.3.

FAILURE PROBABILITY GRAPH

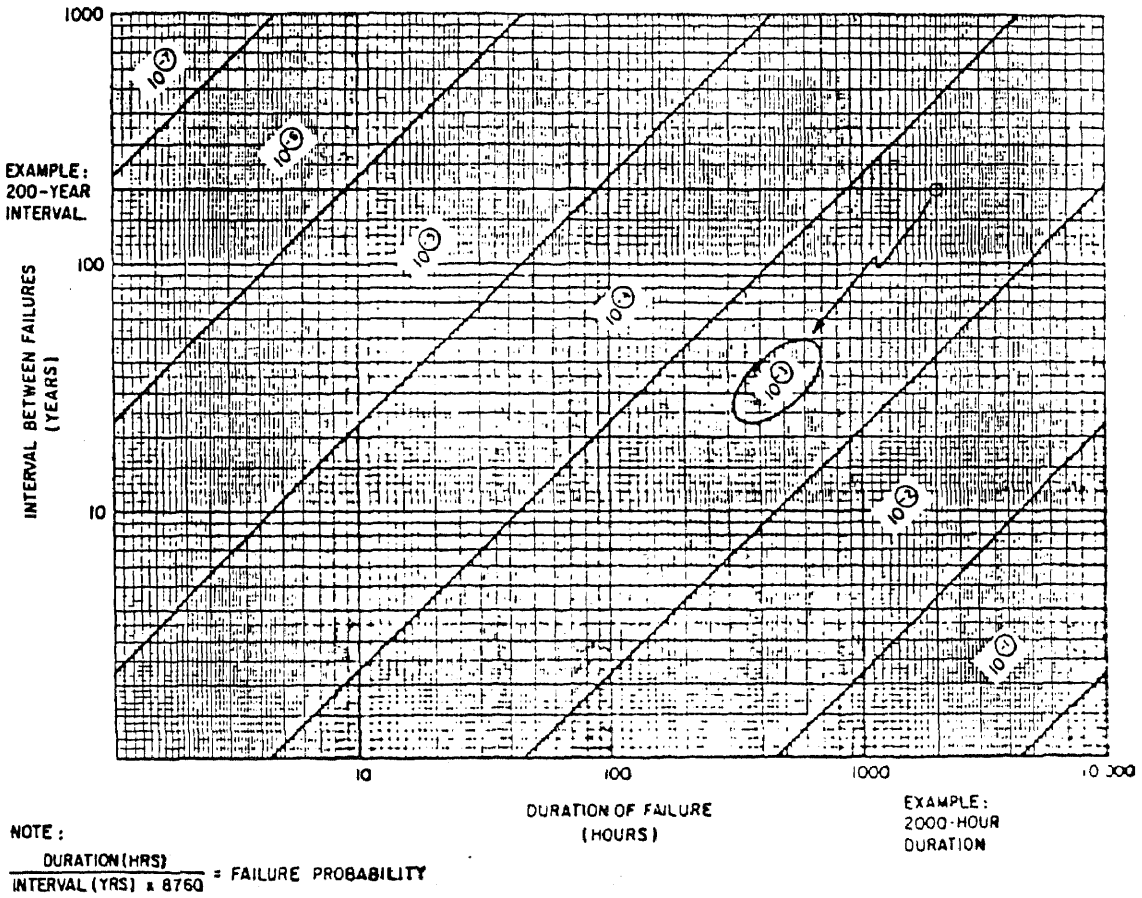
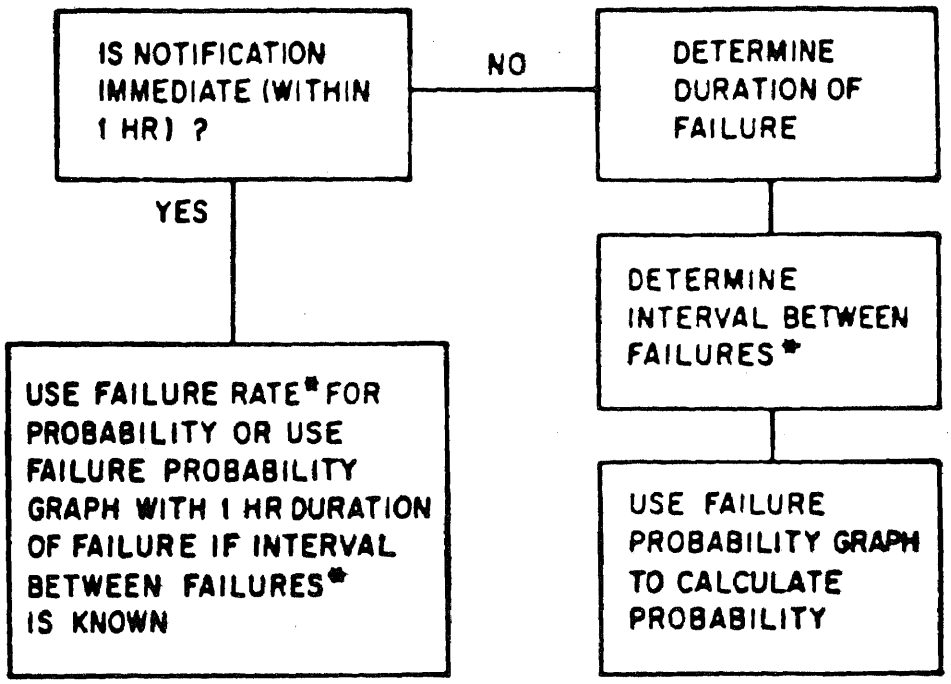


Figure 4

Dupont; Process Hazards Manual, 4th Edition, 1984, Section 9.9

PROBABILITY OF FAILURE DECISION TREE



*
- FROM PLANT MAINTENANCE RECORDS.
- FROM ESTIMATES MADE BY KNOWLEDGEABLE PEOPLE.
- FROM THE TABLES IN THE APPENDIX OF THE MANUAL

Figure 5

Dupont; Process Hazards Management Manual, 4th Edition, 1984, Section 9.95

Detecting and Compensating for Failures (FMEA)

It is necessary to know when a component fails and the potential duration of failure. The shorter the duration of failure, the less chance of a catastrophic event. Therefore, critical components in a process should receive inspection priority or a frequent schedule for testing or both. The duration of failure can be assumed to be at least one-half the interval between inspections and/or tests.

It is not unusual in a given system for components to fail. In many instances, emergency measures can be utilized or the equipment designed to minimize the potential for failures. When reviewing potential equipment failure, the committee should list compensation provisions for each component failure and describe briefly the resultant hazard potential attributable to each component failure.

Priorities for correction can be established through use of a guide number. The guide number provides a scale by which the committee can determine if a component failure is likely to occur and if the safety factor should be enhanced. Any guide number of 10^{-1} or less would indicate correction is warranted. The guide number can be obtained by multiplying the numerical values corresponding to the probability of failure (Table 3) and the Hazard Rating. The Hazard Rating is an estimation of the degree of hazard resulting from the failure of each component and is based on each component being considered to be in a failed state. The rating system used by du Pont follows:[18]

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[18] DuPont, Process Hazards Management, E.I. duPont deNemours and Company (Inc.), fourth edition, revised 1984, Section 6.3.

Table 3 Categorization of Hazard Rating

Category	Degree of Safety	Description	Hazard Rating
1	Safe	The component cannot fail, or if it does, it will fail safe (cannot cause a hazardous situation).	$10^0 = 1$
2	Marginal	Failure of the component will occur without major damage or personal injury.	$10^1 = 10$
3	Unsafe	Failure probably will cause major damage and/or personal injury.	$10^2 = 100$
4	Very unsafe	Failure of the component will cause multiple failures in the process; the failures have serious personal injury or property loss consequences.	$10^3 = 1000$

As an example: If a component with a hazard rating of 10^1 also had an approximate probability of failure of 10^{-3}, the product of these two numerical values would yield 10^{-2} as a guide number and warrant priority correction to be made safe.

Concurrent Component Failures (FMEA)

Consideration of only one component to protect a system from a serious hazard is not considered practical since this would limit the value of the Failure Mode and Effect Analysis. Consideration of combinations of failures will provide the review committee with a more realistic approach to evaluating all possible system failures. When evaluating multiple component failures using FMEA, the committee should:

- o Study the sketches, documented problem areas, and tabulations systematically.
- o Group all components that can present serious hazards if they fail concurrently.

A sufficient amount of time for the evaluation should be allowed by the committee to insure that all possible combinations of failure are examined and any potential serious hazards have not been overlooked. The FMEA analysis should be performed similarly for combinations as is done for each single component.

Following identification of all possible component failures, a list in order of priority of all components and component combinations whose failure will produce a guide number of 10^{-1} or greater must be recorded. Recommendations should be submitted by the committee for all items that appear on this list. The list should also contain recommendations for continuing aspects of the operation without modification. If this occurs, current control measures that are considered acceptable should be noted.

Since Failure Mode and Effect Analysis is equipment-oriented, it does not lend itself to the research environment where dynamic change in discovery work is often experienced. FMEA techniques, however, can be useful to the pharmaceutical researcher as well as the plant chemist. Modifications to the FMEA technique can make it easily adaptable to the discovery and development stages of new drug compounds.

Fault Tree Analysis (FTA)

The Fault Tree Analysis Method was originated by H.A. Watson of

Bell Laboratories in 1961 to evaluate the safety of the Minuteman Launch Control System. Initially, it was suited to batch operations. In the early 1970s, Powers and Thompkins presented an approach for automatically generating fault trees and applied them to chemical processes.[19] Since considerable effort is required in generating fault trees, additional procedures were developed to minimize the effort of generating and evaluating fault trees, yet retain the benefit of acute examination. Because of the complexity of Fault Tree Analysis, its use has been primarily limited to the aerospace industry and only recently has its application been utilized in the chemical and pharmaceutical industry. Some advantages and disadvantages of the FTA method are noted below:

Advantages

1. Shows the relationship between certain component failures that can lead to the undesired major event.
2. Aids in evaluating the combination of unfavorable events leading to the undesired major event.
3. Identifies human errors that can lead to the undesired event, and highlights the system's sensitivity to operator or maintenance errors.
4. Evaluates actual incidents.
5. Makes use of quantitative calculations and combinations of causative events to:

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[19] Fawcett and Wood, Safety and Accident Prevention in Chemical Operations, Wiley Interscience, 2nd Edition, 1982, Chapter 35, p. 729.

- o determine the severity of loss rates (dollars/year) caused by the undesired event.
- o Predicts the probability of the undesired event's occurrence.

6. Allows for comparison of loss rates (dollars/year) of modified and unmodified processes. These rates can be used for cost benefit analysis.

Disadvantages

1. Considerable effort and expense may be required for the analysis of even relatively uncomplicated processes.
2. Fault trees can become very unwieldly and possibly unmanageable in complicated systems.
3. Computerization may be required for construction and evaluation of large fault trees.

Application of FTA and Developing Fault Trees

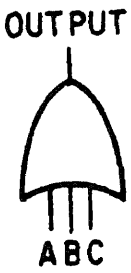
When conducting FTA, the undesired event for review must first be identified. The results of previous process reviews in which the What if? and Failure Mode and Effect methods were used can be used as the basis for selecting the undesired event. The overall objective of the FTA is to determine where the process could fail and how the personnel involved in operations and maintenance could also fail and bring about an undesired event. Therefore, personnel involved with constructing a fault tree should be familiar with:

- o the process equipment and procedures

o control and emergency facilities

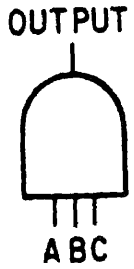
Following selection of the undesired event, a fault tree is designed by setting down the undesired event at the top and determining all possible sequences of events which can bring about failure. The tree is constructed using logic symbols and the events are tiered in descending order of occurrence. Each tier represents a branch of the fault tree and should be examined independently of the other branches. By constructing the tree with logic symbols, the events are quantified and give an idea of what the greatest risks are and where changes should be made to provide the greatest safety for the projected budget. Symbols are used in creating a fault tree, typical symbols and their meaning are shown below:

"Or" Gate



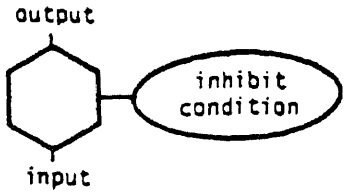
An operation where any of the inputs or feeder events produce an output. This gate is in a failed state if at least one of its inputs is in the failed state.

"And" Gate



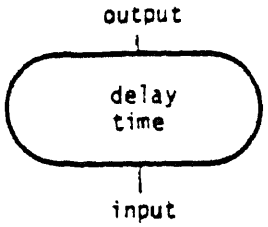
An operation where all of the combined inputs or events must co-exist to produce an output or event. This gate is in the failed state only if all its inputs are in their failed states simultaneously.

"Inhibit" Gate



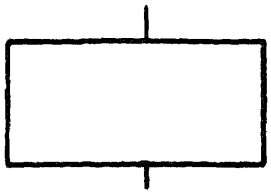
Indicates that the output event occurs when the input event occurs and the inhibit condition is satisfied.

"Delay" Gate



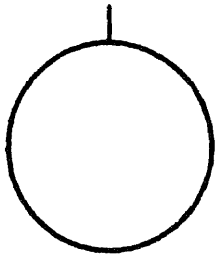
Indicates that the output event occurs when the input event has occurred and the specified delay time has expired.

Subevent



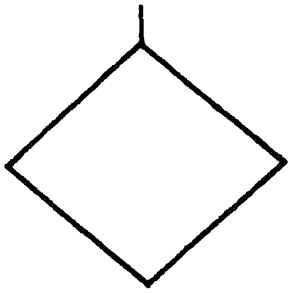
The rectangle describes the event that is the output of a logic gate.

Basic Cause



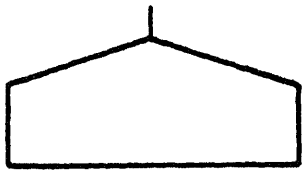
The circle represents a component failure or random fault event that requires no further development.

Basic Cause



The diamond represents a system failure that is not developed further.

Normal Operation



The house represents an event that is normally expected to occur because of design or normal operating conditions. It should be shown if not obvious.

Transfer

The triangle transfers an entire part of the tree to another location on the tree or to another page of a divided tree.

It is important to the analysis that the causes of each event be direct and immediate causes and that the subevents that comprise the downward steps be as small as possible so that failure events or branches will not be missed.

Construction of the fault tree should continue until all members of the committee are satisfied that they have identified all possible events and subevents and the basic causes of each.

A completed fault tree will provide the review committee with insight to the critical path or events having the greatest impact on the top undesired event. Frequently, visual inspection of the completed tree will show just where system improvements may be needed. The sensitivity of the system to basic causes can also be assessed by determining the degree of involvement of the basic causes in the sequence of failures leading to the top event. In cases where a system would require multiple causes to occur simultaneously to produce a failure, the major event is probably not sensitive to any single cause unless that single cause is determined to have an extremely high occurrence. An example of a representative fault-tree structure is provided in Figure 6 on the following page.

Representative Fault Tree Structure

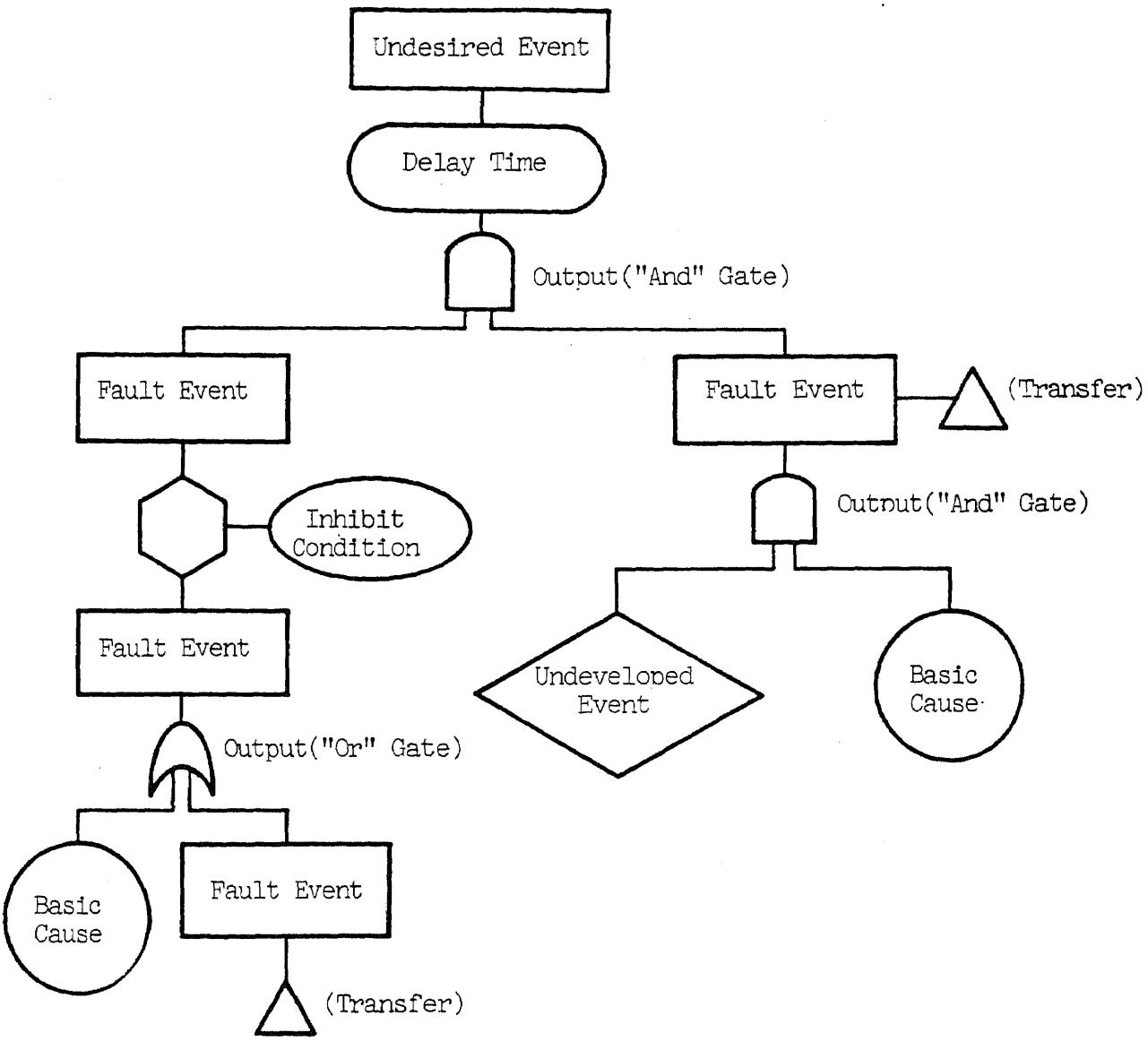


Figure 6

American Institute of Chemical Engineers, 1985

Identification of for Inadequately Controlled Hazards by FTA

In addition to recognized hazards, previously unrecognized inadequately controlled hazards often are identified through the FTA method of analysis. In many processes, the hazards involved in starting up or shutting down a process can be more serious than those which could occur during the continuous phase of operation. Therefore, it may be necessary to combine batch operations with the continuous operation and develop a fault tree which addresses failure experience during the start-up, shutdown, and continuous operation phases.

Where the major event is not sensitive to any single cause because multiple causes must occur to produce a failure, an analysis to determine what is called "critical failure paths" or "minimum cut sets" of the system must be performed. Minimum cut sets are used as a short cut method of analyzing the entire fault tree because events that occur in the tree between basic causes and the top event have been removed.[20]

A complete tabulation of minimum cut sets contains all the failure modes for the system understudy. Minimum cut sets:

- o point out the weakest links in the system
- o show which failures must be repaired or prevented to avoid or minimize occurrence of the top event.

Recommendations resulting from the Fault Tree Analysis method should be practical and will include items such as:

- o Installation of safety devices such as relief valves, rupture disks, or interlocks.

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[20] DuPont, Process Hazards Management, E.I. duPont deNemours and Company (Inc.), fourth edition, revised 1984, section 7.4.

- o Improved design features such as fail-safe components, redundant sensors or controls, or warning devices such as alarm lights or horns.
- o Special procedures such as use of operational checklists or entry of process conditions on log sheets.

A procedure for obtaining critical combinations of failures (minimum cut sets) and ranking of basic causes, plus fault tree construction rules as developed by DuPont Inc. are provided on the following two pages.

As can be seen from this description of the Fault Tree Analysis method, it is a very rigorous method and quite involved, to the point where computerization may be necessary to quantify the various identified causes. Because of this, the FTA technique has been better suited to production sites rather than the research environment where less rigorous methods are better suited and preferred.

Procedure for Obtaining Critical Combinations of Failures (Minimum Cut Sets) and Ranking of Basic Cause

Determining the Critical Failure Combinations (Minimum Cut Sets)

1. Identify each gate in the fault tree with a letter and a basic cause in the tree with a number.
2. Develop a Boolean Indicated Cut Sets (BICS) table as follows:
   a. Start the table by listing the top gate of the tree in the first vertical column of the first horizontal row.

b. Based on the type of gate, make the following substitutions and additions to the table:

- o If the gate is an AND gate, replace it with one of its input elements and place its remaining input elements in vacant columns in the same horizontal row.

- o If the gate is an OR gate, use one of its input elements to replace the gate. Place each of its other input elements in the same vertical column in the next vacant row and copy all other elements in the row where the gate was replaced into the new row(s) in their respective columns.

c. Repeat this procedure until the BICS table contains only basic cause events represented by numbers.

3. Reduce the BICS table of minimum cut sets.

a. Delete from the BICS table any duplicate rows or any duplicate number (basic cause events) within any row.

b. Delete from the modified BICS table any row that includes within it all the numbers (basic cause events) that are given in any other shorter row.

Suggested Fault Tree Construction Steps[21]

1. Identify the top event.

2. Understand the process.

3. Develop the tree structure by showing direct causes.

4. Specify the event state. Be specific about the occurrence and any other components involved.

5. Follow the signal path backward:

   - o Work from the control component (such as a valve) back through the signal path to the detection component.
   - o Assess failures at each component en route.

6. Evaluate each type of failure for each component:

   - o Mechanical (internal).
   - o Command (faulty signal).
   - o External (fire, freeze air loss).

7. Use cut sets to evaluate trees with common mode failures.

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21 DuPont, Process Hazard Management, E.I. duPont de Nemours and Co. (Inc.), Fourth Edition, Revised 1984, section 7.13.

Hazard and Operability Studies (HAZOP)

The basic concept of Hazard and Operability Studies is to identify hazards before an incident and control the risks. The technique aims to stimulate the imagination of designers in a systematic way so that hazards can be identified in the design phase. HAZOP is a flexible technique and can be applied to all types of plants in industry ranging from large continuous operations, through small batch units to individual proprietary items of equipment such as autoclaves or micronizer mills.

A distinguishing feature of HAZOP is the "Examination Session" during which a multi-disciplinary team systematically examines all relevant parts of a design using a structured but creative approach.[22] HAZOP, due to it flexibility, is particulary adaptable to innovative process work and new technology where other methods such as FTA have proven to be overly complex or limiting. Additional notable features of HAZOP study include:

- o It is based on brainstorming.
- o It is structured by using guide words.
- o It is cost effective.

In comparison to traditional methods such as the What if? or checklist, HAZOP reduces the chance that something will be missed and addresses situations for which the solutions are not always obvious.

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[22] Chemical Industries Association Ltd., ICI Central Safety Deprtment, Shell Chemical (UK) Ltd., "Guide to Hazard and Operability Studies", Notes on Presentation, p. 2.

While traditional methods are experience-based, procedural (prescriptive) and collective, HAZOP studies are very systematic, creative, informative, and participant interactive.

Conducting a HAZOP Study

The approach to identifying operating problems and hazards by this method is to search for deviations from the original design intent. It is especially stressed that in a hazard and operability study, the operability part is as important as the hazard part. There are tendencies in some studies to identify more operating problems than potential hazards.

The initial step in setting up a HAZOP study is to provide sufficient time, expertise and available information. Next, a multi-disciplinary team is formed. The team will consist of two types of team members, namely those who will make a technical contribution and those who will play a supporting and structuring role. Technical team membership should include members that have a detailed knowledge of the way the plant is intended to work and a blend of those concerned with the design and operation of the plant. A team should contain enough people with sufficient knowledge and experience to answer the majority of questions without recourse to further expertise. A technical team would, therefore, be comprised of such participants as:

Mechanical Engineer	Production Manager
Chemical Engineer	Project Manager responsible for
R&D Chemist	the project

Supporting team members are utilized to control the discussion, the

major supporting team member normally is identified as the team leader. The team leader will help whomever has commissioned the study to define the scope and may also assist with selection and training of the team members. The major role of the team leader, however, is to guide the systematic questioning and not to be responsible for a major technical contribution.

In addition to the study leader, it is sometimes useful to have a further supporting member to act as a secretary or scribe to make note of the hazards as they are detected.

HAZOP Terminology

Because the examination will be systematic and structured, it is necessary for participants to use certain terms in a precise and disciplined way. Some necessary definitions to be understood before conducting a HAZOP study are:

Intention - defines what is expected and how the part is expected to operate.

Deviation - describes departures from the intention and systematically questions how deviations can occur by applying guide words.

Causes - reasons why the deviations may occur.

Consequences - results of the deviations should they occur.

Hazards - consequences which can cause damage, injury or loss.

Specific guide words are also used to assist in discovering and qualifying potential deviations from the intention. A list of guide words used is given below.

Guide Words

Guide Word	Meaning	Examples
No or Not	No part of the intention is achieved but nothing else happens.	No flow, no agitation, no reaction.
More Less	Quantitative increase or decrease to the intended activity.	More flow, more pressure, lower temperature, less time.
As Well As	All of the intention is achieved but some additional activity occurs.	Additional component, containment, extra phase.
Part of	Only part of the intention is achieved, part is not.	Component omitted, part of multiple destination omitted.
Reverse	The opposite of the intention occurs.	Reverse flow, reverse order or addition.
Other than	No part of the intention is achieved. Something different happens.	Wrong component, start-up, shut-down, utility failure.

By means of the terms and guide words, the process variables or specific parameters of interest are examined by the team and specific deviations detected and addressed as to the probable causes and consequences. In a continuous chemical process for example, process variables would include temperature, pressure, flow, and concentration. These specialized guide words would be used in conducting the study and would be listed as follows:

Guide Word	Variable	Deviation
No	Flow	No flow
Less	Temperature	Low temperature
More	Pressure	High pressure
Part of	Concentration	Low concentration

For batch processes, level, reactivity, and time might be additional parameters considered. For something more specific such as an electrical system, voltage, current, phase, and frequency would be variables that are considered.

When the guide words are applied correctly, a series of important questions will develop about a specific parameter or other parameters of the system. For instance, use of the guide word "no" with the variable word "flow" means "no flow" will occur when possibly there should be flow. As a result, we could ask the following questions regarding the operation and hazards for this aspect of the system.

- Could there be no flow?
- If so, how could it happen?
- What are the consequences of no flow?
- Are the consequences hazardous or do they prevent efficient operation?

- o If so, can we prevent no flow (or protect against the consequences) by changing the design or operating method?
- o If so, does the size of the hazard or problem justify the extra expense?

Additional guide words would be applied as required. To reduce the chance that something will be missed, the guide words should be carried out for any operation that is expected to take place in the equipment being evaluated.

Outcomes of Guide Word Application

One of three outcomes is possible for each guide word application:

1. No hazard or problem exists.
2. A hazard or problem exists. In this case, a suitable record is made to that effect, and the solution will have to be resolved outside the meetings.
3. The team does not have sufficient information to determine whether a problem exists. In this case, a record is made to that effect, and again, the necessary information will have to be found outside the meeting.

HAZOP Flexibility and Benefits

HAZOP's major contribution is that potential process problems are

identified in advance of them becoming a major incident or disaster.[23] HAZOP analysis is also advantageous because:

- o Potential problems are identified and resolved relatively easily, and most subtle hazards are identified at the design stage.
- o Potential problems can be resolved rationally, whereas an incident usually creates an overreaction and expensive, ultraconservative solutions.
- o Engineering change orders during construction and commissioning are drastically reduced.
- o Plant design and start-up is more timely.

Because the methodology is basically very simple and the guide words are general, HAZOP can be applied to many different types of systems such as:

- o Continuous chemical and petrochemical processes.
- o Batch organics, specialty chemicals and pharmaceutical processes.
- o Pilot plants.
- o Bench research processes.
- o Molecular genetics research laboratories.
- o Manufacturing processes.

Since HAZOP is very flexible, the review team should also try to

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[23] Gibson, S.B. and Shafagi, "Hazard and Operability Study: A Flexible Technique for Process System Safety and Reliability Analysis", The Chemical Process Review, ACS Symposium Series 274, American Chemical Society, 1985, page 37.

avoid the pitfall of getting overly enthusiastic and installing expensive equipment to guard against unlikely hazards. HAZOP is a sophisticated technique that should also be used by a company to help utilize its resources more effectively. The method which has been simplified and graphically outlined by Shafagi and Gibson is shown below in Figure 7.[24]

HAZOP Method Flow Diagram

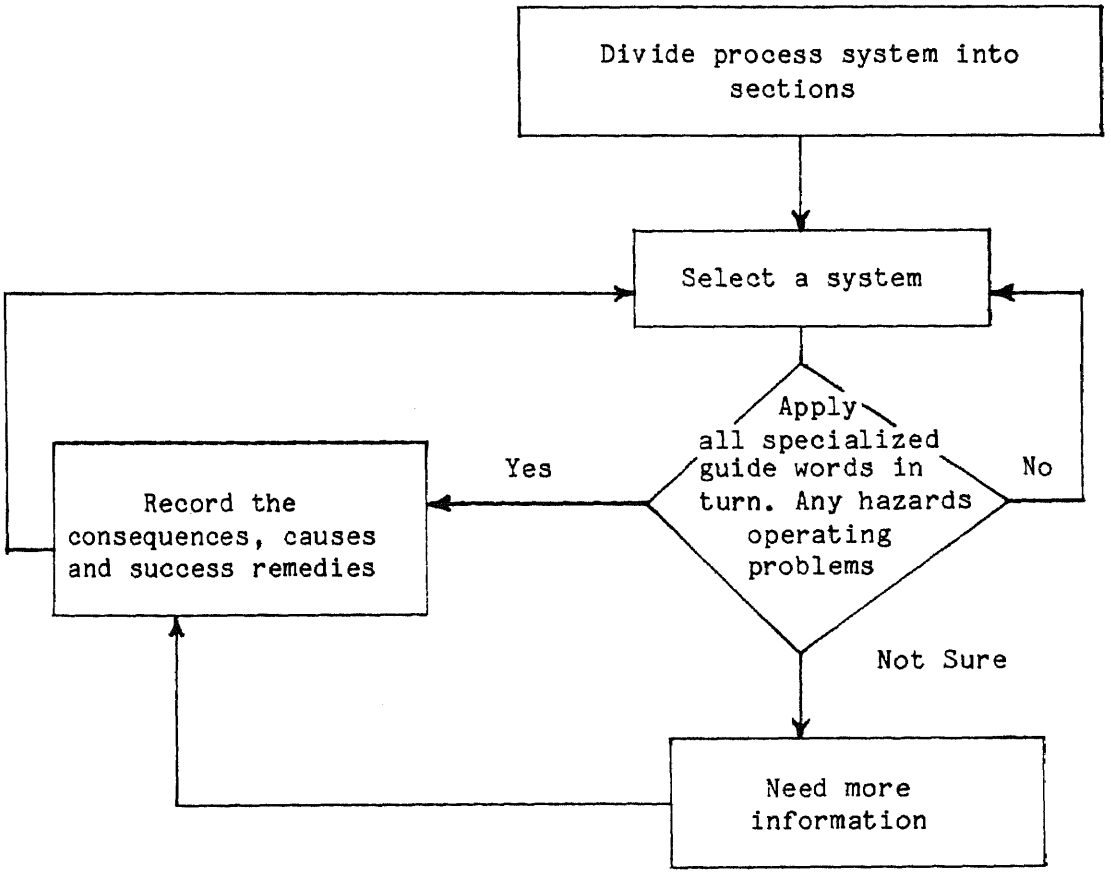

Figure 7

[24] Gibson, S.B. and Shafagi, "Hazard and Operatiblity HAZOP) Study; A Flexible Technique for Process System Safety and Reliability Analysis", 187th National Meeting, St. Louis, Missouri, April 21-23, 1984, page 6.

Additional Analysis Considerations

Two other techniques are noteworthy of mention in addition to the methods which have just been outlined. An information gathering technique known as "incident recall" or "critical incident techniques" can be used to collect both poor and good experience data from experienced personnel. It requires asking people to share difficulties, errors, near misses, accidents, successes etc. they remember in past similar operations and conditions.

This method can generate a greater quantity of relevant and useful information more so than any other monitoring technique. It also can uncover many more minor errors, deficiencies and near misses that otherwise might have been overlooked. The method relates to the familiar Heinrich triangle(42) which predicts that there are many near misses for every accident.

A second technique known as Management Oversight and Risk Tree Analysis (MORT) was developed in the early 1980s and is an even more sophisticated program for managing safety systematically, using logic trees. It is currently used for major government projects in the Department of Energy and the Nuclear Regulatory Commission for project review and start-up and in the investigation of serious accidents. The technique is complex because it not only includes the technical aspects of fault tree analysis but includes logic trees for the deductive analysis of managerial functions, human behavioral factors, and environmental considerations. It can also be cost prohibitive, therefore, only large complex projects that could result in serious

consequences, if failure resulted, can afford to be analyzed by MORT.[25]

Summary of Analysis Methods

The methods and techniques discussed were developed in response to the need for more and better information about chemical and pharmaceutical processes in order to make them safer, more efficient, and commensurate with the safety expectations of both the public and regulatory agencies.

When the techniques described are used, it is assumed that management is competent, and the plant or research lab will be operated and maintained in accordance with good management and engineering practices. If this is not true, then time spent identifying hazards by the methods described will be wasted since no one will be interested in doing anything about them.

Where process hazard reviews have not been used by an organization before, they should be introduced on a small scale. Reviews should be applied to one or two cases initially and hopefully management will find that the reviews are very useful and ask for more and the use of the techniques will grow.

Hazard evaluation methods will also need to be responsive to the needs of industry. As technology and science moves forward, many new materials and drug compounds of increased potency and physiological properties will be developed. The technology necessary to produce

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[25] Van Horn, David J., "Risk Assessment Techniques for Experimentations", Chemical Process Review, ACS Symposium Series 274, American Chemical Society, 1985, page 28.

these products will become increasingly more complex and require hazard evaluation programs of equal sophistication and creativity.

With dynamic change an accepted reality in today's pharmaceutical industry, process development has a tendency to be more of a philosophy than an exact program. Due to the constantly changing nature of this industry, technical management must be constantly on guard for the unexpected and unknown. Suitable process review programs for the pharmaceutical industry should then be flexible as well as structured and become a well integrated part of the research, development, and manufacturing activity of new drug compounds and drug safety programs.

CHAPTER III

THE REGULATED ASPECTS OF DRUG DEVELOPMENT SAFETY

Drug Testing

Finding out if a new drug works to those not involved in the technical development of drug products might appear very simple. A sick patient is administered a new drug by a doctor; if the patient gets better, the drug works; if the patient fails to improve, the drug does not work.

Unfortunately, this procedure can yield nothing but confusion and pitfalls. A strict testing protocol is therefore warranted and thanks to delicate and ingenious testing methods, it is possible to determine that new drugs are safe and effective - if not for 100% of the people 100% of the time, at least for most people most of the time.

The testing of modern day drugs for safety requires the accumulated knowledge of half a dozen scientific disciplines; not merely chemistry and pharmacology but also physiology (of man and many other animals), psychology (because drugs can effect the body through the mind as well as directly in the body), and even mathematics (for an indication of the role that chance plays in the test results). Evaluation of one new drug may take up to seven years - trying it on several different species of animals, administering it to several large groups of people, and analyzing the findings - before finally convincing governmental authorities that the drug should be approved for medical use.

Two unseen ingredients are part of the making of every drug. One is research; the other is testing. Over the past four decades, large pharmaceutical corporations have planned multi-million dollar budgets in an effort to discover and develop new medications. Of the drugs most often prescribed today, many were not even in existence a decade ago.

Drug research begins with the discovery and subsequent isolation and identification of likely materials. Few chemicals remain untried. Even old drugs are re-examined and the subject of intensive research. For if they can be isolated and reproduced in the laboratory, the drug may be improved. With the advent of synthetic drugs, manufacturers are no longer committed to dependence on natural supplies. More important, synthetic drug manufacturing offers the opportunity to provide consistent quality and simplification of production tests that will guarantee uniform products.

Even long after a drug has been discovered, developed, accepted for medical use and marketed, its testing continues. At every stage of manufacture, there are continuous inspections to check whether the compound meets specifications and if prolonged and widespread use may turn up effects that no testing programs, even if it included thousands of subjects and lasted several years, could predict. Quality control testing of drug compounds may involve more than 100 tests, some as simple as the measurement of a tablet thickness and weight, others as complex as delicate analysis of chemical ingredients, still others as elaborate as the precautions taken to ensure the purity of the water used in the manufacturing processes.

The strictest of the tests cover the biologicals, such as

vaccines, and most antibiotics, which cannot be synthesized but must be obtained from living microorganisms. The quality control process does not end when a drug leaves the plant since manufacturers periodically collect shelf samples to test for deterioration.

Under current U.S. regulations, every new drug must be tested on at least two species of mammal [before being given to human beings]. The animals are tested in groups, to obtain various types of information. One group will receive large quantities of drug in order to ascertain how much of a dose will prove fatal. Another group will be given smaller doses - proportional to the dose that is expected to be medically useful in man - then there will be studies over a period of months to determine long-term damage. Ultimately, the animals are killed and their vital organs examined for subtler signs of damage. New drug compounds are also administered to young animals to ascertain whether it affects their growth. Other tests include the determination of the carcinogenic, terotogenic, and mutagenic properties of the drug.

When the animal testing is completed, the tests must be reviewed and a decision made as to how the animal data findings apply to human beings. In the case of bacterial infections, microbes that attack human beings will usually attack other species and a drug that cures the infection in an animal provides hope for a cure in humans.

Human testing generally begins with a small group of healthy volunteers. The small group known as a "preclinical" group receives very limited doses of the drug initially. If there are no negative responses, the dose is gradually increased until there is a positive effect or result. When the subject begins to show toxic effects, the dosage level is cut back. In the meantime, the physical condition of

the volunteers is studied exhaustively.

At this point, the testers concern is still with the drug's safety rather than its effectiveness. The aim is to determine the "dose response curve" which shows the effect of the drug changes with the amount administered. The variability of dose response affect in humans is an important factor to be aware of in new drugs because in some extreme cases, an identical dose of a drug can cure one individual, poison another and leave the third unaffected. Only after the drug has been proven safe for humans does it come to the crucial part of testing: the study of effectiveness. Will the new compound help the disease for which it was intended?

Legislative and regulatory control over drugs have evolved parallel to, although somewhat behind, developments in medical and pharmaceutical sciences over the past century. Controls have crept from purity to safety and, more recently, to concern for the efficacy of drugs and to their manner of use. The controls frequently utilized have impacted the following: (1) labeling, (2) advertising, (3) drug shipments in interstate commerce, (4) investigational plans - good clinical practices (GCP), and (5) good manufacturing practices (GMP), and good laboratory practices (GLP) which have helped to eliminate unscrupulous manufacturers and developers.[26]

The thrust of the U.S. Food and Drug Act and similar laws in other countries is that a drug must be safe and effective for use in medicine. The purpose of phamacological testing is to measure effectiveness, safety, and relative freedom from unwanted side effects

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[26] Hamner, Charles E., Drug Development, CRC Press, Third Printing, 1985, page 2.

including carcinogencity and teratogenicity. In developing a new drug, continued evaluation of test data must be done to identify problem areas early. "Safety" is defined as the limits within which a compound is expected to have a beneficial effect with the lowest possible risk.(44) Those limits must be continually examined, and the risks must be evaluated and assigned a degree of hazard. Assessing hazard is difficult because it involves risk benefit analysis. Factors suitable for assessing the hazards of a drug are entirely different from those used to evaluate a pesticide, food additives, or an industrial chemical, for the simple reason that a drug is intentionally taken for a specific purpose, the exposure is strictly defined, and the person is aware of the exposure. Usually, there is competent supervision of the administration of a drug, so that the risks of serious injury are significantly reduced.

Establishing the Pharmacological Profile

As progress in the pharmacological development of a new compound occurs, there is an accumulation of information from the series oftests on numerous animal models. The results of these studies outline a pharmacological profile to enable insight into the therapeutic range and comparative toxicity of the compound under evaluation.

As a body of information develops on a new compound through study of the animal models, a clearer outline of its therapeutic profile takes shape. Included in the data profile are assessment of activity and toxicity as compared to standard therapy, mechanisms of action, dose response curves, and metabolic fate. As the data develops, it

adds to the understanding of the new drug compound. Although definite decisions cannot be made without sufficient data, judgment is required to decide what particular additional information, if any, would be helpful, what data would be of interest, and what findings may or may not be delayed to a later date. The purpose of this effort is to make decisions concerning the progress of the compound in question and to determine whether or not to proceed.

During this process of new drug development, data has been developed under regulatory guidelines, determined by the FDA. For example, Good Laboratory Practices (GLP) regulations are presently in place throughout pharmaceutical laboratories in the country and a number of research facilities abroad. The data developed under these regulations become part of the official regulatory document.

If the compound is still worthy of development, planning considerations for evaluating the compound in the clinic need to be considered at this time. Regulatory affairs, as well as Occupational Health and Safety personnel should be alerted about possible plans for the drug, if it is to proceed to the clinic. Advance notice to regulatory and health and Safety personnel will be of great assistance in hearing them plan their contribution. A combined effort with program coordination will ensure that proper information will be available for regulatory submission and use in plant process reviews.

Practical concerns should also be considered when a compound is viewed as a candidate for clinical evaluation. For example, is it necessary to consider the ease and economy of the chemical synthesis or the need to conduct further toxicological evaluations, to determine the extent and type of undesirable side effects.

The value of avoiding toxic effects on new chemical agents is essential to both the therapeutic and manufacturing success of the drug compound. Once preclinical data is considered favorable, and the toxicity of the compound acceptable, early drug evaluation or clinical trials in humans can be commenced.

Drug Application Requirements

Clinical trials for new drug compounds are conducted under the watchful eye of government regulators through investigational new drug requirements called an IND, "Notice of Claimed Investigation Exemption for a New Drug" and the NDA or New Drug Application. The IND is relatively new in the area of government drug regulation and originated because the Food, Drug and Cosmetic Act of 1938 prohibited shipment of a new drug in interstate commerce without an approved New Drug Application (NDA). This act, however, was concerned only with safety and thus presented no tactical problem. In June of 1963, amendments to the Food, Drug and Cosmetic Act by Kefauver-Harris, addressed the issue of efficacy and changed the procedures by requiring clinical evaluation to establish that the new drug product was both safe and effective.[27] To comply, provisions were made to ship unapproved drug to clinical investigators for necessary evaluation; the IND was the result of this action. The application is technically an exemption to ship the unapproved drug; however, such a notice must be filed with the FDA prior to clinical testing in the U.S. The information provided in the

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[27]Hammer, Charles E., Drug Development, CRC Press, Third Printing, 1985, page 110.

application summarizes available data on the drug and is the basis for the proposed clinical evaluations. An IND may be filed by a pharmaceutical company, an individual, or an institution, referred to as a sponsor.

An IND is not approved, but the sponsor must wait a minimum of 30 days after submitting the application before initiating clinical studies. This permits reviewers to examine the submission and ask questions regarding any part of the application. The drug may not be administered to humans until adequate data are provided to satisfy the FDA. While an IND is not approved, it can be disapproved or terminated if, in the eyes of the reviewer, it presents a hazard to health that clearly outweighs anticipated clinical benefits.

The New Drug Application (NDA)

When the safety and efficacy of the investigational drug have been established, the sponsor is required to file a New Drug Application (NDA), or give reasons why a NDA has not been submitted. The alternative is to advise the FDA that the exemption has been discontinued with the reasons for such action specified. The requirement to file based on the above precludes continued distribution of the drug.[28]

The NDA procedure was devised in 1938 as a mechanism by which new drugs developed through research could be introduced commercially. The procedure was necessary because new drugs by their very nature, could

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[28] Hamner, Charles, E. "Drug Development", CRC Press, Third Printing, 1985, page 110.

not be generally recognized as safe. Therefore, documentation of safety became a central component of the NDA.

The drug amendments of 1963 added the dimension of effectiveness to the requirements that must be met before a new drug is marketed.

NDA-Evaluations of Safety and Effectiveness

As part of the New Drug Application (NDA) a specific section is provided which calls for a separate summary of all favorable and unfavorable evidence of each claim proposed in the labeling of the product. The evaluation provides the applicant with the opportunity to identify the specific data that supports his conclusion that the drug should be approved for marketing. This section should contain and cite the positive data by study, volume, and page that constitute substantial evidence of safety and effectiveness. Likewise, a similar summary of the unfavorable evidence for each proposed claim is called for in the section. All side effects or adverse experience whether or not considered to be significant should also be tabulated.

The information required in this section in effect then becomes similar to a Chemical Safety Data Sheet which provides the user valuable information about the proper use and handling of hazardous materials. On approved drugs, safety information is required to be included on the package insert which must meet rigid general requirements.

The package insert is a digest of the pertinent scientific and medical information about the drug revealed during the R&D process. This document serves as a regulatory basis for all labeling and

advertising and is a summary of the essential information that a physician needs in order to use the drug safely and effectively for the purpose intended. Labels and labeling are usually included in the initial NDA in order to give the FDA an opportunity to review the proposed content and wording and ultimately gain approval by the sponsor.

The above has provided a brief look at some aspects of drug safety which are monitored by governmental agencies in order to guarantee that a new drug reaching the commercial market will have a high degree of safety when used by the public at the recommended therapeutic dosages. We must, however, recognize that a responsible new product development program applies to all phases of the product life cycle from research, development and design through manufacturing, purchasing, sales/marketing, distribution and customer service. Each function and discipline involved in the phases of the product life cycle must have key roles in assuring that new products developed by the company can be manufactured and used safely.

For this reason, in new drug development the evaluation of safety may be implied to take on a different meaning than say the assessment of an environmental contaminant or an explosion hazard. Safety philosophy with respect to drug compounds is often thought of with respect to "conditions to use" rather than in the processing of the drug material. It must be remembered that a drug is selected for its ability to alter a physiologic function, and is usually biologically active. Under conditions of use, limits can be defined, such as dosage level, nutritional requirements or routes of administration, within which the drug is considered to be safe and a benefit to mankind.

Alternatively, where workers are excessively and unintentionally exposed to them, drug compounds can result in undesirable health effects. Therefore, not only evaluations of clinical exposure to new drugs should be performed, but also occupational exposures and hazards related to the processing and manufacturing of a new drug product.

In the following chapter, a description of operations involved in the production of pharmaceuticals is presented. The purpose of this is to provide some insight into the potential health risks encountered during processing of drug compounds versus those physical risks already established by the general physical characteristics of the raw materials used to synthesize a new drug product.

CHAPTER IV

PHARMACEUTICAL PROCESSING AND ASSOCIATED HAZARDS

Introduction

Understanding of the risk associated with a substance or operation can often determine how to work with it. If it is flammable or explosive, specialized equipment may be needed. If it is a gas or dust, there is a potential for exposure, and an understanding of the material's toxicity and the operations needed to process it may be essential to the engineer designing the plant, as well as the operator and safety professional who will work in the plant.

The need to understand the hazardous characteristics and toxicity of a new compound also depends on the stage of development a substance is in - if it is purely an exploratory material and its use carefully controlled, only limited information may be necessary. As progress is made toward the pilot plant production stage, understanding of associated risks will need to be increased. By the time the manufacturing and commercialization stage is reached, a maximum amount of information will be necessary to control risks associated with the process.

The following describes the operations involved in the production of pharmaceuticals and the availability and the use of controls to reduce potential hazards and risk. The major emphasis is placed on process development and manufacturing.

Process development involves the typical steps of development and

testing of products in the laboratory, design and evaluation of production processes in small-scale pilot plant operations, and the subsequent scale-up, design and start-up of a full scale plant. The processes and operations involved are by no means unique to the pharmaceutical industry. For example, laboratory operations are usually typical of those conducted in chemical and biological labs. The operation conducted in the pilot plant phase of development and in the start-up of full scale operations are generally characteristic of those also found in the chemical industry. Included in these are evaporation, distillation, absorption, esterification, nitration, hydrogenation and many others.

Many of the hazard evaluation procedures that are used most frequently by the chemical process industry for identifying deviations from good practice can be used for drug compounds being developed in the laboratory and pilot plant stages. It is in the manufacturing of pharmaceuticals that a somewhat different type of operation or equipment unique to the pharmaceutical industry is found. These operations, due to the biological activity of the material produced at this point, present unique concerns that should be addressed in a formalized hazard review before manufacturing begins. As with many other industries, the recognition and appreciation of hazards rising from physical and toxic agents have resulted in reductions, and even eliminations of such hazards in the pharmaceutical industry. One can even consider that the present, somewhat dual regulation of the industry by the Food and Drug Administration and OSHA, has provided the impetus to control operations to an even larger degree. It must also be recognized that in the pharmaceutical industry there is an ever

increasing variety of potentially toxic exposures due to the rapid advancement in the life sciences (Biotechnology) and the advent of new chemical substances. It is essential then, that sufficient knowledge of the hazards connected with all processes involved in the manufacturing and processing of a new drug compound be addressed.

Chemical Processing

The processes and operations which can be termed as "chemical processes" are numerous and varied in nature. It is not surprising then that many of the chemical substances used to synthesize pharmaceutical compounds may also be substances of concern when it comes to the health and safety of the process worker.

The concern is developed by the fact that processes in the chemical industry involve chemical or physical change, particularly with respect to the chemical structure and composition of the substances. It applies not only to the chemical industry but to a much wider field which includes such principal products as fertilizers, dyestuffs, pharmaceuticals and medicinal products, explosives, plastics, resins, adhesives, cosmetics, synthetic fibers, detergents, soap, paints and a myriad of miscellaneous chemicals.

Chemical processes encompass a number of operations among which are crushing, grinding, size separation, filtration, drying, heating, cooling, solvent extraction, absorption, distillation, fractionation, electrolysis, mixing, blending, analysis and process control, packaging and transport. As is evident, this list comprises most of the operations utilized in any of the manufacturing industries and much of

the pharmaceutical industry.

If we look at equipment types which are more specific to the actual manufacture of raw materials or intermediates from which industry manufactures its final products, then materials handling and grinding, crushing, and screening equipment for solids can be excluded from equipment or process systems which cause the contacting, reaction, or separation of gases and/or liquids. If we also consider that chemical process companies involved with the manufacture of large volumes of chemicals utilize "closed" systems, i.e. where the chemicals are not blatantly open to the atmosphere, then it can be practically assumed that the potential for the occurrence of an undesirable event to occur would be primarily due to:

1. Loss of containment of flammable, combustible, highly reactive, or highly toxic material sufficient to seriously endanger the health and safety of the plant employees and neighboring public.
2. Intentional releases of contaminant from system component vents.
3. Atmospheric releases from combustion processes.
4. Accidental or unintentional releases due to equipment failure or malfunction.

Hazards occurring due to the loss of containment or contaminant release can often be traced to specific equipment and practices involving the use of valves, conservation tank and process vents, relief valves and disks. Many of the above valves can leak continuously even when supposedly shut, causing the leaks to build up and exposure or explosivity limits to be exceeded. Practices involving

the routine releasing of purges, minor overpressures and system breathing to atmosphere should be subject to recycle collection, scrubbing, or other measures, all of which will reduce or eliminate release.

Prevention of releases of large volumes of contaminant can also be prevented through the use of collection systems. Flares are used to control fume releases, but this is not a simple task because the system must be designed to handle a wide variety of operating conditions, including the possibility of simultaneous release of several streams.

Rupture disks which are used to control overpressure situations and prevent reactor explosions are generally capable of ensuring a secure seal until they relieve. However, they must be properly installed and properly rated for the condition they were designed to protect. Rupture disks can also be used in-line preceding a relief valve to protect the valve until an overpressure condition becomes imminent.

Other sources of contaminant release which can result in an elevated risk condition include:

1. Vapor losses from tank vents and process vents during normal venting practices and during chemical loading operations.
2. Compression packings around the shaft, rod or plunger in pumps. Lubrication for proper operation is provided by the fluid being handled as it flows through the slight clearance between moving parts and the packing. Such leakage it if reaches an undesired leakage rate would increase contaminant concentrations.
3. Leakage from valves and flanges which are subject to crevice

corrosion, leakage from screwed joints and gasket failure also are a source of contaminant release and increase the possibility of fire and explosion hazards.

Typical solutions to reducing exposures and hazards associated with the above would be tightening of flanges, the use of welded or flanged couplings instead of "leak-proof" threaded couplings, investigation of better gasket materials and pump seals, the use of larger capacity equipment and process changes to reduce the frequency of cleaning operations.

Drying Ovens

Drying can be defined as "the removal of a liquid from a solid by external means".[29] Oven drying equipment is classified into three category types and depends on the transfer of heat to the material being dried. The first category includes direct dryers in which gases are in direct contact with the material, and carry away any vaporized substances to be exhausted. Direct drying equipment can be subcategorized with regard to their operating mode such as continuous or batch. Continuous drying is accomplished in equipment such as tray dryers which function by circulating heated air across a wet material until sufficient drying has occurred or spray dryers where the material to be dried is atomized and spray droplets are formed and exposed to an upward flow of heated air. Because the surface area-to-volume ratio of the material in droplet form is quite large, drying is accomplished

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[29] Perry, R.H., and Chilton, C.H., Chemical Engineers Handbook, 5th Edition, McGraw-Hill Book Co., New York, 1973.

very rapidly.

Batch drying equipment falls basically into two categories, through circulation type, in which the material is positioned on stationary trays through which hot air is forced and compartment dryers which support material on trays across which hot air is passed. A uniform flow into all parts of the tray chamber is essential because the material to be dried remains stationary.

The second type is called an indirect dryer in which the drying heat is transferred to the moist solid through a conducting wall. In this type of dryer, any vaporized substance is removed independently of the heated air. There are four types of indirect drying equipment which are of interest; the agitated pan dryer, the vacuum rotary dryer, the vacuum try dryer, and the freeze dryer. Agitated pan dryers incorporate the use of a circular tray which is steam heated from underneath while the material is agitated to keep fresh material in contact with the heated pan. Vacuum pan dryers consist of a chamber containing shelves. The shelves are designed so that they can be heated. Conduction of the heta occurs between the shelves and metal trays in which the material is placed. The application of vacuum makes it possible to do lower temperature drying and solvent vapor recovery. Freeze drying takes advantage of the process whereby frozen solvent is removed by sublimation. This equipment can be of the shelf type, cylindrical vessel, or horizontal rotary vacuum design.

Radiant-heat and dielectric heat dryers fall into the third dryer category. The operation of the former is based on the generation, transmission, and absorbtion of infra-red rays. The latter relies on heat generation within the solid when it is placed in a high frequency

electric field.

Control of employee exposures to contaminants from drying ovens is a legitimate concern in pharmaceutical drug development. The ACGIH Industrial Ventilation Manual[30] contains criteria for the control of employee exposures to contaminants from ovens and recommends:

1. A slot type hood located around the top portion of the entrance or exit doors and a canopy type which is also installed over the doors.
2. For the slot hood, an exhaust volume of 100 cfm per square foot of door area plus one half the product of combustion.
3. For the canopy, the recommended rate is 200 cfm per square foot of hood face plus the same correction for combustion products.

Oven dryer operations also come under concern in the National Fire Codes.[31] The codes address the need for ventilation of ovens and furnaces to control flammable or toxic vapors. Batch process ovens are reported to usually require a minimum of 320 cfm per gallon of solvent present.

Although oven ventilation systems design is intended to control and carry away contaminants, fumes and vapors often can find their way into the working environment through inlet and outlet openings and opened doors in batch ovens. Ventilation system designs should include local exhaust hoods at inlet and outlet openings and at

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30 Industrial Ventilation: A Manual of Recommended Practices, 13th Edition, Committee on Industrial Ventilation, American Conference of Governmental Industrial Hygienists, Lansing, Michigan, 1974, page 2-4.

31 National Fire Codes, Vol. 8, 86A, National Fire Protection Association, Boston, Mass. 1975.

batch oven doors to prevent release to the general atmosphere.

With regard to safety, there are two very important reasons for controlling the environment in and around a drying oven. The first is the maintenance of a low concentration of flammable solvent vapor to eliminate the possibility of fire or explosion. The second is to ensure that toxic contaminants are not released into the breathing zone of workers. Oven design and usage, therefore, must be given serious consideration during any process review to insure effective control of hazardous materials and a safe operation.

Grinding, Crushing and Screening

Many industries, especially the pharmaceutical industry utilize grinding, crushing, and screening equipment to obtain size reduction or dispersion of solids or pastes. Use of this equipment necessitates the control of dust or vapor emissions to prevent potential fire or explosion and exposure of workers to toxic contaminants released during operation of the equipment.

Crushing and Grinding

Size reduction involves the mechanical reduction in size of solid material. Crushing and grinding represent two methods of achieving that reduction, but the terms do not represent the same operation. Crushing generally refers to a relatively slow compressive action while grinding involves an attrition or rubbing action as well as interaction between individual pieces of material. Pulverizing and disintegration

are terms related to grinding. Pulverizing usually applies to an operation in which a fine powder is produced, grinding refers to the breakdown of relatively weak bonds holding solids together, such as those present in caked powders. There are many types of equipment designed to perform the above operations. Some of those used in the pharmaceutical industry are:

1. Hammer crushers or mills - used for crushing or pulverizing. Hammers mounted to a rotor shaft run inside a housing that contains grinding plates. The rotor is enclosed by a cylindrical screen or grating through which the product is removed.
2. Roller mills - used to process powders and pastes. Here the substance is passed through closely spaced rollers which revolve at different speeds and in opposite directions to effect some degree of dispersion and/or size reduction.
3. Tumble mills - consists of a horizontally-mounted chamber containing a loose packing or grinding medium which moves about the grinding charge to provide the necessary impaction and attrition. The media can be balls, tubes, rods or pebbles.

Screening

Once the size of the material has been reduced, it is often necessary to assure size uniformity. This can be accomplished through several techniques such as screening, centrifugal classification, pneumatic classification and aqueous classification. Screening is the

most commonly used method.

Screening involves the mechanical separation of particles on the basis of size, and is also known as sizing, sifting, sieving, or separation. Screening surfaces are usually moved or vibrated to facilitate material flow.

Use of screening equipment can produce hazardous dust exposures involving the release of small particles easily suspended in air. These particles can be released to the plant environment if proper controls are not utilized. Where organic solvents are used in paste or ointment formulations, solvent vapors may also be evolved. When flammable solvents are used as the vehicle for pastes to be processed, ventilation requirements may need to be reconsidered, bearing in mind the allowable concentration of the contaminant in the workplace environment and the lower explosive limit (LEL) of the solvent.

Depending on the equipment used, the materials handled, and the operating conditions, many of these chemical processing operations can result in worker exposures and increased risks of property damage if uncontrolled. Increased risk may occur as a result of the actual operation or as a result of loading and unloading the equipment. Emphasis, therefore, should be placed on three main control areas: preventing release of contaminant to the general atmosphere, examination of fire and explosion risk and physical hazard potential.

Laboratory Operations

Laboratory operations as previously noted in this paper include small-scale experimental research and testing activities conducted in

either academic, or industrial research operations. Laboratory operations are highly variable and, to a large degree, can be very unpredictable. Many aspects of laboratory operations are of concern and the types of hazards which can be generated and the ways of generation are unlimited. For example, some operations will produce contaminant release to the atmosphere as part of the "normal" operating mode such as with the evaporation of volatile liquids from storage or process vessels. With many laboratory operations, controlling spillage, container failure, or potential explosion will substantially reduce the risk of property loss or personal injury.

General practice in protecting laboratory personnel and property from personal exposure and physical hazards has been the use of general purpose protective equipment and personal protective devices. The most common protective measure is the use of ventilated enclosures, such as laboratory fume hoods, glove boxes, and biological safety cabinets. This equipment can also be designed to protect personnel from explosions, fire, and equipment breakage. To some degree, the use of free standing open exhaust hoods has also come into practice in laboratories as a means of providing a controlled environment.

Because laboratories often work with experimental material which has not yet been fully characterized with respect to toxicity and/or general hazards, control is of particular importance and should be considered based on a combined review of toxicity levels of contaminants generated and the physical properties of the material.

In general, problem areas experienced in laboratory operations can be adequately controlled with ventilation. There are, however, some areas which would require special attention to ensure proper control of

contaminant release or contact with hazardous substances. Laboratory operations using radioisotopes, carcinogens, and biological agents present special problems from that of general hazard control for less hazardous materials. Criteria for the control of these special hazards have been published as Federal Regulations in the "Standards for Protection Against Radiation", Code of Federal Regulations, Title 10, Chapter 20 U.S. Federal Register; "Industrial Exhaust Systems", chapter 22, 1973 Systems Handbook, American Society of Heating, Refrigeration, and air conditioning engineers, and National Sanitation Foundation, Standard 49, Class II (Laminar Flow) Biohazard Cabinetry, May 1983.

In particular, control of biological agents can present a problem which is different from other hazard control problems in the laboratory in that two-way control is generally required. In addition to protecting laboratory personnel from biological agents, it is also necessary to isolate the biological materials from contaminants found in the laboratory environment.

Because of the rapidly changing nature of work in the laboratory environment, all operations in a laboratory should be examined for their hazard potential and guidelines established to address them.

Manufacturing Equipment and Operations

Pharmaceutical products are usually marketed in three major forms - tablets, capsules, and liquids. This involves the use of specific equipment designed to produce the finished product in the desired form. Typical equipment and operations utilized to produce final product forms are compressing machines, pressure sealing, mixing, filtration,

emulsification and/or esterification. Hazards connected with the use of the above equipment usually involve vapor and dust exposures or generation of a flammable vapor environment. Drug production operations are, therefore, designed to handle any number of the above operations by providing a floor plan layout which consists of a number of rooms, one each to handle the major operations conducted: weighing, blending, drying and grinding, tablet compressing, and packaging. Batches of materials more often than not are manually handled at almost every step of the operation and manually transferred to the next area of the line. The manual handling of active pharmaceuticals is a major concern in pharmaceutical manufacturing. In response to this concern, continuous efforts are directed at identifying contaminant levels and exposures resulting from the use of pharmaceutical production equipment. In addition, physical hazards presented by equipment operations such as compressing mixing, rotating, and slicing would also require close scrutiny in order to engineer out any recognized hazards.

A brief description of the currently utilized equipment and operations utilized in the industry to generate the three major forms of products is provided below:

Tablet Manufacturing

The machinery used to produce tablets from granulations are compressing machines. These machines produce three types of tablets - compressed, cores for coating, and effervescent. The machines are capable of producing thousands of tablets per minute, but are dependent on a steady supply of free-flowing, uniformly granulated material.

Tablets are measured by volume instead of weight. Three methods are employed to ensure tablet uniformity.

A wet method, where the active ingredients are milled and mixed, fillers and coloring materials added and the mass mixed again with a binding agent added. The resulting wet mass is screened, dried, and blended with other ingredients, and charged into a mixing machine. A dry method for granules is employed where the nature of ingredients will not allow exposure to heat or moisture without decomposition. The powder is then compressed by heavy duty machines into large "slugs" which are than broken up into the desired granulations, blended with other ingredients and charged into a compressing machine. A direct method is used when materials possess the physical properties desired without additional treatment.

Coated tablets are produced from compressed tablet cores with rounded edges. Prior to coating, the tablets are screened to remove dust and broken cores. Equipment used in actually coating the tablets consists of metal rotating pans and canvas lined polishing pans.

Effervescent tablets are commonly made by the addition of an alkali bicarbonate with citric or tartaric acid to the formulation. The method followed is to warm the preparation in a rotating pan, rapidly dry under a vacuum and compress in a room with low humidity. Special care must be taken to eliminate moisture from the process to avoid material decomposition.

Capsule Manufacturing

Capsules are produced in two types, a hard type made of gelatin

and water used to contain powder type medications, and a soft type, of gelatin containing glycerol, usually used for containing oily medications. Hard capsules are made leak proof by a very close fit and the processes for making them are usually fully automatic. The capsule body is formed, filled with powder from a hopper, sealed and blown dust free. Soft capsules are filled similarly and made leak-proof by pressure sealing.

Liquid Processing

Liquid pharmaceuticals are processed by mixing, filtration, emulsification and/or homogenization. Three types of formulations are produced - aqueous, hydroalcoholic or oily.

Mixing liquid formulations is accomplished in chemically resistant tanks of various types. Some are jacketed to allow heating, cooling, or sterilization. Others are designed to withstand pressure and/or moderate vacuum. Storage tanks, sometimes fitted with agitators are also used to store batches of product until needed.

Filter equipment is used to ensure and give clear, particle free appearance to a formulation if required. Filter equipment used generally is of the plate and frame type. Homogenizing and emulsification are conducted on some formulations to give them a more uniform consistency.

Ointments and fatty preparations of semi-solid consistency are manufactured in the same manner as liquids except that they may be passed through a piece of equipment called an ointment mill.

For liquid injectable products, manufacturing conditions must be

sterile. These areas are usually small, enclosed, and constructed and furnished in such a manner as to facilitate cleaning. Control of air purity, temperature, and humidity is necessary as a support to other measures taken as part of the sterile design. Rooms are generally maintained under a slight positive air pressure to prevent contamination of the environment from unconditioned air in other areas. Periodic checks are made of the bacteria and fungal counts to ensure stability.

Extraction

Extraction plays an important role in the pharmaceutical industry and must be included as an important part of the manufacturing operation. In extraction, pharmaceutical substances are usually ground to a smaller particle size to increase the surface area an then charged into a closed vessel. Solvents are introduced which are capable of dissolving desired active ingredients contained in the material. The solution is then recovered from waste material by filtration, centrifugation, heat vacuum evaporation, or a combination of the methods.

Packaging

Packaging materials are used in the pharmaceutical industry to protect products against damage, contamination, pilferage, and decomposition. Depending on the preparation, these operations may involve bag filling with powders, bottle filling with pills or liquids,

blister sealing, filling of aerosols, and others. Most of the equipment and procedures used to accomplish these operations are standard in the industry, but special equipment does exist for the filling of ampuls and vials.

Ampuls and vials designed to contain liquids are filled with either single fill or multiple-fill equipment. The hypodermic syringe is the basis for single fill equipment. Multiple-fill equipment utilizes multiple stations of various designs, but all have the objectives of placing a precise quantity of medication into a receiving container. Jets of steam or a warming flame may be used to remove droplets or moisture remaining on the lip. The ampuls are then passed through high temperature sealing flames, followed by annealing flames to relieve stresses in the glass.

Filling of dry powders into ampuls or vials is often accomplished in a small hood with sleeved outlets into which the operator inserts his gloved hands. This apparatus is usually called a "glove box" and use of it allows the operation to be accomplished either manually or automatically by means of a feeder in a totally enclosed environment.

Process Exposures and Controls

The processes and operations employed in tablet, capsule, and liquid product manufacturing are designed to produce the maximum product in the minimum amount of time. The actions of the machinery, no matter what the basis for operation, can create both physical hazards and worker exposure to hazardous material.

For example, the high velocity action of a tablet compressing

machine can create dust, noise, and pinch point type hazards. Fortunately, many hazards are controlled through the use of safety-interlocks, ventilation, and enclosures. Many of the controls are designed into the equipment as a result of regulations passed by the Occupational Safety and Health Administration.

One feature of the type equipment described is that much of it is used for batch type operations. It is not unusual to find in this type of operation the need to physically fill the bin or hopper above the machine. The transfer of fine powder materials from one container to another may release product to the general environment and cause a potential exposure problem. With active pharmaceutical materials, there would be a need to keep these exposures to a minimum if not totally eliminated altogether. The use of local ventilation installed near the emission source generally is used to control this type of situation.

Where rotating pans are used for tablet coating purposes, the equipment primarily consists of a metal pan resembling a small cement mixer tilted at an angle, or a canvas lined polishing pan similarly mounted. Dust release from the rotating action of the pan which causes the tablets to impact against one another is the primary hazard of concern. Noise levels and rotating equipment hazards also are of concern with this type of equipment. Substances added to the pan to assist the coating of the tablets may also be of concern depending on their respective chemical and physical properties.

Again, localized or general ventilation is a major technique used to minimize dust and vapor exposures. Guards generally are used to eliminate potential physical injuries from the rotating parts of the

equipment.

In capsule filling machines, because the capsule bodies are filled from a hopper and are often blown "dust free" after filling, dust exposures again are suggested as a potential problem area. Noise, product contact, and physical hazards are also associated with the operation of this equipment. Again localized ventilation or enclosure of the operation helps to reduce exposures.

The use of mixers and blenders in the preparation of solid and semi-solid formulations requires the same consideration as other equipment when it comes to hazard control.

Many of the equipment operations and associated problems described are similar to that commonly used and experience in other industries, therefore, hazard controls used to reduce or eliminate those hazards can also be considered in pharmaceutical manufacturing. The adequacy of controls, however, which should be designed to protect the worker from an assortment of physical and toxic agents produced by operation of the above equipment, should be resolved prior to any operation and/or process start-up. It would be a lot easier if all the product line machinery in this industry were designed in a similar manner, totally enclosed and virtually free of any hazards. Unfortunately for the pharmaceutical industry, this is not the case, nor is it a feasible or practical concept because of the usually high volume continuous demand of its products. The need is to be flexible. Equipment must be usable in various combinations to allow "changeovers" from one product line to another as well as rapid development of methods to produce new products with existing equipment.

CHAPTER V

SUGGESTED PROCESS HAZARD EVALUATION GUIDELINES FOR DRUG DEVELOPMENT

General

The previous chapters developed a background in Process Hazard Review techniques, what process reviews are about, regulated drug safety, and equipment processes and operations necessary to produce new drug products.

The purpose of providing the background was to show that process safety can cover a wide spectrum of concerns in any operation let alone a drug manufacturing operation. In actuality, process safety goes beyond just looking at process failures. It involves attitudes and motivations of designers and production people, employee/management support, human factors in supervision, effects of the legal system, exchanges of information, available responses, public sentiment and many other non-technical but vital influences on the attainment of an acceptable level of risk control

Safety should be given full consideration whenever a new product is to be developed and the full consideration philosophy should be part of any process review program.

This leads to the primary reason for adopting the systems review approach to safety, and is very nicely expressed in a recent system safety publication.

> "It replaces the crisis management of accident prevention of the past by preplanned preventative control: avoid the crisis by

foreseeing them".[32]

Examination of a process or equipment for hazardous exposures to personnel and to property are necessary and should be held from both a theoretical and a practical view. Theoretical studies of chemical process have been made and often can predict occurrences more severe than actual experience. The purpose of conducting the theoretical studies is to give a feel for the seriousness of a situation and highlight the effect of a particular variable on the probability or outcome of an accident. Unfortunately, theoretical calculations and highly structured analysis many times apply to very specific cases and require a great deal of time and effort by specialists in various areas if the results are to be reasonable and meaningful. Process reviews are often not conducted or discourgaged because of this problem.

Hazard identification does require very careful thought to analyze things as they are and to conceive of how they might be. The results of the logical thought process are then compared with the desired end result to determine the nature and extent of the hazards. Procedures and guidelines are, therefore, helpful in reaching the desired result. Clear thinking by informed and questioning minds is absolutely essential.

The objective of process hazard guidelines then is to provide those necessary elements which will provide a road map to the desired result. These guidelines and procedures, however, should be practical enough so that they can be applied in an effective reasonable manner. Although the need for quantitative methods is recognized, the primary

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[32] "Hazard Prevention", Journal of the System Safety Society, Vol. 22, No. 1 page 10.

emphasis of the guidelines presented are qualitative. This is based on the opinion that the pharmaceutical industry is already well controlled by the Food and Drug Administration regulations with respect to product toxicity and that implementation of a process review program will help to close the gap in areas that are not so closely regulated such as the processing of the raw materials and intermediates used in synthesizing the final drug product.

Where the intent of typical process reviews is to look at process failure, the guidelines presented in this thesis are intended to provide a broad scope look at any problem that may be encountered when a new drug is developed, and to also provide guidance in the specific hazard problems encountered in the areas of research, development, and manufacturing. The guidelines presented do not provide a complete management plan or program for process safety in the pharmaceutical industry because no single procedure can be considered "best" for all cases. The suggested guidelines presented also favor the "what if", "checklist" and "Hazop" methods because these procedures are ones that are used most frequently by the chemical industry, are easier to handle, can be accomplished in a reasonable amount of time, and are more cost effective.[33]

Process Safety Guidelines for Research

Hazards evaluation is important throughout the exploratory phase,

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[33] Guidelines for Hazard Evaluation Procedures, Battelle Columbus Division for the Center for Chemical Process Safety, American Institute of Chemical Engineers, N.Y., N.Y., page xviii.

however, exploration work is the most difficult area in which to apply process safety review principles because:

1. There is little or no hazards information regarding the experimental design at this stage.
2. There is minimal or no experimental experience.
3. The experimental design is likely to undergo significant major modification.

Safety guards for addressing problems encountered in initial experimental work can be addressed through utilization of a combined approach which is suggested below:

1. First - all available information related to the research project and all hazards information observed during discovery must be documented and accompany the process. Because risks are often uncharacterized during exploratory work, particular attention should be directed at very specific cases. If the results are to be reasonable then particular attention must be paid to:

- o known hazardous reactions.
- o observed exotherms.
- o evidence of rashes, irritations, reactions, odors, etc.
- o reactions using chemicals or biological agents that are highly toxic.
- o drug activity.
- o Radioactive compounds and radiation sources (ionizing/non-ionizing).
- o carcinogens, mutagens, teratogens.
- o laboratory operations where standard glassware or plastic will be under pressure.

- o handling of compounds with respect to their unknown, yet significant potential pharmacological properties.

2. Second - Controls should be incorporated for identified hazards. When the risks are uncharacterized, hazards may be minimized and protective safeguards established through:
   - o Generic Controls - use of personal protective equipment.
   - o Avoidance procedures - such as avoiding conditions of:
     - evaporation to dryness.
     - incompatibilities.
     - excessive stoichimetry.
     - reagent preparations.

To ensure that a proper evaluation is conducted in the exploratory stage of work, all information must be carefully obtained and evaluated for potential hazards, in accordance with the ongoing evaluation of research. The summarized information from the experimental work should now accompany the project to the next logical step, major revision or scale-up.

When the exploratory stage of work has been completed, the R&D chemist should summarize the important details of a particular process for all products scheduled for future pilot plant operation. The researcher's assessment of the exploratory experience should include:

1. A step-by-step summary detailing the individual operations required for a particular transformation and any pertinent chemical structures.
2. A tabulation of the potential hazards associated with variations from the correct process conditions, e.g charging a reaction to fast, loss of agitation, too much heat, etc.

3. A summary of any liquid or solid waste (filter cakes, washes, mother liquors or distillates) which would be produced in the process. The composition of each particular waste stream should be given as well as any indication of an associated disposal problem.
4. Recommended safe shutdown procedures in the event of a reaction problem or a building emergency which would require evacuation. This generally is intended to cover only special shutdown procedures that are not covered by a standard format or policy.
5. A summary of the potentially serious process deviations which could result in problems during the various process steps. This helps to put the whole process in perspective. Any general impressions about the process not already recorded should also be documented at this time.

Process Safety Guidelines for Development (Scale-Up)

Scale-up is a term used when going from small glassware (100ml or smaller) to larger glassware (1-5 liters) or to even larger glassware (12-22 liters). It is most frequently used when going from glassware (1-5 liters) to equipment in formulation laboratories or pilot plants (5-10 gallons or more).

Process development is a complicated process which begins with transfer from the discovery laboratory. Development may take several years or just a few months, during which time the process may again undergo frequent and significant change. At the development stage,

however, there may still be considerably less safety related data available and a variety of uncharacterized potential hazards. Faced with this situation, process development, likewise, has the responsibility to safeguard personnel and facilities and also to provide a safe, final process for production.

Accomplishing these objectives requires continual examination of the developmental process to identify potential new hazards that may be introduced by change and scale-up.

1. Change complicates the hazard evaluation procedure by introducing new components, whose hazards may be unknown, into the process. These changes not only introduce new unknowns, but may also negate previous safety information.
2. Scale-up, particularly initial scale-up, presents significant potential hazards and requires very close evaluation.

   Initial scale-up often presents the largest risk potential in development processes. Uneventful experimental reactions on a milligram scale can result in dramatic events on a 500 gram scale (10,000 x increase). In particular, hazards to be concerned about during scale-up include factors involving:

   - o concentration
   - o heat dissipation
   - o side reactions
   - o time differentials
   - o equipment changes

   In scale-up, hazard evaluation test data should be an integral part of any new drug development program review. While it may not be appropriate to write a schedule of tests or to require

excessive testing, there are certain tests which can be conducted preceding and during process operation to provide valuable decision data. Some of the tests include the following:

- o Physical tests such as differential scanning calormetry (DSC), thermal gravimetric analysis (TGA), etc. should be completed on isolated intermediates and products.
- o Industrial Hygiene Monitoring Studies to evaluate containment equipment and practices.
- o Biological and radiation testing for "abnormal" reaction conditions or contaminant release.

Testing should be designed to provide basic information on the hazard potential of the products and intermediates. Flash point explosivity, permissible exposure limits, and lethal dosage data represent some of the more important data that should be obtained. Many of the tests can be performed by developmental laboratory personnel while more sophisticated testing can be obtained through commercial testing facilities.

As the process proceeds through development, more experience and data are obtained and procedures designed to address specific hazards should be established. Controls should also be more specifically defined at this point.

The above factors combined with the considerable experience with the process will form the basis for the technology transfer into the manufacturing facility. Like the R&D chemist, the Process Development chemist should summarize the work completed in the Pilot Plant and provide experience and observation data to the summary file initiated

during the experimental stage.

Process Safety Guidelines for Manufacturing

As interest in the new drug compound grows and the process moves toward the production plant, a more formalized hazard assessment must be accomplished to ensure that the process is safe once it moves into full scale production.

The scale-up from the developmental stage to manufacturing operations is of great importance. Enlarging the scale of reactions or processes to the manufacturing level brings with it its share of hazards and safety requirements. A review of procedures, investigation and communication of knowledge involved in transmittal of a process to manufacturing is, therefore, in order.

The primary responsibility for determining or obtaining all necessary process information including full information on safety aspects about the designated manufacturing process, lies with the project group leaders and their technical associates. This responsibility should be accepted as a continuation of review work started and transferred from the laboratory and pilot plant side.

Much of the responsibility can be met by the preparation and distribution of a checklist carefully designed for this purpose. A guide of this type is desirable in all stages of the drug development process, but becomes most urgent from the safety aspect when a large scale-up such as from the pilot plant to manufacturing is planned. This is because certain items that will appear on a large scale checklist may not be critical in small scale operations but are

critical on scale-up.

Preferably, technical and engineering persons in manufacturing should become involved with the new process while it is in the process development stage. In this way, there can be early recognition, anticipation and correction of potential hazard areas. Ideally, when transfer of a product from development to a production unit or directly from a laboratory to a production unit is contemplated, review of process data, using a checklist guide, should be started with the plant personnel as early as possible prior to the transfer. At this point, it is up to the manufacturing department to make sure that all of the data necessary for safe production has been obtained and reviewed.

Considerations in Manufacturing Reviews

Several important considerations are involved in the scale-up to a manufacturing operation. For example:

- There must be a review with the Safety and Risk Management Departments and others concerned with safety in the manufacturing department.
- The review should include a complete beginning-to-end narrative of the process, with flow sheet covering process equipment.
- A material balance on the equipment flow diagram should be set up.
- There should be a clear definition of potential pollution and health problems as well as physical, chemical, and biological hazards.

- o The process should be analyzed critically for possible consequences of operator error and malfunction of equipment.
- o Process procedures and equipment should be thoroughly inspected and attempts made to visualize effects of variations such as temperature, pressure, pH, sequence of and rate of addition of raw materials and under or overcharging of materials that could result from operator error, mechanical failure, or loss of services.
- o A job safety analysis or a study of the operation, element by element, should be made to anticipate hazards and to remove them or neutralize them by clearly defined means.

Preparation and Use of a Checklist

As the process reaches the production or manufacturing phase, safety across the various stages of process scale-up has been dependent on many interrelated factors, including types of equipment, process variables, properties of materials used in the process, manning, and many others. Attention at this point should continue to be primarily focused at safety and health in an even more organized manner. With this emphasis in mind, the use of process/system checklists are recommended to provide direction in the evaluation and communication of the minimal acceptable level of hazard evaluation that is required for a particular process regardless of scope.

The checklist will also serve as a form of approval by various staff and management functions before actual manufacturing is allowed to begin. A checklist can be as detailed as necessary to satisfy the

specific situation, but should also be applied conscientiously in order to identify problems that require attention and to ensure that procedures are being followed. With this in mind the checklist which is designed by a given manufacturing unit might well include the following safety and health items.

Chemistry of Process

- Safe parameters of such variables as temperature, pressure, pH, rates of addition of reactants, under and overcharge of materials.
- Process kinetics and thermochemistry.
- Known side reactions.
- Possible side reactions.
- Stability of raw materials, reaction system, intermediates, and final product to heat, light, air, water, metals, oils, pH, and storage time.

Process Flow Sheets

- Description of process.
- Material flow streams.
- Heat, cooling and other services.
- Equipment and instrumentation.
- Necessity of dual or redundant instrumentation.
- Necessity of interlocking devices.
- Fail-safe requirements.

- Materials of construction.
- Effect of improper control or side reactions on materials.

Chemical Hazards

- Possible induction effects, exothermic reactions.
- Estimated decomposition energies of reactants and products.
- Flammability characteristics of materials (i.e. flash point, explosive range, auto ignition temperature).
- Hazards of drying or grinding.

Biological Hazards

- Handling procedures for biological agents - bacteria, viruses, fungi and parasites, infected or potentially infected human or animal cells, recombinant DNA molecules, and infectious nucleic acids.
- Pathogenicity of biological agents.
- Disposal practices.

Equipment Practices

- Effect of failure of services, vacuum failure, air or water leakage, and metal exposure.
- Fouling of heat transfer services and instrument sensing units.

Health Hazards

- Acute and chronic toxicity data or reactant products and by-products including oral, dermal, and inhalation data.
- First aid treatment and antidotes for various exposures.
- Notification of medical department of work on toxic materials.
- Procedures for safe handling of materials.
- Procedures for decontamination of toxic or obnoxious materials.
- Personal protective equipment needed.

Operating Procedures

- Possible effects of any deviations from the recommended range of operating variables.
- Preparation of a step-operating chart.
- Procedure for discarding unsatisfactory product or intermediates.
- Procedures for proper waste disposal.
- Emergency shutdown procedures or action to be taken in the event of having to terminate a reaction.

Analysis and Process Controls

- Analysis of reactants and products.
- Controls; physical, chemical, and biological during processing.

Final Products

- Labeling requirements.
- Container size and type.
- Pertinent DOT regulations.
- Shelf-life or storage stability.
- Special warehousing requirements.
- Sensitivity to contamination.

Summary

The application of these suggested guidelines can be effective in the identification and subsequent management of process hazards no matter what phase a process is in - research, development, or manufacturing. The primary emphasis has been on qualitative procedures for hazard identification, although some procedures for quantitative hazard analysis may be needed to fully identify all hazards for more complex operations.

Actions to reduce hazards and improve the safety of a particular process operation, however, are no better than the extent to which hazards are recognized in the first place. No single procedure is best for all cases. A good process safety hazard identification program requires the continuous feedback of information between research, development, and manufacturing units and will be rewarded with a continuing improvement of process safety throughout the project and an accident free performance record at the eventual termination of the project.

CHAPTER VI

OTHER FACTORS INFLUENCING DRUG DEVELOPMENT SAFETY REVIEWS

General

The degree of safety achieved in any safety program depends primarily on management support and emphasis. The success of the process hazard review effort also depends largely on management support and their taking definitive action on recognized safety hazards. Their support is also necessary in order to translate written recommendations into practical principles and techniques to eliminate and/or control the recognized process hazards.

It also must be realized, however, that the total success of a process review program in drug development, or for that matter, any manufacturing industry, also depends on factors other than management emphasis and effective guidelines. There must be an overall awareness about the potential for acute hazards which should also encompass such areas as:

- o Information - Manufacturers who in the past have been reluctant to tell the public what hazards are contained within the plant confines need to work together with public officials to reduce heightened concern about their operations.
- o Emergency Plans - Manufacturing plants in the past have been ill equipped to handle or cope with toxic chemical incidents. Emergency response plans should be formulated and included as part of the Process Review Program to handle any potential for

an incident which would involve the public.

- o Plant Safety Programs - Safety programs vary widely among drug and chemical manufacturers due to management commitments and cost factors. This can be especially true in older plants where improvement to meet safety standards could quickly escalate costs to figures approaching the original cost of the plant.
- o Training - Good training in safety principles should be part of every company's training program. New operators should receive orientation training in both safety procedures and job responsibilities. Annual refresher training should also be included as part of the overall company training program.
- o Auditing - In addition to recommended process reviews, plants should be regularly audited to evaluate the effectiveness of their safety programs and to analyze their overall risks.
- o Computer Controls - Utilization of computerized process controls to curb such events as runaway reactions helps to eliminate the human error factor. However, many times decisions to implement computer controlled process are often postponed due to the associated costs.
- o Company Culture - Company philosophy and culture needs to be examined. Consider what is valued, what attention is focused on and how it is administered. Are responsible individuals promoted to key decision making positions? This play an important role in the commitment to plant safety.
- o Worker Practices - Workers should be required to employ good work practices in carrying out their job duties. Such work

practices are the results of good training and education programs in the potential hazards associated with each job, and the requirement for personal safety protection.

A good Process Hazard Review Program in drug development, therefore, needs to be proactive and not reactive if the pharmaceutical industry is to avoid further government regulation and the increased threat of liability lawsuits. In fact, experts say that regulation cannot guarantee safety, only a will to be safe can.[30]

Hazard Reduction and Application of Experience

The pharmaceutical industry as other industries has accumulated a wealth of documented safety related experience based on accidents, incidents, failures and testing which if used properly could be most effective in improving the safety performance in current and future drug development programs. The problem that is faced, however, is how do you effectively apply this experience.

A paper by Earl M. McNail of Martin Marietta Aerospace aptly describes a concept for applying the experience factor. In doing so, it supports the need for a relatively simple technique to identify potential hazards in new product development and the benefits of using checklists.

Mr. McNail believes that technology disclosures reach our universities and corporations in a relatively short time, but that new technology is usually a small part of each new product program. Major

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[34] Dramand, Stuart, "Problems at Chemical Plants Raise Broad Safety Concerns", New York Times, Monday, November 25, 1985, page D11.

deficiencies and resulting accidents or incidents are largely related to design and operational conditions in areas where there are 10 or more years experience. Because much of the documented experience which experience which has been developed to aid in the reduction of hazards has been implemented through educational techniques, such as handbooks, manuals and hazard type catalogs aimed at the individual, a need now exists to develop improved methods for effective application of the documented experience.

Within the improved methods is the inherent role of management and all technical disciplines involved in product development and its intended use. This responsibility has been inherent in engineering, quality, reliability, and other activities, but in reality much time is not really spent reading hazard catalogs, statistical information or accident investigation reports. In addition, despite recognized efforts by corporations in acknowledging the need to coordinate all technical disciplines, specifically from a safety standpoint, and the documented experience in the form of special studies, accident-incident summaries, technical interchange meetings, etc., many of the same mistakes which have caused accidents, incidents or failures in the past are still being made over and over in each new program. McNail feels that even with increased emphasis, System Logic Analysis and many other forms of analysis, certain type of hazards and subsequent failures have continued to occur.[35]

The McNail report identified three basic objectives that were

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[35] McNail, Earl M., "Hazard Reduction Through Allied Experience" Martin Marietta Aerospace Skylab Operations, Huntsville, Alabama, System Safety Society International Symposium, July 1973, Paper No. 11B-7, page 2.

factored into a study to develop a technique to increase effectiveness in applying retained safety related experience to the design and operation of plant equipment. [36]

1. The first objective was to provide for systematic application consistent with each phase of program development. Flow charts were developed to provide an overview of the evolutionary process by which a product is developed, from conceptual design through final product utilization.
2. The second objective was to provide a method to assist all disciplines in the application of safety related experience. This took into consideration many problems which have been facing safety managers and engineers throughout the industry. Some of the factors considered were:
    - o Limited number of safety personnel.
    - o Limited multidiscipline experience of safety personnel.
    - o Cost constraints limiting the development of large safety organizations.
    - o Limited visibility and understanding of the functions and activities of safety personnel by the various engineering, production or operations personnel at all levels of the organization.
    - o Limited effectiveness of safety personnel to influence product design and development. Factors affecting this particular area include: late assignment to a program,

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[36] McNail, Earl M., "Hazard Reduction Through Allied Experience" Martin Marietta Aerospace Skylab Operations, Huntsville, Alabama, System Safety Society International Symposium, July 1973, Paper No. 11B-7, page 2.

late completion of hazard analysis for designs reaching the production phase, and a limited number of safety personnel in combination with safety engineering time spent in developing plans, procedures and techniques required to implement specified program level safety requirements.

Recognizing that such factors either individually or in combination can vary greatly, Mr. McNail felt there was no universal solution apparent. It was at this point, however, that he notes that "to be effective such a technique would have to be relatively simple and compatible with established policies, procedures and practices of many disciplines within a wide variety of programs."[37]

3. The third objective was to provide a method to determine the effectiveness of the application of retained safety experience. To achieve this objective, visibility of results was required. Safety program performance based on conventional indicators such as accident frequency, severity or lost-time was not considered to be sufficient enough to achieve the objective. The primary concern was on accident prevention with emphasis on recurrence control. Here he determined that a method to test effectiveness would be initially based on potential hazards identified and actions taken to control or eliminate known accident or incident causes. Statistical trends could then be developed for

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[37] Op. Cit. page 3.

individual accident causes or groups of accident causes for comparison with similar factors taken from accident history. Future records could then be compared with previous records to determine performance improvements in specific areas of concern.

Mr. McNail provides this example:

> Inadequacy of relief protection has historically been a factor in equipment loss or damage. Although relief devices have been installed to protect against over-pressurization from such causes as regulator failure or human error, they have in many cases failed to do so. They have been found to be undersized with respect to the maximum flow capacity of an upstream failed-open regulator; found to be improperly set with respect to protection for the end product being pressurized; and found to be inhibited by caps, plugs or valves. Improper sizing of relief devices as a single design feature could be identified, corrected and actions recorded as part of the systematic technique selected for applying retained experiences. The effectiveness of the method (or system) could then be determined by visibility of hazards identified and corrected in current systems or products, and ultimately by comparison of past and future accident records.
>
> To bring about the actions necessary to correct deficiencies, the approach taken would also have to provide management visibility to aid in making decisions associated with cost, schedule and risk.[38]

Mr. McNail goes on to develop a concept for experience retention techniques, one which he classifies into two categories.

1. The first category is the retention of the individual having experience and relates to the application of education and experience of individuals with the objective of tailoring and maintaining the organization to meet the needs of a specific program or task.

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[38] Op. Cit. Page 3.

2. The second category involves the retention of the collective experience of all individuals. This category involves the development of standards, manuals, processes and a variety of management systems and methods to direct and control technical and production operations. It is in this category that McNail believes we should focus our attention in order to improve our effectiveness in the systematic application of the collective experience that so much time and expense was taken to document.

Mr. McNail follows by challenging the need to utilize advanced methodologies and variations of those methodologies for hazard identification. It is his belief as well as the author's, that cost, limited numbers and experience of analysts, complexity of techniques and differences in established management practices within organizations have resulted in limited acceptance of many of the more sophisticated techniques. He further indicates that studies have shown that the ultimate success of a hazard analysis, regardless of the method used, is directly related to the knowledge and experience of the analyst. An understanding of analytical procedure does not necessarily ensure that an adequate hazard analysis will be performed. He believes, therefore, that a logical tool that can be applied to all methodologies to assist in the identification of hazards, is a checklist; specifically, a checklist based on tests, field operating experience and accident history. A checklist approach incorporating certain unique features necessary for disciplined implementation was considered by McNail to be the most practical in meeting the stated objectives. Using criteria which have become generally accepted

throughout industry, Mr. McNail offers the following logical sequence for the reduction of hazards.[39]

- o Design for minimum hazards (implies inherent safety in product development and design as an ultimate goal).
- o Incorporate fail-safe features to minimize the effects of inherent hazards in the event of failure or the occurrence of undesired events due to improper use or human error.
- o Incorporate hazard detection and corrective action features to warn of an impending or out of tolerance condition and to provide means to limit or control the effects.
- o Develop special operating instructions and precautionary notes or warnings within procedures to identify hazards associated with improper or out-of-sequence operations. This hazard reduction technique is especially important to manufacturing processes, assembly instructions, test procedures and repair or maintenance procedures. Many hazards thought to be reduced by design features have resulted in failures or accidents due to improper assembly.
- o Provide training and certification of assembly, test, inspection, and operating personnel to ensure their awareness of identified residual hazards. This training should be developed to familiarize personnel with design or procedural controls which have been established in order to minimize risk.

The factors of cost and schedule also bear great influence on decisions once a new product development program idea is released and

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[39] Op. Cit. page 4-6.

the exploratory, development, manufacturing and testing have started. This often results in the tendency to apply procedural controls or rely more on individual knowledge or awareness rather than team knowledge to control potential hazards in order to minimize change. It is important, therefore, to recognize that hazard identification and reduction improvements must be initiated at the outset of program development and that these improvements towards risk reduction become a team concept and priority.

Mr. McNail concludes that the basic concept of progressive "total program" application of system safety checklists can be effectively implemented on any program, subsystem or product of any size or complexity. A master set of checklists can be developed from which applicable sections or criteria statements can be selected to fit a given discipline, product or program. This approach would minimize continual redevelopment efforts on each program or for each product. However, the need to select and tailor the criteria to the specific product, operation, or program is essential to the achievement of the stated objectives.[40]

Professor Kenneth Andrews of the Harvard School of Business Administration noted that every accident, no matter how minor, is a failure of organization. A repetition of the accident or incident is difficult to excuse if preventative information is available and not used.[41] This statement has proved to be very true in light of the information known about the challenger Space Craft prior to its

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[40] Op. Cit. page 14.

[41] NASA Safety Program, Manned Space Program Accident-Incident Summaries, March 1970.

disastrous space flight in February 1986.

To further improve our performance in current and future product development programs, the following additional points were also suggested by Mr. McNail:

- Management Acceptance that the development and issuance, in itself, of documentation such as hazard evaluation procedures, operating procedures, accident/incident summaries and similar data, does not ensure that it will be effectively used.
- A systematic method to determine the effective application of hazard information must be implemented within each program or for each product development activity.
- The cost of an effective accident prevention program may be far less than an accident, the subsequent investigation, corrective action and damage to public relations.

Figure 8 shows an example of a concept that process review in a pharmaceutical drug development program is "global" in practice and depends on the collective input (experience) of all participating groups. Process safety checklists and HAZOP type analysis progressively applied throughout drug product development, along with transfer of information, will also increase knowledge of conditions that exist from previous experience which have caused accidents, incidents or failures in the past. Management recognition of these conditions in a timely fashion is essential to their making decisions about cost and risk at an early stage so they will ultimately cost less to eliminate or reduce to an acceptable level.

Mr. McNail's concept of progressive application of experience data and use of checklists provides a good basis for developing a practical

GLOBAL CONCEPT OF PROCESS REVIEW IN DRUG DEVELOPMENT

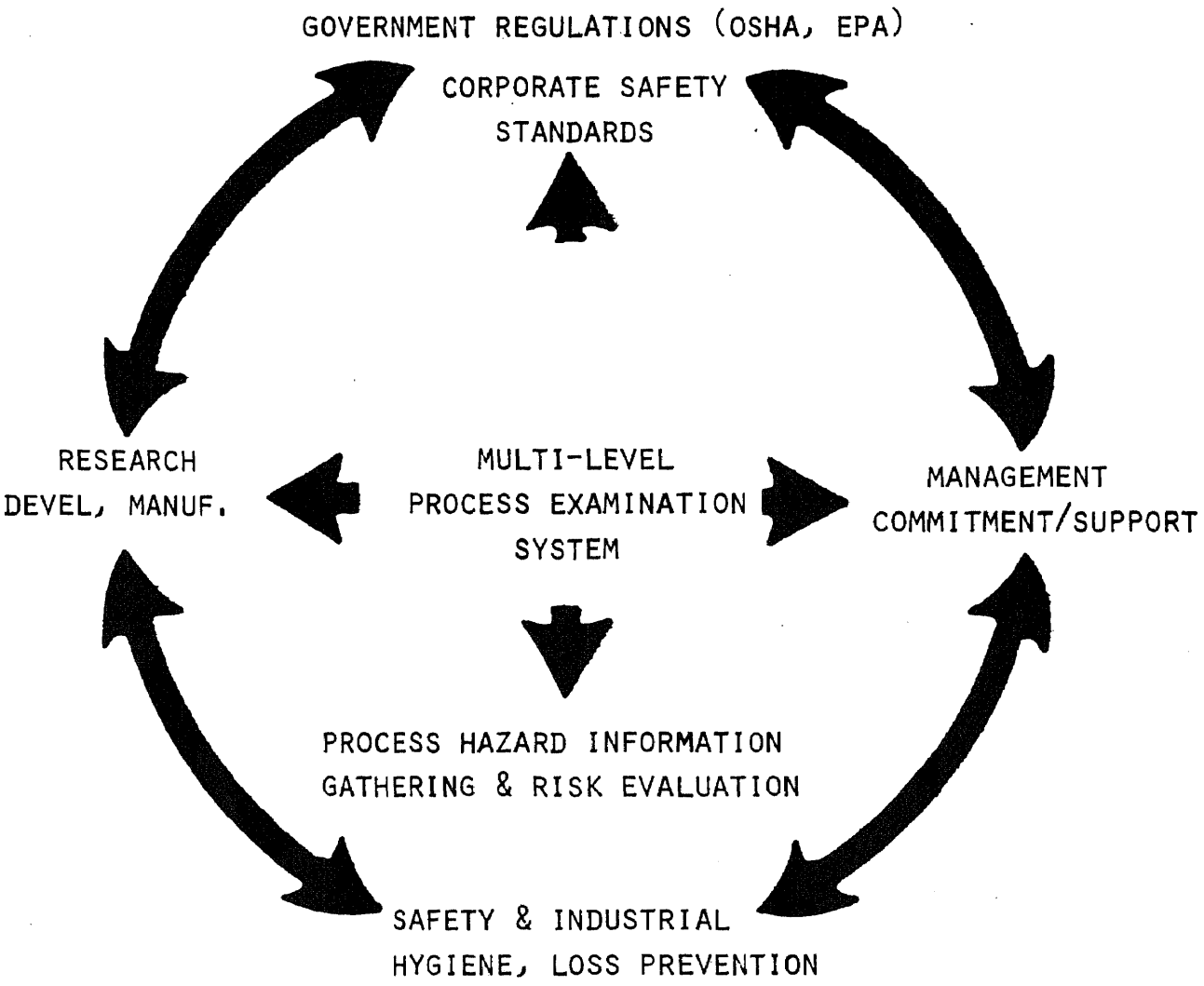

Figure 8

and useful process hazard review in drug development. As noted earlier, the use of laborious analytical techniques for hazard identification are not presently attractive to an industry that is already closely regulated because they manufacture products which are consumed by living human beings. The simplified more practical approach, as suggested by the latter techniques, would gain far greater support for safety professionals attempting to implement a process review program in the pharmaceutical industry.

Computer Assistance in Process Safety

Computers have become well established as tools to increase the productivity of the general work force. Word processing, electronic spreadsheets, and data base management software packages now provide their users with welcome relief from tedious computations and burdensome recordkeeping activities. The pressing need for increased productivity and greater safety are moving process safety toward this new formidable technology.

In the production of drug products process measurement and control become important factors not only from a quality standpoint but from a safety standpoint. By utilizing computer technology, safety is guaranteed by monitoring both the potential courses of emergencies and their consequences. Process Hazard Review programs can also be made easier to handle by using a computer to ease the job of gathering and maintaining process safety information. Typically, applications of the computer to which the average individual is exposed is that of data collector and processor. Another area of application which is now

seeing increased usage is the computer as a device for the transfer of expert knowledge.

For example, information may be needed on regulations governing proper storage of chemicals, correct usage of a particular chemical or correct disposal methods and procedures for chemicals. Even for simply handling the chemicals, several sources of information may need to be investigated.

Recordkeeping is another reason for utilizing a computerized information system in process hazard review. A good information system can effectively manipulate data, and reorganize it in any fashion for the process review team to use to best advantage. For instance, various type of recordkeeping files that could be maintained and easily updated for process hazard review meetings are:

- Personal Protection - who has been assigned equipment, for what purpose, what type, and when issued.
- Training records - types of training, frequency, and subjects.
- Environmental data - such as personal sampling data, environmental sampling data, spills and releases.
- Medical Surveillance data - audiometry, blood contaminant levels, spirometry results, etc.
- Risk assessment data - accident and injury statistics for both accident prevention as well as development of training programs and statistical evaluations.
- Emergency response procedures.
- Material Safety Data Sheet information - giving information on acute and chronic exposure symptoms, how to handle chemical hazards, physical properties, incompatible materials,

antidotes, toxicology and more.

A further advantage of adopting a computerized information system for a process hazard review program in drug development is the ability to network independent computer systems at various site locations into a central computer thus providing greater freedom and flexibility of information transfer. Networking also provides the advantage of pooling of information resources, standardization of data, and prevention of duplication of effort. It is further evident that in promoting process hazard reviews in the exploratory, development, and manufacturing phases of drug development, the ability to transfer safety data as the process progresses becomes of extreme importance in preventing and controlling hazards at the earliest stage possible.

The use of a computer in process review may in fact be most important during the exploratory stage of drug development. In most research and development, much of the effort goes into literature searches for the pertinent information. By having access to an information and/or data management system an experimentalist can manipulate data and retrieve it in a desired format. Records of abstracts from engineering/technical literature; reliability and failure data; microfilmed product catalogs, mechanical and physical properties of materials, requirements by various standard setting agencies such as ANSI, ASME, NFPA and others can be quickly and easily obtained to provide the most information possible when design of a process is in the conceptual stage.

Even while the review of a particular process is taking place, the computer may play an important role in helping to resolve unique potential problem areas. For example, a review could look at the

changing interfaces between people, processes, the equipment they run and the compounds produced. One area currently being explored is the use of computer controlled robots. Computer controlled robots are increasingly being used as substitutes for humans in dangerous operations. In drug development, robots can be utilized to replace workers performing tasks with potent drugs. In manufacturing operations, robots can be used as a mechanical manipulator to provide physical separation between the worker and the chemical or physical source of the hazard.

As a data base information resource and a process control device, computers will provide a process review team with the ability to get to the roots of potential process hazards quickly, reduce the overall time needed to conduct a process review and provide greater safety, productivity and overall cost-savings for the process as well. In today's highly technical world, the computer becomes a natural tool for assessing and managing process risks.

Role of the Material Safety Data Sheet (MSDS) in Drug Process Reviews

A. The Material Safety Data Sheets (MSDS) is a document which describes the specific identity of a material. The MSDS will:
   1. Define a material's chemical characteristics which may result in hazards in the workplace;
   2. Recommend methods of protection against these hazards;
   3. Outline the health effects of the material; and
   4. Suggests procedures for worker protection during emergency situations.

B. Use of Material Safety Data Sheet information will also help to:

- o assist management and process review teams in making decisions relative to facility and process planning.
- o provide line managers with safety and health information on drug substances and assist them in ensuring employee protection.
- o assist in meeting regulatory compliance requirements.
- o help minimize losses from injury, illness, fire and explosion.
- o provide safety and health data prior to initiating exploratory work and for process transfers to pilot plant and production facilities.

In new drug development, Material Safety Data sheets more than likely will be only available for the raw materials used to make the new drug compound. Therefore, it is imperative that commencing as early as the exploratory phase that safety data developed on the new drug product be developed into an MSDS. This should occur at two distinct phases in the drug development cycle:

1. A preliminary MSDS issued on completion of preclinical toxicological studies (development phase).
2. A final MSDS - about the time of NDA submission when clinical studies are completed (prior to production).

Information for a new pharmaceutical active should be collected from in-house toxicology data, in-house experience data, and other resources, compiled into a preliminary MSDS, and reviewed by a special committee. If available information is not adequate for hazard

determinations, then additional testing should be performed before a new process is allowed to continue towards scale-up.

While gathering of information by the process review team may seem to be an overwhelming task, the use of material safety data sheets, if available, will certainly make it an easier and less formidable one. The eight basic information sections provided on a MSDS sheet will give valuable information related to:

1. Identification - the chemical name, trade name and any synonyms by which the material may be called. The Chemical Abstract Service (CAS) number and structural formula are also given.
2. Hazardous Ingredients or Components - this section lists any hazardous ingredients that make up at least one percent of the total mixture. It also lists the Threshold Limit Values (TLV) which is a measure of the health effects. A PEL or Permissible Exposure Limit is a similar level set by OSHA.
3. Physical Data - listing of this data helps to identify the substance by observing its physical properties. It will describe the material's physical appearance, odor, boiling point and other technical data.
4. Fire and Explosion Hazard - this information lets you know beforehand how to control a fire, it contains the flashpoint and flammable limits of the material.
5. Reactivity Data - reactivity data alerts the user to conditions the materials must avoid in order to prevent dangerous reactions.
6. Health Hazard Data - this data provides the routes of entry as

well as effects of overexposure. Emergency and first aid information provides methods of treating overexposure.

7. Precautions for Safe Handling and Use - outlines steps that should be taken to clean up the material if it is spilled. Also provides methods for waste disposal and handling and storage precautions.
8. Control Measures - includes recommendations for respiratory protection, or any other special safety equipment needed for working with the materials.

The overall purpose of a Material Safety Data Sheet, therefore, is as a vehicle to inform employees of the potential hazard of a material and to assist management in meeting requirements for protecting the safety, health and well being of employees. If properly used by the process review team, the MSDS can be one of the most valuable tools in the identification of process hazards.

CHAPTER VII

Conclusion

The scope, organization, process review format and method, regulatory effects, types of drug manufacturing processes, and background as related to a new drug development process in the pharmaceutical industry have been discussed throughout this paper with the purpose of recognizing that there are a variety of "safety review systems' available to systematically review a process or project for identifiable hazards. Most as noted earlier are too laborious to be practical and/or applicable in pharmaceutical research or scale-up work. In concluding this thesis, the concept of a multiple level review method which incorporates those guidelines discussed for research, development and manufacturing are developed into examination worksheets which can be easily used and transferred between major operations or locations.

The multiple level review method is a three level information gathering approach that is designed to enable a comprehensive yet practical assessment of a new drug process or product from the regulatory, safety and occupational health viewpoints.

The multi-level approach can be used as a tool to evaluate the safety of new processes as they develop to assure compliance with applicable governmental regulations, company/corporate standards, and most importantly to provide the necessary vehicle for early recognition of hazards and risks. It can also assist the business area management in conserving development resources by evaluating processes early

enough in the development stages so that those approaches which have less health, safety, or environmental concerns, can be selected over others with a high degree of recognized hazard.

Examples of the type of forms or checklists that should be used to collect and organize information in each major phase of a drug product's life (research, pilot plant, manufacturing) are discussed below and provided in Appendices A-C. These forms are necessarily general, and include both a checklist and discussion type format for items to be reviewed. The checklists should be specifically tailored to suit the priorities of the individual company, plant, product, or operation to achieve the most success.

Level I Process Examination Worksheet - Exploratory Phase

Since laboratory and bench-scale experiments often involve the short term use of small quantities of material, the materials can often be of unknown or little known toxicity. Because of the large numbers and variety of materials used in R&D work, it is not always possible or practical to obtain complete safety data on each material before proceeding with experimental work. Therefore, even though the scientific background of the experimenter may be very advanced, work is usually conducted under the assumption that any material of unknown toxicity is in fact highly toxic and should be handled accordingly.

Preparation of a Level I examination form encourages early documentation of any concerns for employee health and safety in the research stage of drug development. If the researcher addresses these questions and records the information, the researcher and other

employees exposed to the material(s) should be able to proceed with a high degree of confidence and safety. If a material or class of materials has a recognized problem, the information can be documented and the problem eliminated or controlled before an exposure or major incident can develop. A manufacturer's MSDS should be requested whenever a new sample of a chemical material is ordered. If not available from the supplier, other sources should be investigated. The Level I package should include information on the chemical's identity, physical properties, hazardous properties (fire, reactivity), health effects, sources of supply and locations where it will be used or made in the facility. For new compounds, this package is the basis for identification of data gaps such as physical property characterization, analytical method development and toxicological testing development.

Level II Process Examination Worksheet - Pilot Plant Development

New drug materials once through the exploratory stage will move on for further development in the Pilot Plant. At this level, materials are used in larger quantities and for greater periods of time. The potential for a negative process event involving the material or equipment becomes greater and control becomes more difficult because more people are working with the material. Much more information is needed at this point and the major concerns of the process are addressed by the Level II examination form. This package is more of an overview and focuses on the new product or process and not on the individual raw materials. A committee to handle the Level II examination should be formed at this time and a thorough review of the

Level I package completed before proceeding with the Level II examination.

As a minimum effort, a material safety data sheet should be prepared if one is not available in the exploratory Level I stage. Handling procedures should also be reevaluated at this point to assure that they are appropriate for the scale of work being performed and the hazard involved.

At this point also, appropriate toxicity tests for new materials and materials where toxicity is not well understood, should have been completed during R&D work and passed on before the process is transferred to the pilot plant. Additional literature searches and possibly acute toxicity testing, might be appropriate at this stage.

Since the new material will be processed in larger quantities, the need to begin to look at the concern for prevention of environmental pollution due to a release or other factors becomes important. Information obtained in Level I and Level II examinations is extremely valuable in preparing premanufacture notifications and forms the basis for the overall objective of examining not only safety and health, but also environmental and property loss. The Level II package sould include any new, or changes of, materials involved, changes in the process or people involved, location of trials, safety precautions, quantities of materials and types and quantities of wastes, along with information such as whether samples will be shipped to potential customers. This package is completed prior to any trials and is reviewed and approved by all company environmental, industrial hygiene and safety groups, and the process review committee.

Level III Process Examination Worksheet - Plant Production/ Manufacturing

At full scale production, new concerns are raised. Information documented at Level I and Level II is essential in order for plant supervision to recognize and evaluate similar and possible newly introduced hazards resulting from the increased scale-up.

Full scale production represents a greater commitment, use of an even larger amount of material and poses even greater problem with regard to process hazards than the laboratory or pilot plant studies did. There are increased numbers of workers handling material, equipment is larger, and potential pollution and exposures may be greatly increased.

Governmental regulations become significant at this point and the handling of a material from receipt as a raw material to customer use of the finished product must also be reevaluated. The Level III examination form addresses these key areas of concern and provides a good information base as the plant prepares to process the new drug material. The Level III examination package should include:

- o A review of Level I and II packages.
- o A complete process description with estimates for production volumes .
- o Descriptions and specifications for protective equipment, safety precautions, monitoring procedures.
- o Information regarding any potential for spills.
- o A discussion of any potential for and route of possible employee exposure.

- o A review of all toxicological information from both literature and testing programs run during product development.
- o A description of any testing in currently in progress.
- o A description of environmental release information and waste disposal procedures, if any.
- o Methods for transportation of raw materials, intermediates and final products.of the customers processing.

Prior to production, this examination form should be reviewed by the company Industrial Hygienist, Safety, Product Safety, Pollution Control and Medical Director as well as the site Environmental, Industrial Hygiene and Safety personnel. Production is authorized only after the Level III package has been approved.

Implementation of the Multi-Level Review Program

Effective implementation of the Multi-Level Process Examination Program requires those personnel in charge to assume and carry out their responsibilities through all phases of the review program. In the Level I area covering research and development, the research scientist in charge of product or product development should bear the responsibility of preparing the process examination form for each new process handled in the laboratory and for the "final product" being developed.

The research scientist should also involve site safety and industrial hygiene personnel at this point if a literature search was completed and little or no information was found. Attempts should also

be made to obtain toxicological data from the supplier, in order to obtain as much safety data as possible as early in the project development as possible.

Experimentation should not be initiated until the review form has been fully examined by Safety and Industrial Hygiene and Environmental personnel. Information related to identified hazards and recommended procedures for eliminating or controlling them should be documented on the form and communicated to the research scientist in charge.

At Level II or the Pilot Plant Scale-Up/Trial phase, all Level I information should be provided by the research scientist to pilot plant personnel in charge of the process. In many cases, a cooperative effort is needed with both pilot plant and research personnel in charge to effectively transfer the safety data learned in the exploratory phase to the development phase. A "meeting of the minds" also benefits the need to provide an accurate and safe production scheme and process material balance. Level II and III examination should be conducted by a committee similar to that described on page 14 of Chapter I. A separate review committee should be commissioned for each examination.

A separate Level II data sheet should now be completed for each plant trial or run to be conducted. Level I and Level II data sheets with attachments should then be submitted to the Safety and Industrial Hygiene and Environmental Departments for review, comments and recommendations before any plant trial runs are scheduled. Again, the form with any recommendations from the latter will be returned with appropriate recommendations and any additional requirements.

At this stage, it can now be seen that it becomes easier and less time consuming to accumulate information as the drug development

program progresses, rather than trying to obtain it all at once.

Since plant trials can be conducted at different locations, approvals to conduct a trial at this level should be confined to the specific location. The reason for this is that each location generally will have a different set of safety and health considerations, therefore, a review conducted at one location will not necessarily be appropriate for another. A separate Level II review is, therefore, required under these circumstances.

When the new drug process reaches the commercialization stage, a Level III review should be completed by the Production Supervisor and any other department personnel responsible for the manufacturing and production of the material. A complete information package from Level I and Level II reviews should be submitted prior to the Level III review. Again, since information has been accumulated as the process progressed, this review should be less time consuming with a lot of valuable information available to production personnel.

The entire package containing Level I, II and III information should be reviewed by Safety and Environmental personnel for approval as in the past reviews. "Transfer of knowledge" meetings between pilot plant and production are highly recommended at this point, especially since the magnitude of scale-up is many times greater than that experienced between the exploratory and development phases.

Final hazards assessment should be prepared by the department in conjunction with safety, environmental, legal, and risk management personnel. Upon approval from these groups, the entire process review package (Levels I, II and III) are returned to the production location.

The suggested use of a more simplified process hazard review

format in new drug development does not preclude the need for quantitative or more complex methods. Many companies have detailed process review programs or policies in place. It is the author's personal experience after working in both the chemical and pharmaceutical industries that there is a reluctance to get involved with the more complex, time consuming and costly effort involved with these approaches. Rather than not have a review of a potentially hazardous process at all because no one wants to get involved, this writer sees the philosophy to be one of practicality while at the same time casting an eye towards the more quantitative review methods on an "as need basis".

The approach to process hazard review in drug development or any product development program is dependent on an organizational commitment to safety and consideration of safety early in the design/development of the process. There must also be a commitment to the broad consideration of safety issues to assure that safe operating, programming and maintenance procedures are in effect. Project Management must be aggressive in dealing with safety by:

- o assigning responsibility for safety
- o establishing an accountability mechanism for results
- o consideration of safety at each milestone
- o ensuring that relevant safety information is forwarded to the next operational level in a timely fashion.

As a concluding point in support of a process review program in drug development to prevent major incidents, a reference to a Bible passage in an article by G. Kinsley in a 1983 edition of Professional Safety magazine perhaps provides an apt ending. The article titled

"Potential Accident Analysis" quotes the following words of advise.[42]

> "If you dig a pit, you fall in it; if you break through a wall, a snake bites you. If you work in a stone quarry, you get hurt by stones. If you split wood, you get hurt doing it. If your ax is dull and you don't sharpen it, you have to work harder to use it. It is smarter to plan ahead."
>
> Ecclesiastes 10:8-10

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[42] Kinsley, George R., "Potential Accident Analysis", Professional Safety, July 1983, page 25.

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WARNER LAMBERT

January 21, 1987

Mr. Rudy Schwarz

Dear Rudy,

My thanks to you for asking me to review your Masters Thesis: "A Process Review Program for Drug Development. I very much enjoyed reading it and think it will serve as a valuable resource to the safety community.

I offer the following comments for your consideration. I believe they will enhance the thesis by making more complete;

1. Add examples of FMEA, FTA and HAZOP. They will aid in understanding of these hazard analysis techniques.

2. Add a flow diagram of the drug development cycle to Chapter 3.

3. In Chapter 4 you describe a number of chemical and pharmaceutical process steps and types of equipment. Add examples of equipment to the various sections to provide a reference.

4. On page 82 you begin a discussion of pharmaceutical manufacturing, followed by descriptions of tablet and capsule manufacturing. As several of the processing steps described in tablet manufacturing ie. weighing, blending, granulation, milling, also apply capsule manufacturing, consider rearranging this section to make this clear or preface the sections on tablet and capsule manufacturing with the description of these process steps.

5. Include examples of physical tests, such as, differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), etc., as part of your discussion on "Development Work" on page 98. These tests should also be included in Appendix B, Level II Process Review Form.

Again, my thanks for asking me to review your thesis. I hope the comments are of value.

I'd like to take this opportunity to congratulate you on completing the Masters of Science Program in Health and Safety Management at NJIT. Your hard work and determination have paid off.

Best regards,

J.M. Galat
Manager, Safety
U.S. Operations

JMG/no
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January 26, 1987

Mr. Rudolph R. Schwarz

Dear Mr. Schwarz:

I have reviewed your thesis paper entitled "A Process Hazard Review Program for New and Existing Drug Development Programs". The paper is well organized and provides an excellent framework for the establishment of a formal process hazard review program. The sections on system safety and phamaceutical processing are valuable in acquainting the new safety professionals with the concepts used in this industry. The inclusion of specific forms in the appendices will promote the effective use of the process hazard review process.

Sincerely,

David J. Struebel, CIH, CSP
Industrial Hygienist

/tb

Schering-Plough

Schering-Plough Corporation
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January 16, 1987

Mr. Rudolph Schwarz

Dear Mr. Schwarz:

I have completed reading your thesis "A Process Review Program for Drug Development" and found it interesting, informative and of value to the Pharmaceutical Industry.

By bringing together the many basic elements of essential hazard control procedures in combination with the highly specialized techniques of Pharmaceutical Research, Product Development and Manufacturing, your thesis describes an important, timely application of the latest technology to the problem of identifying the hazards involved in drug development.

Of particular importance to Safety and Health professionals is the development of a systematic and organized approach to the collection of data and related information at key steps of the research and development process.

While the basic procedure has been simplified for broad based application, it can easily be enhanced through more complex analytical and mathematical methods as operational skill develops or as the need arises.

In my opinion, your thesis makes an important and useful contribution to the resources available to the Safety and Health profession and will prove a valuable tool to the Safety professional.

Yours truly,

Theodore G. Meglis
Manager, Safety & Industrial Hygiene
CSP No. 7167
P.E. No. N.J. GE 13778

TGM/kdy

SCHERING CORPORATION

60 ORANGE STREET BLOOMFIELD, N. J. 07003

CABLES: SCHERING BLOOMFIELD, N.J.
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January 28, 1987

Mr. Rudolph R. Schwarz

Dear Rudy:

First of all, let me congratulate you on the completion of your Master's degree requirements. You've worked hard during the past several years and should be proud of your achievement!

I read your thesis with personal interest since I have minimal experience with chemical process hazard reviews. My overall impression is that your dissertation is a thorough review of the process hazard review mechanism and is an excellent starting point for a newcomer to the field. The in-depth description of the "What If?", Failure Mode and Effect Analysis, Fault Tree Analysis, Checklist and Hazard and Operability Study techniques provides a useful reference for safety professionals pursuing this topic.

Sections III and IV deal specifically with the pharmaceutical industry and its unique hazards. This is particularly useful for an individual who has not been previously associated with the safety of drug manufacturing.

The process examination review forms in Appendices A, B and C completely outline the process hazard review program for research, development and production. They are well-formated and can be reproduced directly for immediate use. The References section is both current and extensive, indicating a broad consideration of the topic.

Specific criticisms regarding content and style have been discussed with you and appropriate changes have been made in the final document.

Thank you for providing me the opportunity to review your thesis.

Sincerely yours,

Joseph Van Houten, Ph.D.
Manager,
Safety & Industrial Hygiene

/tb

APPENDIX A

LEVEL I PROCESS EXAMINATION REVIEW FORM

LEVEL I PROCESS EXAMINATION REVIEW FORM

(To be completed by Principal Researcher)

Name of Project_____

Name of Initiator_____

Proposed Location_____

Process Information

I. A. Give a brief description of the work you propose. Mention main equipment items, attach rough sketch.

_____

_____

_____

B. On what scale do you plan to run?

_____

_____

_____

II. Give equations illustrating chemistry involved including significant side reactions (show temperatures, pressures, solvents, etc.):

_____

_____

_____

III. Will project personnel require (check appropriate box(s))

_____additional training.

_____personal protective equipment.

_____medical surveillance.

Briefly explain need: _____

_____

_____

IV. Does the experiment or process present any of the following hazards? (check appropriate box(s))

____ hazardous reactions ____ environmental hazards

____ explosive hazards ____ health hazards

____ thermal hazards ____ fire hazards

____ mechanical hazards ____ other type hazards

Briefly explain any hazards checked: _____

_____

_____

_____

_____

V. A. Can this work cause pressure to develop?

Yes ____ No ____ Explain if yes: _____

_____

_____

_____

V. B. Has a relief device evaluation been performed?

Yes ____ No ____ If no, explain: _____

_____

_____

_____

VI. Any other safety concerns to be addressed, if so explain:

_____

_____

_____

Reference Searches

Indicate references searched by checking box and attaching a copy of data sheet to this form. If no information was found, indicate none.

Literature Reference Sources:		Computer Searches (note date)	
Supplier MSDS	_____	Chemline or Chemdex	_____
Internal MSDS	_____	Toxline	_____
Patty's	_____	RTECS	_____
Sax	_____	NTIS	_____
NIOSH RTEC	_____	Hazardline	_____
ACGIH Doc.	_____		
Merck Index	_____		
Others	_____		
	_____		

SPECIAL CHARACTERISTICS OF EXPLORATORY COMPOUNDS

Check appropriate characteristic if it applies and list those materials including the final product next to the characteristic applying, indicate not applicahble (N/A) if characteristic does not apply:

Characteristic	Materials Involved
____ Suspected Teratogen	_____
____ Carcinogen/Mutagen	_____
____ Sensitizer	_____
____ Corrosive	_____
____ Eye or Skin Irritant	_____
____ Fire Hazard	_____
____ Product Safety Concern	_____
____ Pollution Concern	_____
____ Limited Toxicity Info	_____
____ Hygroscopic	_____
____ Skin Absorber	_____

EXPERIENCE DATA AND INFORMATION SECTION

List in this section any experimental deviations experience during exploratory work and any supplemental safety data acquired as a result of the exploratory work.

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Completed by _____ Date _____

(Principal Researcher)

Reviewed by _____ Date _____

(Safety & Industrial Hygiene)

Reviewed by _____ Date _____

(Environmental Engineer)

Approved by _____ Date _____

(Process Review Committee Chairman)

APPENDIX B

LEVEL II PROCESS EXAMINATION REVIEW FORM

LEVEL II PROCESS EXAMINATION FORM

(To be completed by Pilot Plant Supervisor)

Name of Project _____

Project Leader_____

Proposed Location _____

Complete questionnaire and attach all available safety data. Forward completed form to Process Review Committee Chairman.

I. Has the Level I examination package from research been forwarded and attached to this form? Yes ___ No ___ If no explain.

_____

_____

II. Will further literature searches or additional testing data such as explosivity, rash point, differential scanning colorimetry (DSC), thermal gravimatric analysis (TGA), etc. be required before proceeding with its proposed scale-up? Yes ___ No ___ If yes explain.

_____

_____

III. A. What level of scale-up is proposed?

_____

_____

B. Has a process flow diagram and material balance been completed for the process? Yes ___ No ___. Attach copies.

IV. Are any new materials being introduced into the process at this point? If so, list below in conjunction with any associated hazards. Attach MSDS if available.

New Material	Hazard
_____	_____
_____	_____
_____	_____
_____	_____

VI. Will elevated temperatures or pressures be recognized to run this process? Briefly explain trial conditions.

_____

_____

_____

_____

VII. Are emergency relief systems installed to protect the equipment. What type? Note Briefly.

_____

_____

_____

_____

_____

VIII. Identify any process variables other than temperature or pressure that could or will approach hazardous conditions.

Variable	Hazardous Condition
_____	_____
_____	_____
_____	_____
_____	_____

IX. Could any hazardous situations develop from equipment or utility failure? If so, explain.

_____

_____

_____

_____

_____

X. Do emergency procedures exist to handle potential releases, spills, fires, etc.

Yes ___ No ___.

XI. Do process directions exist for each step of the process and have they been reviewed with the personnel assigned to conduct the plant trial.

Process Directions	Reviewed with Personnel
Yes ___ No ___	Yes ___ No ___

XII. Will personal protective equipment be required. If yes, indicate type:

_____ Respirator	_____ Safety Shoes
_____ Safety Goggles	_____ Acid Suit
_____ Safety Shield	_____ Hand Protection
_____ Safety Glasses	_____ Head Protection

XIII. What type of equipment is planned for Use? (Check appropriate types).

_____ Reactor	_____ Mill
_____ Mixing Vessel	_____ Crusher
_____ Large Volume Glassware	_____ Grinder
_____ Centrifuge	_____ Distillation Column
_____ Pumps	_____ Filters

XIV. Have standard operating procedures been established for the equipment checked above? Yes ___ No ___

XV. Recommendations Section (to be completed by the Process Review Committee and returned to the project leader for corrective action before sign-off approval.

Recommendations

_____

_____

_____

_____

_____

_____

_____

_____

_____

Completed by _____ Date _____

Pilot Plant Supervisor

Reviewed by _____ Date _____

Safety and Industrial Hygiene

Reviewed by _____ Date _____

Environmental Engineering

Reviewed by _____ Date _____

Toxicology

Approved by _____ Date _____

Process Review Committee Chairman

APPENDIX C

LEVEL III PROCESS EXAMINATION REVIEW FORM

LEVEL III PROCESS EXAMINATION REVIEW FORM

(To be completed by Production Supervisor)

Name of Project _____

Production Supervisor _____

Proposed Location _____

Complete questionnaire and attach all available safety data. Forward completed form to Process Review Committee Chairman.

I. Have the Level I and Level II data package been forwarded and attached to this form? Yes ___ No ___

If no, briefly explain why below:

_____

_____

_____

_____

_____

II. What level of scale-up is proposed for production purposes?

_____

_____

_____

_____

_____

III. What type of material handling system will be required for this operation:

Manual transfer _____ Closed system transfer _____

Explain briefly the specific transfer operation:

_____

_____

_____

_____

IV. What type of process equipment will be used in the production process?

_____ Dryer

_____ Crusher

_____ Grinder

_____ Mill

_____ Tablet Compressor

_____ packaging machine

_____ screening equipment

V. Have controls been implemented to reduce or eliminate contaminant release and/or personnel exposures? Describe what type:

_____

_____

_____

_____

VI. Will there be storage of raw materials, products and/or intermediates. If so, how much? Location of storage? Indicate below:

_____

_____

_____

_____

_____

_____

VII. Are hazardous conditions expected to develop in this operation due to: (check items that apply, provides a brief explanation below).

_____ temperature	_____ flow
_____ pressure	_____ changes in process variables
_____ stability	_____ toxicity of material
_____ spills	_____ flammability
_____ release	_____ reactivity
_____ equipment failure	_____ freeze-up or plug
_____ adding wrong material	_____ loss of inerting blanket
_____ loss of air/vacuum	_____ loss of cooling capacity
_____ loss of ventilation	_____ loss of utilities

Explain:_____

_____

_____

VIII. Are personnel assigned to operate equipment adequately trained in special hazards, precautions, procedures and/or use of process directions? ___ Yes ___ No. If no, explain below why not and what additional training will be required.

_____

_____

_____

_____

IX. Has a description of the process and/or process flow diagram been attached? ___ Yes ___ No.

X. Are emergency response and shutdown procedures in place?

___ Yes ___ No.

XI. Are new materials being introduced into the process at this point. If so, identify below and attached Material Safety Data Sheet.

Material	MSDS Attached (Check)
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

XII. Note any other hazards that may not have been covered by this questionnaire:

_____

_____

_____

XIII. Recommendations Section (to be completed by the Process Review Comittee and returned to the production supervisor for corrective action before sign-off approval)

Recommendations

_____

_____

_____

_____

_____

_____

Completed by _____ Date _____
Production Supervisor

Reviewed by _____ Date _____
Safety and Industrial Hygiene

Reviewed by _____ Date _____
Environmental Engineering

Reviewed by _____ Date _____
Toxicology

Approved by _____ Date _____
Process Review Committee Chairman

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