A Systems Approach to Pharmaceutical Problems

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The *systems approach* is a method of systematically studying and solving complex problems. Engineers have been using this method successfully to solve a wide variety of problems, ranging from the control of traffic congestion to interplanetary travel. Large corporations such as TRW and Rockwell routinely use systems engineers to define, articulate, and design many of the unique projects that are produced by these corporations. Motivated by the initial success of the systems approach, many nonengineering disciplines are becoming interested in applying this methodology in their fields. The purpose of this article is to explore the relevancy and the role of systems engineering in the pharmaceutical sciences. Although many books have been written on the subject of the systems approach — and, in fact, precisely because many books have been written on this subject — there remains an ambiguity about the true definition of the term. This article presents some of the fundamental ideas that are associated with the systems approach, such as goals, objectives, and indicators.

The concept of a "system" is perhaps as old as civilization itself. A *system* may be regarded as a set of interrelated elements, and the nature of the elements that are involved in the system as well as the relations that might exist among the elements depends on the type of system under consideration. The fact that a system can be regarded as a collection of sets as well as the relation between these sets allows for the application of principles from the fields of set theory, topology, and function theory. This is exactly what engineers and mathematicians do when they work with a system.

Almost all of the disciplines that use a systems approach also use the concept of a model as a basis for developing solutions to problems; the differences among such models is more semantic than it is methodological. Aided by the advent of the computer, the systems approach and the modeling of systems rapidly evolved and accumulated an impressive record of successes in many areas of problem solving.

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Goals, Objectives, and Indicators

One of the first steps in the systems approach is *problem specification*. On first encountering a human need, one first must define the outlines of the need, the resources available to meet it, and the level of performance that is necessary to justify the solution to the problem. In other words, one must define the problem in terms of goals, performance criteria, and constraints. Nothing is more important in systems studies than defining the right goals. Working out solutions to improperly conceived goals — no matter how elegant the methods that are used — is tantamount to answering the wrong questions. Setting goals is therefore important to provide frames of reference for making decisions.

The next step in the systems approach is to supplement the goals by defining objectives or by establishing performance measures. This is important because when a plan is prepared with a particular goal in mind, there must be a means of measuring the amount of progress that is made toward achieving that goal. For example, consider the goal of developing a useful set of stability guidelines for the pharmaceutical industry. Although it sounds like a useful goal, this statement fails to provide a clear basis for designing a plan. To translate this goal into an objective, it is necessary to identify the *indicators of stability*. Typical indicators of stability are the rate and degree of degradation within a specified set of environmental conditions and within a given amount of time. A typical objective is to minimize the time and resources that are required to perform an accelerated stability study that yields optimal predictions of a product's shelf life.

To be able to measure the degree of success that is achieved in reaching a goal, it is first necessary to translate the goals into objectives that can be expressed in terms of quantifiable attributes. Then, one must have a "yardstick" to use to measure the distance, or "error," between the status that is attained and the selected objective. Such yardsticks are called *indicators*. It is often useful to make a diagram of goals, indicators, and objectives, as shown in Figure 1.

The formulation of objectives and the identification of appropriate indicators is not always an easy task. Often it is necessary to construct a hierarchy of decompositions in order to develop a true understanding of a genuinely complex problem. The complexity that is associated with selecting goals, objectives, and indicators is illustrated here by an example from the area of pharmaceutical stability guidelines.

In the pharmaceutical industry, there is an increasing concern about FDA's stability guidelines for human drug products. Some

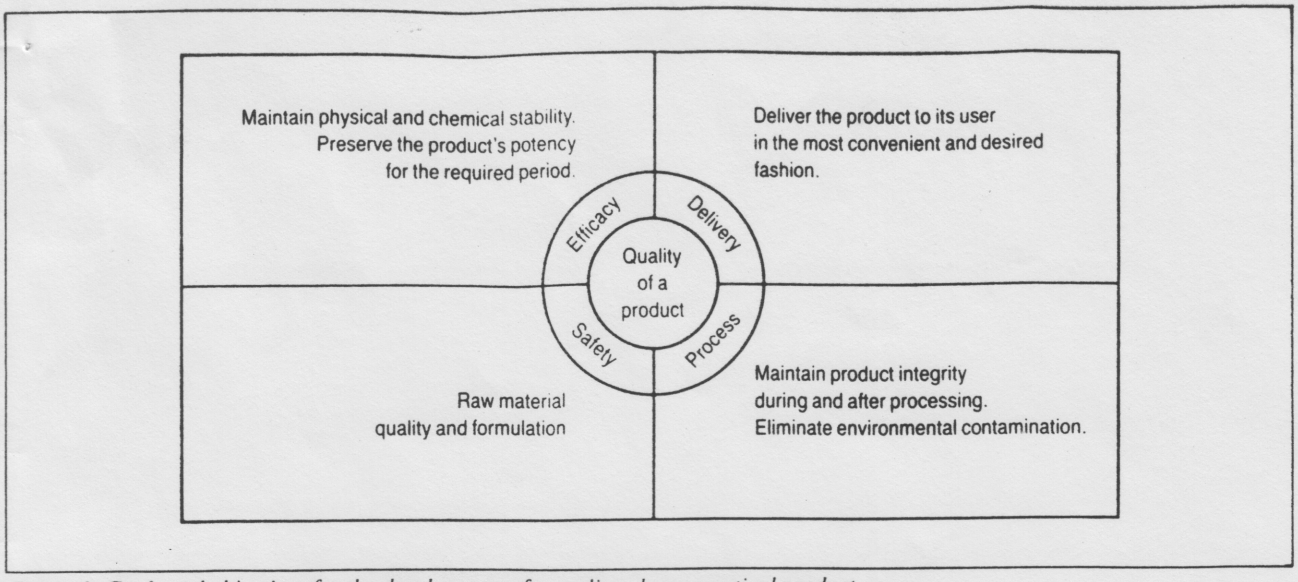

Figure 1: Goals and objectives for the development of a quality pharmaceutical product.

of this concern has arisen because of economic and legal considerations. In planning for drug stability studies, one might have to ask questions about the true nature of FDA's requirements or whether a difference exists in designing a stability study for prescription drugs versus designing one for OTC drugs. Other questions that might be appropriate to ask include whether it is necessary to show a correlation between accelerated stability data and ambient stability data and at what stage this correlation is to be presented to FDA. How much data is acceptable to FDA, and in what format should the data be submitted?

A traditional indicator of a new product's shelf life is the chemical stability of the product — that is, the ability of the product to maintain a certain level of potency, such as at least 90% of the potency level that is claimed on the label, at the time the product is dispensed. It should be remembered, however, that this 90% label-claim definition of stability should not be regarded as universally acceptable. A more recent view is that the stability of a dosage form also includes other dimensions of the product, such as its degree of physical parameter acceptability.[1] This change in attitude is partly the result of a growing recognition that the quality of a product is not solely determined by its chemical potency but also by its drug-release characteristics, appearance, bioavailability, and other attributes.

It is important to establish stability protocols that can successfully predict a product's shelf life as well as yield data that will be acceptable to FDA. This example is meant to illustrate the difficulties that can be encountered in setting goals and in formulating an objective. Although a large number of indicators must be identified specifically for individual products, many indicators can be applied to a range of products. Typical indicators that are widely used in stability studies are listed in Table I.

Table I: Stability indicators (phases) in developing a new product.

Aspect	Typical Indicator
Physical stability	Drug release, appearance, dissolution, etc.
Chemical stability	Chemical integrity of the active ingredient(s)
Bioavailability	Changes in absorption, distribution, and elimination of the drug
Excipient compatibility	Interaction between active ingredients and excipients

As Table I suggests, the quantification of a dosage form's behavior is not always feasible. Also, it is not always easy to determine which parameters or indicators are most appropriate to use in attaining the goal that is specified in a given stability study. For example, it is seldom obvious which single parameter to select in order to quantify the objective of improving a drug formulation. Drug dissolution profiles, in vivo drug-release profiles, changes in the appearance of a dosage form over time, and bioavailability are a few of the characteristics that can serve as indicators of drug quality.

Several attempts have been made to devise a single in vitro indicator that can describe the in vivo behavior of drugs.[2-4] For example, a composite of several factors can be adjusted in an in vitro dissolution test to predict the in vivo behavior of a dosage form, as shown in the following equation:

$$I_d = f(A,P,T,C,\ldots) \quad (1)$$

where

I_d = dissolution index
A = geometry of the apparatus
P = revolutions of the paddle per minute
T = temperature of the water bath
C = composition of the medium.

The rate of dissolution is dependent on each of these parameters and can be defined so that it does not exceed a predetermined value.

Choice of Performance Measures

As was mentioned previously, a measure of performance — also known as a *performance metric* — is usually a function of the indicators. Because it is possible to define a variety of such functions, it is necessary and convenient to choose one function, known as the *objective function*, and to maximize, minimize, or

optimize the value of this function. Selecting a properly formulated objective function is of paramount importance in reaching the stated goal. The particular objective, or objective function, that is used has a direct influence on the model that is obtained and consequently has an influence on the subsequent decisions that are made as a result of studying the model.

Usually, an objective reflects the overriding concern of the designer or the analyst in achieving the stated goal. The nature of the problem and the constraints that are imposed determine whether this task can be accomplished. A *constraint* is a limit on a required characteristic, which is imposed on the system for any reason. Under such constrained conditions, it is possible that no means exist that are strong enough to influence the system to achieve its goal. In such cases, an analyst seeks solutions by relaxing the constraints. A problem is properly formulated if there exists a means by which to reach the stated goal subject to the prescribed constraints.

From an operational viewpoint, *system effectiveness* is a measure of the extent to which a system can be expected to achieve a set of specific mission requirements and is a function of system availability, dependability, and capability. *Availability,* which is a condition of the system at the start of a mission, can be determined by the following equation:

$$\text{Availability} = \frac{MTBF}{MTBF + MTTR} \tag{2}$$

where

$MTBF$ = mean time between failures
$MTTR$ = mean time required to restore the system to an operating state.

$MTBF$ can be determined using the following equation:

$$MTBF = \frac{\text{System operating time}}{\text{Number of observed failures}} \tag{3}$$

Dependability is a measure of the system's condition at one or more points during a mission, taking into account the condition of the system at the beginning of the mission. *Capability* is a measure of a system's ability to achieve the objectives of a mission, taking into account the condition of the system during the mission. Using these terms, a system's effectiveness can be defined as follows:

$$\text{Effectiveness} = \text{Availability} \times \text{Dependability} \times \text{Capability} \tag{4}$$

For example, consider the operation of a tableting machine. During a typical calendar year, the machine might be on a maintenance status for three months and on a functional status for an aggregate period of nine months. The efficiency of this machine is 9/12 or 3/4.

Another method of judging the performance of a system is from the viewpoint of profit or loss. Profit can be defined as follows:

$$\text{Profit} = V - C \tag{5}$$

where

V = value received
C = cost expended.

An optimum system is one that maximizes profit. Alternatively, the rate of return, or R, can be maximized by the relationship $R = (V - C)/C$. It should be noted that the rate of return has an optimum value at the origin, which implies that an optimum solution would be to not build a system at all; obviously, this is a solution of no interest to the manufacturer.

A third method by which to judge the performance of a system is to use the cost-effectiveness ratio (CER) as a criterion. The CER can be defined as follows:

$$CER = \frac{C}{V} \tag{6}$$

The CER is time-dependent in the sense that the short-term ratio usually differs from the long-term ratio.

All of the performance measures that have been described so far involve some drawbacks. The usefulness of these measures is contingent upon the establishment of a unit for measuring items such as dependability, value received, and benefits accrued. Yet it seems difficult to measure the "value" of a benefit because not all benefits can be translated into monetary units.

For example, consider a situation in which a pharmaceutical firm intends to build a manufacturing facility for the production of target delivery dosage forms for treating cancer. To achieve this goal, the company must look into several types of economic, technical, and social objectives. The importance of technical objectives is usually subordinated to that of economic and social objectives. No company would build a plant that violates the regulations of the Environmental Protection Agency merely because the idea is technically feasible. However, after the decision to build a facility has been made, the technologist has the responsibility of implementing the decision in a proper fashion. At this point, one must look at objectives from a technical point of view.

In devising an objective function to arrive at a well-formulated problem, there are three considerations that are generally useful to take into account. One must be able to achieve the specified goal in a reasonable period of time, and the resources that are necessary to reach the goal must be within reasonable bounds. In addition, the intensity of effort that is required to effect the necessary transition must lie within acceptable bounds as well.

In the purely technical problem of developing a target dosage delivery system, the three considerations mentioned above lead to the use of objective functions that involve technical details such as minimizing drug-excipient interactions, minimizing drug release to the zero-order level, minimizing side effects, and maximizing safety and efficacy. In the context of drug delivery systems, the three considerations mentioned above lead to the use of objective functions that optimize the development process. The aggregate of the objective functions that reflect concern about the technical performance of a system is known as the *performance index.*

Each objective function has its own merits and must be considered separately. The choice of an objective function must be realistic, and it must take into account mathematical and computational considerations; there is no point in choosing an objective function that will involve complex computations unless the selection of such a function can be justified. For example, an objective function that seeks to minimize the square root of the sum of the squares of errors — in other words, the *least squares* criteria — is insensitive to wide fluctuations about the mean as long as those fluctuations are well distributed. This would be a poor choice of objective function if the function were to be used in the context of determining the therapeutic regimen for a toxic drug such as digoxin.

For these reasons, the formulation of an objective function and the subsequent solution of the optimization problem requires careful consideration. Although it is mathematically more difficult to handle than the least squares criterion, mini-

mizing the absolute value of the largest excursion of a drug's serum concentration — that is, the *minmax* criterion — might be more suitable for use in digoxin therapy. Similarly, in defensive therapy, a physician might wish to use the *maxmin* criterion, in which the minimum benefit is maximized.

The analog to the integral square error (ISE) objective functions, in the context of a dynamic system, can be described by the following equation:

$$J_{ISE} = \int_0^T [\hat{x}(t) - x(t,p)]^2 dt \qquad (7)$$

where

J = criterion function
T = time
p = parameters used in the model
xt = experimentally observed value of an attribute at time t
$x(t,p)$ = value predicted by the model.

The variable p in the argument $x(t,p)$ indicates that the value for $x(t,p)$ depends on the parameters p that are used in the model. The mean square error (MSE) objective function can be expressed as follows:

$$J_{MSE} = \lim_{T\to\infty} \frac{1}{2T} \int_{-T}^{T} [\hat{x}(t) - x(t,p)]^2 dt \qquad (8)$$

The objective function that involves the integral of the absolute value of the error (IAE) is given by the following equation:

$$J_{IAE} = \int_0^T |\hat{x}(t) - x(t,p)| dt \qquad (9)$$

The J_{ISE} criterion is often used in *parameter identification* problems, such as those that are found in the compartmental models of biological systems. The J_{MSE} criterion is easy to handle mathematically and is particularly useful if a system's inputs are statistical in nature. However, it is uncertain whether J_{MSE} will be sensitive to small changes in parameters. Because of this, the J_{MSE} criterion is not usually recommended for parameter identification and modeling problems. Nevertheless, the design of a system that is relative to a given performance index should minimize the degradation of performance caused by parameter variations such as sensitivity analysis. Under circumstances such as these, the criterion J_{MSE} is useful. Although the J_{IAE} criterion assigns less relevance to large errors and more relevance to small errors than does the J_{ISE} criterion, J_{IAE} is more difficult to implement computationally.

It is possible to derive an objective function that is specifically suited to a given situation. The only difficulty with such made-to-order objective functions is that because little is known about their behavior, caution must be used when applying them.

Uncertainties, Value Conflicts, and Multiple Criteria

In the design, planning, and evaluation of many complex systems, it is not only difficult to choose representative goals but also to select one criterion. This methodological difficulty is particularly vexing because the arbitrary selection of the "best" action from among several alternatives, each of which would result in one of several possible outcomes or consequences, involves a considerable degree of subjectivity.

For example, consider the goal of improving the quality of a drug product. Does this goal imply that the cost of the product will be decreased or that its level of palatability will be increased? Will the product's drug-excipient interactions be minimized along with its recuperation period? Will the probability of relapse or complication be minimized as well? Should the minimization or optimization be accomplished with respect to the patient's recovery as a frame of reference or with respect to economics? If all the objectives are of a cooperative nature, it initially appears that there is nothing to worry about because all the objectives are intended to achieve the same goal. Nevertheless, there is an element of uncertainty in human decision making that must be taken into account.

The decision maker who faces a problem of such complexity must overcome several hurdles. For example, the individual must decide what constitutes an exhaustive set of alternative plans and which attributes are relevant in characterizing each plan. A fundamental question that underlies the selection of attributes is whether the attributes that the decision maker thinks are important are, in fact, the same attributes that people actually use in responding to the decision maker's actions. This leads to further questions concerning how and when the market survey should be performed. The answers to questions such as these depend on the ability of the decision maker to evaluate values and attitudes. This can become a complex measurement problem.

To appreciate the degree of complexity that is involved, it is useful to think of specific factors. Assume that a finite and exhaustive set of plans exists from which the decision maker must choose one plan to pursue. Such a set can be represented as follows:

$$P = \{p_1, p_2, \ldots p_m\}$$

where

P = plan
m = last in series of possible plans.

Each plan is evaluated with respect to a finite set of attributes or a finite set of criterion functions that can be nonlinear functions of the attributes. The set of attributes can be represented as follows:

$$A = \{a_1, a_2, \ldots a_n\}$$

where

A = attribute
n = last in series of possible attributes.

The set of criterion functions can be represented as follows:

$$F = \{f_1, f_2, \ldots f_n\}$$

where

F = function
n = last in series of possible functions.

The set of values that the attributes would attain for all plans can be arranged in an array as shown below:

	a_1	a_2	$\cdots$	a_n
P_1	x_{11}	x_{12}	$\cdots$	x_{1n}
P_2	x_{21}	x_{22}	$\cdots$	x_{2n}
P_i	x_{i1}	x_{i2}	$\cdots$	x_{in}
.	.	.		.
.	.	.		.
.	.	.		.
P_m	x_{m1}	x_{m2}		x_{mn}

where

i = number of plan

x = value that the attributes assume in a given plan.

In the arrangement shown above, the attributes represented by a_j, in which j equals 1 through n, might include toxicity studies, formulation time, stability studies, efficacy determination, bioavailability, and others. Even if all these attributes were measurable — an assumption that cannot be justified — they typically would not be measured with respect to the same unit of measurement. Some type of scaling on the raw attribute scores is necessary to facilitate comparison between attributes. One possibility is to express the attribute scores as standard deviations. This is done by replacing the x_{ij} values in the array shown above with y_{ij} values, which are defined according to the following equation:

$$y_{ij} = \frac{x_{ij} - \bar{x}_j}{\sigma_j} \qquad (10)$$

where $\bar{x}_j$ and σ_j represent the mean and standard deviation of x_{ij}, in which i equals 1 through m.

Alternatively, all the raw attribute scores can be mapped into a closed interval on the real line, although this mapping becomes arbitrary if one is dealing with nonphysical attributes. In addition, there is no universally acceptable basis for choosing one scale over the other, and a mapping into the real line assumes that every pair of attributes is comparable. Examples of much more general systems can be found in Kenneth Arrow's Nobel Prize-winning work on the voting paradox.[5] After the scaling has been accomplished, it is possible to solve the problem of multiple attributes using a number of techniques. There are several advanced books that deal with this topic, including those by Wagner, Arrow, Murakami, and Saaty.[5-8]

Conclusion

Although systems concepts are often used without consideration of the systems approach, the sequential representation of some of these concepts is useful in solving a problem optimally. This article has applied principles of the systems approach to situations in the pharmaceutical field to show the utility of systems concepts in solving problems of interest to pharmaceutical scientists.

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