

**A Task and Problem Focused Approach to the  
Development and Regulation of Drugs**

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### **Abstract:**

**This paper describes an approach by which the pharmaceutical industry and the Food and Drug Administration can communicate and interact more effectively in the drug development process. An electronic system is proposed that with constant updating would organize data and other information by issues. These issues—tasks and problems—would be carefully expressed, only as can be justified by available data. Using a shared task and problem list and an electronic space in which communication is captured, developers and evaluators would interactively resolve these issues in a stepwise fashion. This approach encompasses aspects of information and project management. It would also support the evolution of good review practice and increase understanding of the drug evaluation process. This proposal is intended to improve the effectiveness, efficiency, and speed of drug review at FDA without adding any burden to drug developers.**

Modern development of drugs and other therapies is among the most complex of all scientific endeavors. The involvement of numerous disciplines, huge volumes of data, interdependent decision making among professionals in different organizations, and demanding economic realities all contribute to this complexity. Rapid, efficient, and productive drug development is hindered by outmoded approaches to information and decision management. Cooperation among drug developers and regulators has increased significantly, and electronic technology has been applied to automation of data handling and analysis. However, the basic format for communication between developer and regulator remains largely unchanged. A new approach is needed for transfer and storage of information, which will promote and organize effective interactions among multiple participants. To succeed, this approach requires a system that is highly dynamic, “focused on issues”, simple to use, reduces work, and provides transparency. The salient features and advantages of such a system are described below.

In its most rudimentary form, this system would provide an intuitively organized and easily accessed **record keeping system** for all participants. Taken another step, the proposed system would **increase the quality, speed, and efficiency of communication** within and between the drug developing and regulating organizations. This system would thereby support a seamless, integrated approach to drug development and review. Ideally, it would begin with drug discovery and proceed through drug marketing. Applied in the context of the Food and Drug Administration (FDA), this approach would **help define, encourage and advance the understanding and use of the Good Review Practice concept**. This system would incorporate the latest electronic technology in the creation of a Web-like environment. The electronics,

however, must only support and not drive the system. It has been repeatedly shown that electronic technology provides relatively little when used to automate existing business processes, but can lead to quantum increases in productivity when used to catalyze and support fundamental changes in how the work is done.

The proposed system is called Task and Problem Focused Development and Regulation of Drugs (TPF). TPF is conceptually related to the Problem Oriented Medical System (PrOM) developed by Weed, Hurst, and others<sup>1,2,3</sup> to enhance diagnostic and therapeutic effectiveness in the practice of medicine. The fundamental principle of PrOM is that patients do not present with diagnoses, but with problems. Rarely is it appropriate to arrive at an immediate diagnosis of a patient with, for example, chest pain. Instead, the available data must be considered, and then the problem precisely stated only as can be supported by these data. As additional patient history information, physical findings, and laboratory data are collected, the problem can be stated more precisely. Ultimately, the diagnosis (problem statement) may be a serious disorder like angina pectoris, or a trivial one like costochondritis. At each resolution step, the physician must decide which explanations can be ruled out and which must continue to be considered.

PrOM's most obvious effect on medical practice has been to organize the patient medical record into a format that better serves the increasing complexity involved in describing human disease. Another useful feature of PrOM is that it allows the noting of problems that do not require further resolution but simply need to be kept in mind, for example, a drug allergy. Other problems may require further resolution but do not reach the threshold for active pursuit, for

example, an isolated lab abnormality that is expected to be normal the next time the test is repeated.

The practice of medicine and development of therapeutic products differ fundamentally in that medicine aims at maintaining a created product while drug development aims at creating a product. However, both medicine and drug development share a number of close analogies. For example, both enterprises constantly deal with the resolution of straightforward needs such as performing a bioavailability study or closing a laceration. These undertakings can be easily characterized as tasks. Both medicine and drug development also deal with complex challenges that are not straightforward, such as establishing a drug's causal relationship to an adverse reaction or to the etiology of an unusual symptom-sign complex. These challenges are better described as problems. Many issues in medicine and drug development fall somewhere within the middle of this task-problem spectrum.

In the field of drug development, it is easier and perhaps more appealing to avoid categorizing issues as “problems” or “tasks.” The proposed Task and Problem Focused approach simply encompasses all issues that require action or possible future consideration in the development and regulation of therapeutic agents.

## **The Concept of Task and Problem Focus**

TPF is analogous to PrOM in its application to the drug development and review process. First, TPF would provide an easily used format for **record keeping and problem tracking**. TPF would also **facilitate clear communication** among drug developers and reviewers. Most importantly, TPF, like PrOM, would **entail an intellectual discipline** in which reviewers and developers alike could precisely state each issue—whether a task or problem--only as the available data allow. Both TPF and PrOM are issue-based approaches, in contrast with their predecessor approaches, which were categorical. The current approach to record keeping in the drug development process involves amassing information and sorting it in pre-defined categories. Conclusions are enumerated after pulling out relevant information from the categories in which the information is stored. TPF entails the examination of information as it is obtained and organizing it among new or previously identified issues, known as tasks or problems. With TPF, information is not just organized but it is assessed as it is stored. Ideally, this highly interactive assessment would occur between drug developer and drug evaluator. As a part of this process, additional information, e.g., concerns, decisions, commitments, would be created and stored.

Unlike PrOM, which deals only with problems, TPF addresses both tasks as well as problems. Tasks are not included in PrOM because PrOM developed during a time when preventive medicine was not emphasized, and medical practice was largely conducted in response to problems. In the development of drugs, the accomplishment of tasks is just as important as the

resolution of problems. Tasks in drug development include performing a specific kind of clinical trial, animal test, or biostatistical analysis. Most tasks are obvious or can be derived from various kinds of instructions. For example, an FDA guidance for developing a therapeutic indication can be converted into a list of specific tasks for the drug developer. The value to the drug developer of knowing these tasks prior to conducting the first human study is obvious. The detailed and comprehensive expression of specific tasks for developing therapies could significantly facilitate drug development.

### **Level of Resolution Principle**

The level of resolution principle is fundamental to TPF. It provides a means for the accurate and precise description of a given problem/task based only on available information. Since additional information will usually continue to become available, the description of the problem/task, according to this principle, will change dynamically. The practice of medicine itself is illustrative: prior to PrOM, physicians were forced to arrive at a presumptive diagnosis on the basis of very limited data. A patient with severe chest pain, for example, would require a diagnosis at the time of hospital admission. On the basis of the patient's history and an electrocardiogram, the physician might write "myocardial infarction" as the diagnosis. The patient could turn out to have any number of problems ranging from indigestion to dissecting aortic aneurysm. The problem-oriented approach demands that the physician state not a diagnosis, but the problem precisely as the existing information allows. Thus, on admission the

problem in the above case might be stated as cardiac chest pain. A final diagnosis would be achieved only after the required data became available.

It is also increasingly understood that medical diagnostic categories are arbitrary, blurred, and limited by the current inadequate understanding of pathophysiology. Many medical conditions are poorly understood syndromes or appear on a spectrum, such as those like scleroderma-CREST syndrome<sup>1</sup> or multiple myeloma-monoclonal gammopathy. Patients with these conditions are not amenable to immediate categorization. The level-of-resolution principle serves to keep the physician's mind open to a wider range of diagnostic and therapeutic options.

Drug development and review involve very similar diagnostic challenges. When a previously unreported adverse reaction associated with drug therapy occurs, the reviewer would be unwise to draw a final conclusion about a causal relationship. It would also be unwise to ignore and fail to record this report just because it is the first case. The reviewer should simply state and record the problem. In this case, it would be one report of X reaction associated with drug therapy Y. As additional cases are reported, the problem might be stated: 22 cases of X reaction out of 1100 patients exposed to therapy Y. After receiving four reports of positive re-challenges, the reviewer might be justified in concluding that this reaction is caused by the drug and modify the description of the problem accordingly. However, this problem can be resolved further. Epidemiological data could reveal an occurrence rate, that the reaction occurs only in a small ethnic subgroup, or occurs only when the patient is taking another medication.

Conversely, FDA reviewers are inundated with thousands of adverse drug reaction reports that will never prove related to therapy. The reviewer needs a simple, cost-effective means for expressing and recording these problems. The level-of-resolution principle provides such an approach and prevents premature conclusions.

This principle is not confined to safety "problems," but is important in describing tasks to show "efficacy". A clinical study alone does not prove that a therapy is effective. The results merely show that one or more measures of effectiveness could be attributed to therapy with a calculated probability. A bioequivalence study may prove that two drug products are equivalent according to a chosen regulatory standard, but one study may not prove bioequivalence in every situation. Thus, the precise expression of a therapy's efficacy or effectiveness will change as more information is acquired

It is important for reviewers to distinguish between the positive findings of a single study--and the ultimate conclusion based on multiple studies that a drug is effective and safe. Sometimes, many studies can only support a tentative conclusion that a drug has a favorable benefit/risk relationship. This assessment may change years after drug approval. A reviewer, by precisely stating at the proper level of resolution just what has been learned from a study, could state what remains unknown and what exactly needs to be done.

### **TPF as a Means of Supporting More Effective Communication**

A powerful feature of TPF is its potential to promote continuous communication between the developer and the evaluator as they work to resolve each issue. TPF would, thereby, support the seamless development and review of therapeutic agents from drug discovery to post-market surveillance. This approach ideally would start with the drug developer during the earliest stages of compound isolation and discovery. A task and problem (T&P) list would be initiated as each new compound is identified. Most such lists would never be seen by the FDA, but when an original Investigational New Drug Application (IND) is submitted, it would be accompanied by a task and problem list. It would summarize current manufacturing issues and pre-clinical problems. The list would also include any clinical problems identified in previous studies conducted outside the United States. The list could even present the sponsor's interpretation of what clinical studies will be required for New Drug Application (NDA) approval as understood from existing guidelines and precedents. After reviewing the application, Agency professionals would suggest to the company additions or changes to the task and problem list, and this interactive, issues oriented-process would proceed.

The T&P list would be updated as additional information was received. The list would begin to reflect specific agreements between the sponsor and Agency about the details of additional animal and clinical studies. It would also include administrative problems and tasks. TPF would eventually help to smooth the interface between IND and NDA review. Consistently reviewing the huge volume of IND submissions on a substantive level is nearly impossible without a standardized, more accessible means of presenting information to reviewers. During the IND

phase of drug evaluation, an issues-oriented approach would allow drug developers to interact more closely with the assessment team to design studies more efficiently, quickly, and with a greater probability of achieving success. With greater reviewer participation in the study design stage and a more accessible data base, reviewers could provide more substantive evaluations at earlier stages. It is conceivable that major pivotal studies, particularly of high priority therapies, could thereby be definitively reviewed prior to formal NDA submission. Pre-NDA review could lead to earlier discovery of issues requiring resolution that would otherwise delay drug approval.

It is important to note that TPF should add no additional burden or obligations to sponsors or to reviewers, nor does it require the sponsor to submit any more information than is currently required. TPF would simply be a commonly accepted format for documenting and communicating what would otherwise be stored and transmitted by both parties. TPF serves the sponsor by providing a standard format for presenting information that enhances Agency response. A sponsor, for example, could solicit an early decision on what kind of pivotal studies would be required for indication approval by including on the list a specific description of the studies (i.e., task) believed to be required. The reviewer could accept this statement or respond that "we haven't decided what will be required" and, therefore, ask that the task be expressed at a low level of definition (e.g., two pivotal clinical studies required, description pending). At the very least, with this approach to communication, the sponsor could put their proposal on a very visible record and expect a timely response.

## **TPF in an Electronic Environment**

Although a T&P list could be maintained manually on paper, it would be more versatile if displayed via a specifically adapted groupware program. Groupware is an increasingly important tool of business communication and process re-engineering that provides an electronic environment to facilitate communication and work among several parties. Increasing expectations of greater speed, quality and efficiency in the new drug approval process necessitate that Agency reviewers utilize an interactive and integrated review model. A carefully designed groupware environment is essential for fully achieving the potential benefits of this model. In the context of interactive, integrated review, the T&P list can be viewed as the "page everyone works off."

A T&P list for a particular drug can be visualized as a computer screen presentation of an up-to-date set of all precisely defined problems and tasks that remain to be resolved. Hypothetical examples of T&P lists are presented in the Appendix. The first screen reveals to any authorized person, in effect, the "tip of the iceberg,"--that is all the active tasks and problems at their present level of resolution. This first screen also serves as the table of contents for the entire database and administrative file. Appropriate software, however, will allow the viewer to cone down on one problem or task and follow it back through each stage of decreasing resolution to its beginning. Furthermore, with the click of a mouse, the viewer could see a menu of the data, statements, communications, or reviews that allowed a task or problem to be taken to a higher level of resolution. If needed, the viewer could then pull up any of these items on the menu.

Thus, the electronic incarnation of TPF serves as a means of organizing and storing the entire database and administrative record of a drug development project from its inception through post-approval surveillance.

As an immediate benefit, TPF would provide a way to highlight issues that require attention. The retrieval of any needed data or information would also be facilitated by a TPF system. However, TPF's record keeping and retrieval features are essentially just a useful automation of the manual or electronic processes presently employed. TPF provides a means for going a step beyond automation of current business processes. If TPF were the basis for a standard, integrated communication system for all drugs reviewed by the Agency, it could serve as a framework for organizing the entire database of drug research and review. Such a system could be queried by key word or term, indication, drug class, problems, specific kinds of studies, statistical methodologies, etc.

This would allow a kind of meta-analysis of not just experimental data, but of the reviewing practice itself. For example, a reviewer might have a drug associated with isolated, transient transaminasemia during the first 3 months of therapy. Studying the experience of other reviewers facing the same problem would be beneficial. This could readily be accomplished by querying the system for all drugs in which transient transaminasemia was noted. If this yields too many cases, further specifications could be applied to narrow the field. The reviewer could then observe the way that other drugs with this problem have been handled. Instructive case studies could easily be provided by retrieving any TPF drug development record. A meta-view of these

case studies might reveal, for example, that a liver biopsy never served any value when transaminase levels remained below a certain group average and duration.

### **TPF as an Intellectual Approach**

TPF encourages and documents the resolution of tasks and problems in small, well-defined bites, which is a subtle but powerful feature. In the course of reviewing IND and NDA files, virtually all reviewers engage in task and problem resolution, but lack a systematic approach for this purpose. This is a substantial impediment to collaboration of team members during the review process. More fundamentally, this lack of system impairs the reviewer's inner-dialogue, analytical thinking, and ability to express the steps of logic that were taken in coming to a conclusion .

A typical approach to reviewing an NDA first involves mastering the database contents. The reviewer then reaches broad, sweeping conclusions without formally outlining the reasoning steps leading to the conclusions. The skilled reviewer makes notes along the way and, in the discussion section, presents lines of reasoning. Yet, even the skilled reviewer tends to assimilate large chunks of information and then analyze these chunks in long strides. TPF allows and encourages making smaller, logical steps based on assessments of discrete pieces of information. Thinking that involves large, logical steps stultifies the review process and is more likely to lead to faulty or premature conclusions. Long, logical leaps are also usually harder for others to

follow. TPF, however, is a system that constantly demands precise statements of the current understanding based on available data. The ability to make progress in small steps is conducive to a steadier work pace and greater productivity.

### **Summary**

TPF is an issues-oriented approach that in addition to providing conventional record and retrieval functions, also focuses intellectual energy of both the drug developer and evaluator on all issues relevant to the development and approval processes. While TPF would clearly help all professionals involved in these processes to use their time more productively, it would also promote continuous improvement not just of the review product, but of the review process itself. The intent of this approach is that ultimately much needed therapies would be made available faster, more efficiently, and less expensively and that information about these therapies would be expanded and better organized. The following section provides interested readers with additional details about the TPF concept.

### **Appendix:**

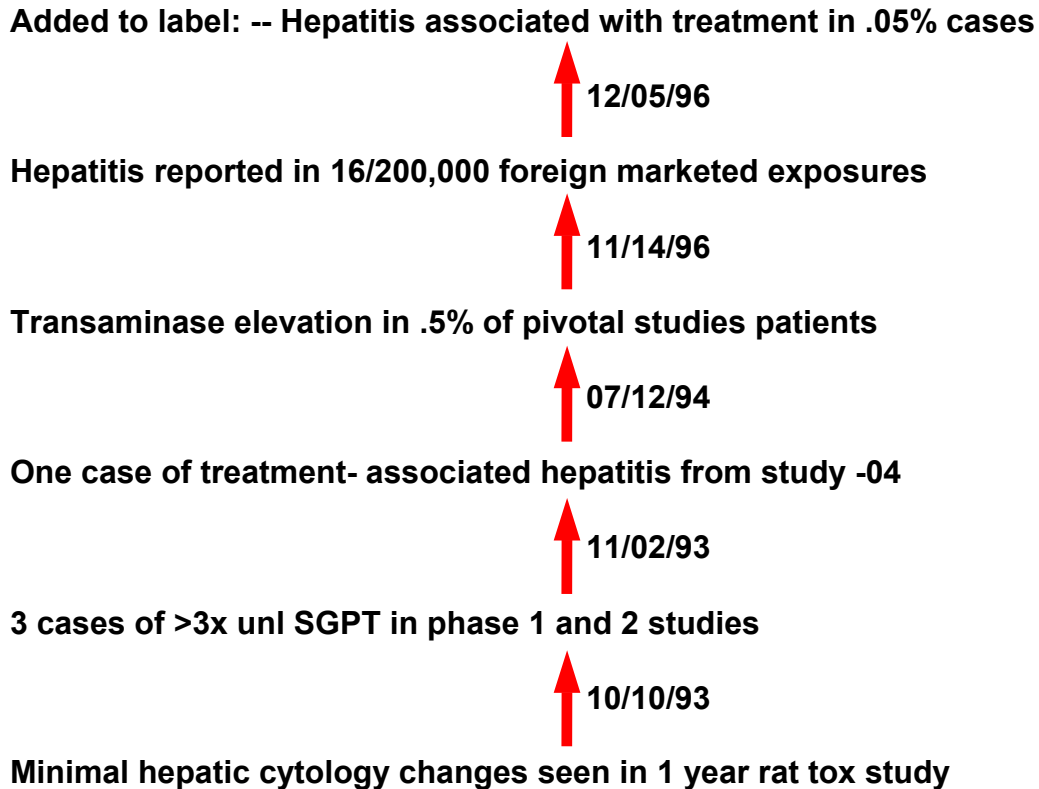
## **"On-Paper" Examples of TPF Applied to Drug Development**

TPF can most readily be understood by examining a T&P list for a drug at any point during the developmental-marketing process. Such a list could be used as the skeleton of a record-keeping system that begins with drug discovery and continues through marketing. Because additional information becomes available throughout this process, the tasks and problems are constantly being restated at higher levels of resolution. Because each change is based on one or more pieces of information, this list, when electronically formatted, can serve as a table of contents to a drug's entire development/marketing process. Imagine the T&P list examples at the end of this article as being the initial screen that appears on a viewer's computer after entering the IND/NDA number. The examples show only the latest expression of each task/problem. In its electronic version, the reviewer can go "backwards" from this "tip of the iceberg" to see, at the click of a mouse, the entire series of increasingly less-resolved expressions of the tasks/problems that precede the current version. To understand the functionality of an electronic implementation of the TPF approach, examine the following task/problem entry:

**# 22 Added to label: Hepatitis assoc. with treatment in .05% cases**

If desired, one could bring up the progression of increasingly less-resolved statements that preceded the current statement. A screen that looks something like this would appear:

**#22 Task/Problem Resolution Sequence:**



Restatement of a task or problem at a higher level of resolution requires additional information to be submitted and discussed. This would have occurred prior to each of the steps above. The interested viewer could easily retrieve the information and discussion that formed the basis of any restatement. As an example, one could view the basis of resolving the problem to the current statement by clicking on the date, “12/05/96.” This would bring up a menu like the one on the following page:

**Resolution menu – 12/05/96**

1. **sponsor documents**
  - a) protocol 2201
  - b) clinical study report
  - c) response to 7/7/96 request
  - d) response to 8/3/96 request
  
2. **FDA documents**
  - a) M.O. review (6/23/96)
  - b) M.O. review (8/14/96)
  - c) Project manager memo
  
3. **On-line communication**
  - a) 05/02/96 sponsor-fda
  - b) 06/24/96 fda-sponsor
  - c) 06/26/96 sponsor-fda
  - d) 07/01/96 sponsor-fda
  - e) 09/11/96 fda-sponsor
  - f) 11/11/96 sponsor-fda

The viewer could then retrieve any of the listed documents or discussions by simply clicking on the entry. The entire document would become available, but in the case of long documents, the relevant passages could be flagged and the document would open at the first flagged passage.

### **Examples of T&P Lists at Different Stages of Drug Development**

## Compound 1222

### A. Manufacturing

1. Production scale under development →

### B. Pharmacotoxicology

1. hepatic adenomas in 1 year rat study →<sup>6/7/89</sup> accepted as species specific by FDA
2. serum transaminasemia in 5/10 dogs from high dose group of 1 year study →<sup>3/9/90</sup> to be stated in label
3. carcinogenicity study, final report 1/95 →
4. lens opacities in 3/10 dogs from high dose group of 1 year study →<sup>9/9/91</sup> to be stated in label
5. reprod. studies →<sup>9/9/91</sup> category X

### C. Clinical

1. Pharmacokinetics studies
  - a. P-PD, bio HAD-420
  - b. bioequivalence →<sup>4/4/94</sup> review complete
  - c. drug interactions no deficiency
4. Pivotal study 1222-12, 1/3 primary endpoints failed →<sup>4/7/92</sup> advisory committee 9/7/94
5. Study 1222-14, primary efficacy confirmed in 3/3 end points →<sup>1/5/93</sup> advisory committee
9. Transaminase elevation in 22 patients →<sup>2/4/93</sup> label to recommend q4 week serum enzyme testing to 6 months
10. One case of Stevens-Johnson →<sup>7/6/92</sup> patient treated with Bactrim for UTI →<sup>8/3/92</sup> not related to 1222 tx
15. Five new lens opacities in 5/1013 patients of studies 1222-12,-14,-16 →<sup>2/4/93</sup> propose yearly slit lamp exam to be recommended in label, propose phase 4 study to FDA
17. Decreased clearance with theophylline (122-23) →<sup>5/2/93</sup> consult to R. Woosley →
18. Elevated serum creatinine levels in 9/12 subjects from study 1222-23 →<sup>4/4/93</sup> drug interference with picric acid method →<sup>7/1/93</sup> state in label

### D. Administrative

1. FDA guidelines for oral hypoglycemics under revision →
5. NDA review completion date 12/1/94 →
6. NME requires ODE II approval →
9. Patent expires 9/23/96 →

## Compound 1324

### A. Manufacturing

1. racemic mixture →
2. 5% impurities →
3. 0.8% yield, multi-step process →

### B. Pharmacotoxicology

1. modest efficacy in ob/di rat →
2. estimated therapeutic index=2.0 (dog) →

### C. Clinical

1. Initial IND submission under FDA review →

## Compound 1355

### A. Manufacturing

1. stereoisomer of C-1324<sup>5/5/04</sup> → pyridinium moiety under NMR analysis

## Compound 1111

### A. Manufacturing

1. stereoisomer C-1324 →

### B. Pharmacotoxicology

1. ~~2/3/09~~ minimal activity <sup>3/9/79</sup> → discontinued

## Compound 1122

### A. Manufacturing

1. Stereoisomer C-1200  $\xrightarrow{9/9/79}$  unstable at 25  $\xrightarrow{1/7/78}$  discontinued

**Compound 1200**  $\xrightarrow{12/31/90}$  NDA approved  $\xrightarrow{2/1/90}$  marketed

### C. Clinical

1. post-marketing study 1200-74  $\rightarrow$
2. post-marketing study 1200-75  $\rightarrow$
3. non-company sponsored UK mortality study  $\rightarrow$
4. Three reports SIADH  $\xrightarrow{2/1/92}$  consider label statement if additional reports received  $\rightarrow$

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