

Knowledge Acquisition Session Report

Session Date: Dec 9,1997

Session Topic: NCI Regulatory Affairs Branch

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Organization: CTEP, National Cancer Institute

Type of Session:

Interview Task Analysis Scenario Analysis
 Concept Analysis Observation Structured Interview
 Other:

Documentation: KA Session Report, Transcript of the Interview of 12/9/97

General Topic Area

NCI Regulatory Affairs Branch

Session Goal

Outline the role that the Regulatory Affairs Branch plays in bringing an Investigational New Drug to the FDA for clinical trial approval

Report Summary

Dale Shoemaker, Ph.D. is the Chief of the RAB (Regulatory Affairs Branch) of CTEP (Cancer Therapy Evaluation Program). RAB personnel collect and prepare the documents needed for CTEP IND (Investigational New Drug Application) submission. The Coordination Group of the RAB negotiates research and development agreements with pharmaceutical companies. The Drug Regulatory Affairs Section of the RAB acts as a liaison between the NCI and the FDA (Food and Drug Administration). RAB is responsible for the dissemination of Adverse Events to FDA and principal investigators.

Regulatory Affairs Branch

The National Cancer Institute (NCI) is comprised of eight divisions. Each division contains Programs. Each Program contains Branches. Figure 1 shows the Regulatory Affairs Branch's place in the NCI organization:

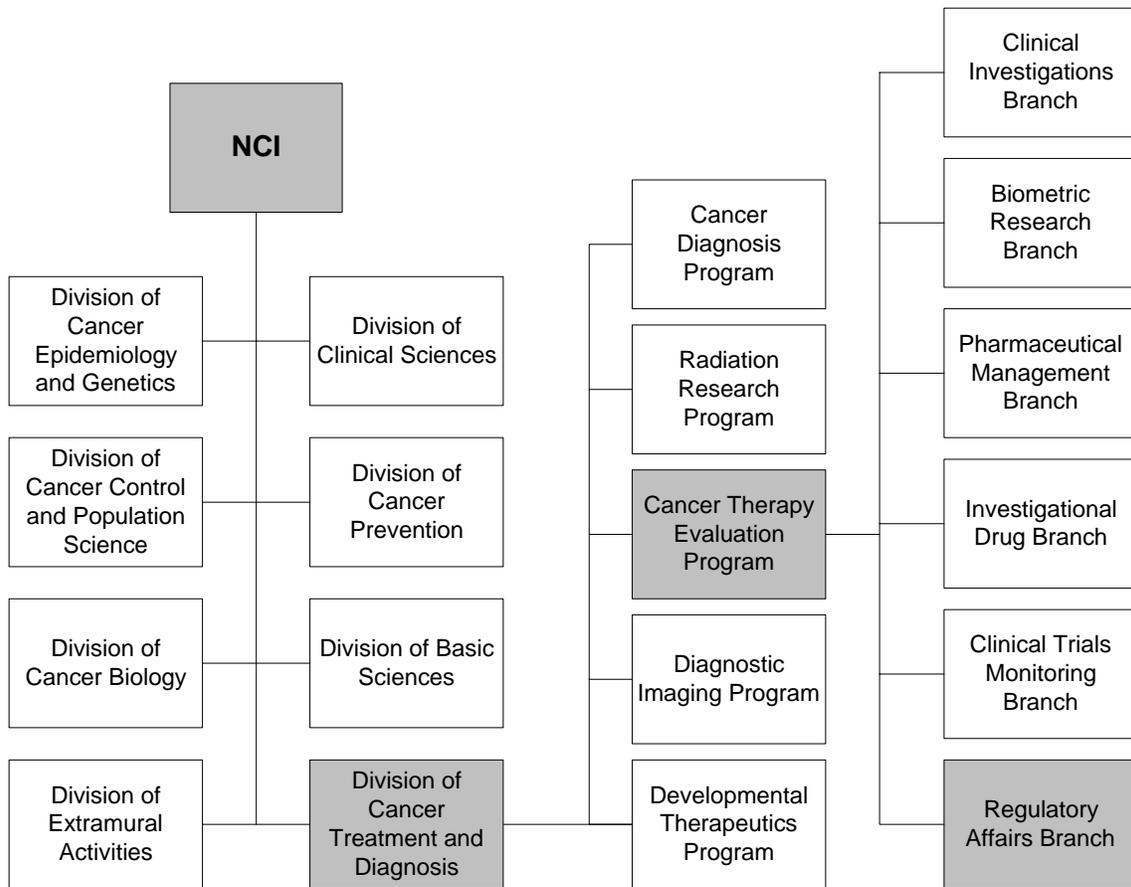


Figure 1: The Regulatory Affairs Branch within the NCI

The NCI's Division of Cancer Treatment and Diagnosis contains the Cancer Therapy Evaluation Program (CTEP), which includes the Regulatory Affairs Branch (RAB).

RAB Missions

The RAB performs two main functions:

1. Negotiate agreements with pharmaceutical companies who want to test new agents for use in clinical trials
2. Prepare the Investigational New Drug Application (IND) for clinical studies conducted through CTEP

Figure 2 shows how the RAB is organized to perform these two functions:

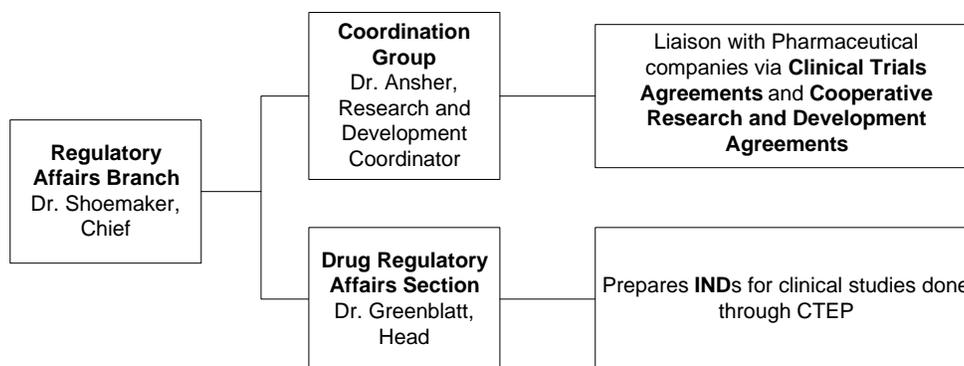


Figure 2: Organizational chart of the Regulatory Affairs Branch

The Coordination Group interacts with pharmaceutical companies. The Drug Regulatory Affairs Section (DRAS) interacts with the Food and Drug Administration (FDA).

Coordination Group

The Coordination Group is responsible for developing and implementing research agreements with industry collaborators who wish to use a new agent in a clinical trial. The group negotiates two types of research agreements:

1. Clinical Trials Agreement
2. Cooperative Research and Development Agreements

The Coordination Group negotiates Clinical Trials Agreements (CTA) when a new drug will be tested in a human clinical trial.

The Coordination Group negotiates Cooperative Research and Development Agreements (CRDA) when CTEP is working with an outside collaborator to further develop a technology for commercialization.

Drug Regulatory Affairs Section

DRAS serves as a liaison between the Food and Drug Administration and organizations preparing to conduct a clinical trial. Organizations can include any program within the Division of Cancer Treatment and Diagnosis. RAB also receives IND proposals from cooperative groups, and pharmaceutical companies.

RAB's Involvement in the Investigational New Drug Process

The Food and Drug Administration's (FDA) Form 1571 is the two-page Investigational New Drug Application (IND) that is used as the legal mechanism under which experimental drug research is conducted in the United States. The FDA must approve the IND before a study may begin administering experimental drugs.

The process for submitting an IND application involves the management of large amounts of data as well as communication with a number of participants.

Compiling the IND

Each IND submitter is responsible for conducting the necessary pre-clinical work including:

- Anti-tumor activity
- Toxicity
- Pharmacology data related to the agent

Further KA is required to determine if other pre-clinical work is required. RAB personnel meet with FDA staff every third Thursday to discuss issues of agent and IND approval. IND submitters provide additional data as requested during the meeting.

DRAS personnel write summaries of the data and compile the IND in the FDA specified format.

DRAS personnel must also collate and staple each IND application. A typical IND can contain thousands of pages in multiple volumes. IND contents include:

- Schedule used in pre-clinical testing
- Pre-clinical trial data
- Proposed schedule for clinical trial
- New clinical protocol
- Protocol amendments
- Expected Adverse Events (AE)
- Pharmaceutical data
- Letters of Intent

DRAS attaches all required data to Form 1571 and submits it to the FDA. The FDA sends a receipt of the IND by paper letter. Once the IND is submitted, the FDA has thirty days to review and approve or disapprove it. The RAB learns of the approval by phone call, fax, or through email. The FDA sends a formal paper approval letter a month after approving the IND.

Tracking IND Submissions

Form 1571 contains explicit instructions for the numbering of IND submissions. The initial IND is the primary document and is identified as “Serial Number: 000”. Additions to the initial IND are numbered consecutively in the order in which they are submitted. DRAS personnel attach a new Form 1571 to each addition listing the new serial number.

The RAB maintains a database index of IND submissions. With the aid of this database, RAB personnel are able to track any additions to an IND. Figure 3 illustrates the IND numbering system.

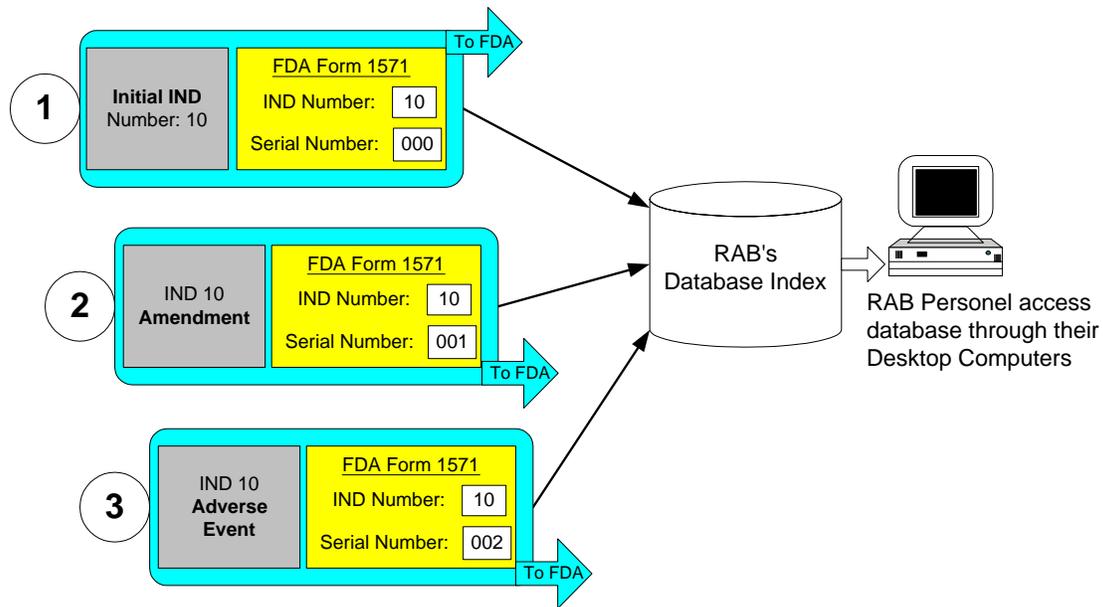


Figure 3: RAB database index of each IND Submission

The database helps RAB personnel refer to a specific document when queried.

Adverse Events

An unfavorable reaction to a Chemopreventive agent is called an Adverse Event (AE). If the event is serious enough to cause unexpected harm to, or risk the life of the patient, it is categorized as a Serious Adverse Event (SAE). The FDA receives a report from RAB documenting all AEs and SAEs.

Expected Adverse Events

Expected Adverse Events are anticipated reactions to an agent. Based on pre-clinical research, the initial protocol specifies the criteria for expected adverse events. Expected, or known events are not reported to the FDA until the annual report.

How RAB learns of an Adverse Event

Principal Investigators report adverse events to RAB personnel. The frequency of the reporting depends on the phase of the trial:

- Phase I (reporting frequency is most intensive)
- Phase II (reporting frequency is done a little less often)
- Phase III (reporting is done annually)

How the Food and Drug Administration learns of an Adverse Event

The RAB submits an annual report to the FDA on each protocol that includes all adverse events (expected or not). The FDA requires all adverse events to be categorized by body site according to National Medical Terminology codes.

Table 1 shows the criteria the RAB uses when reporting AEs to the FDA.

Circumstance	Immediate Reporting or Annual Report to the FDA
Expected Event	Annual
Unexpected Event	Immediate: Called in within three days with a written report submitted within ten days

Table 1: Adverse Event Reporting Schedule

Investigational Drug Branch (IDB) staff physicians determine whether an adverse event was drug related (i.e. expected) or not.

How other Principal Investigators learn of an Adverse Event

Principal Investigators (PI) receive information about adverse events during regularly scheduled teleconferences with RAB personnel. RAB also uses fax, individual phone calls, and letters to inform PIs of AEs. Principal Investigators then monitor their own patients for any recurrence of the AE.

Progress Towards Needed Electronic Mechanisms

The Food and Drug Administration (FDA) and RAB personnel are developing electronic mechanisms to ease the workload created by large amounts of paper documents. The FDA has guidelines for the formatting of electronic IND submissions. RAB and the FDA are developing a web-based system for the reporting of adverse Events. Both groups are also defining the criteria for reporting adverse events.

RAB requires an electronic protocol review and tracking system with the following mechanisms:

- Track all documents used in the IND process
- Provide accurate and up-to-date patient accrual information
- Track protocol status via an electronic complete sheet
- Track all Adverse Events by protocol and body site

Entries for Domain Dictionary

Phase I trial: Phase I trials are the first step in testing a new treatment in humans. These studies test the best method of administering a new treatment (for example, by mouth, intravenous infusion, or injection), as well as the best dose. The dose is usually increased a little at a time in order to find the highest dose that does not cause harmful side effects. Because little is known about the possible risks and benefits of treatments being tested, phase I trials usually include only a small number of patients who have not been helped by other treatments.

Phase II trial: Phase II cancer trials test whether a new treatment has an anticancer effect (for example, whether it shrinks a tumor or improves blood test results) and whether it works against a certain type of cancer.

Phase III trial: Phase III trials compare the results of people taking a new treatment with results of people taking standard treatment (for example, which group has better survival rates or fewer side effects). In most cases, studies move into phase III trials only after a treatment seems to work in phases I and II. Phase III trials may include hundreds of people.