

## Director's Forum

# Advanced Practice Programs in Hospital Pharmacy – Investigational Drug Services

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The *Director's Forum* series is written and edited by Michael Sanborn and Robert Weber and is designed to guide pharmacy leaders in establishing patient-centered services in hospitals and health systems. Another specific goal of this column is to address many of the key challenges that pharmacy directors face today, while providing information to foster growth in pharmacy leadership and patient safety. This month's Forum focuses on developing a pharmacy-based investigational drug service in a hospital pharmacy department. As part of a patient-centered pharmacy department, a investigational drug service can significantly contribute to the research mission of a hospital.

### INTRODUCTION

Hospitals can be primary centers for clinical research investigations on new or investigational drugs; it is likely that hospital pharmacists will at some time be involved in the handling of these special drugs. The extent of the involvement will depend on the type of hospital facility, the willingness of the pharmacist to accept responsibility for investigational drugs, and the amount of service required. In order to carry out this role effectively, it is important for the pharmacist to know the laws governing the use of investigational drugs and the general methodology for handling and evaluating new drugs.

The development in recent years of new classes of drugs and new methods of creating drugs, as

well as new regulations and guidelines related to research has produced an evolution in the way in which research is performed in the United States and in the role pharmacists play in carrying out research. The pharmacy director developing a patient-centered pharmacy service within a hospital can explore this role for pharmacists in developing and coordinating a pharmacy-based investigational drug service (IDS). In fact, the role of the pharmacist in providing IDS has been well-known and documented since the early 1970s.<sup>1,2</sup>

While the Food and Drug Administration (FDA) does not require that investigational drugs be stored and dispensed through a hospital pharmacy,<sup>3</sup> most hospitals require that all clinical investiga-

tional drugs be registered and stored by the hospital pharmacy for dispensing on orders from specifically authorized investigators. This policy provides control and monitoring of the security and storage of these medications. Finally, most hospitals have established a policy that no investigational drug be administered to a patient by a nurse or physician unless it bears a pharmacy department control or registration number. As a result of these policies, pharmacy departments should be actively involved in the dispensing of investigational drugs.

The objective of this article is to provide the pharmacy director with an introduction to developing pharmacy-based IDS. The specific aims of this article is to (1) describe key fundamental terms related to investigational drugs; (2) list the steps in developing pharmacy-based IDS; (3) describe the structure and operations of pharmacy-based IDS; and (4) list the metrics to measure the effectiveness of the service.

### FUNDAMENTAL TERMS RELATED TO INVESTIGATIONAL DRUGS

At the present time the clinical investigation and marketing of new drugs is governed by the 1938 Federal Food, Drug and Cosmetic Act and the Kefauver-Harris Amendments of 1962. These statutes have been implemented by a series of FDA regulations that were published in the Federal Reg-

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**Table 1. Basic and Specialized Pharmaceutical Services for Investigational Drugs**

<i>Basic Services</i>
Maintain drug accountability logs
Medication computer order entry
Prepare dispensing procedures
Maintain specific logs wherever the drug is stored
Prepare drug monographs
Verify that the patient has signed the informed-consent document
Provide inservice education to pharmacy staff
Provide patient counseling pre-discharge
Provide inservice education to nursing staff
Obtain written prescriptions
Maintain patient profiles
Prepare patient reminder cards
<i>Specialized Services</i>
Compound special dosage forms
Generate randomization schemes
Assist in protocol development
Use special drug-delivery systems
Assist in subject recruitment
Review charts and collect data
Perform clinic audits and inspections
Administer doses to patients

ister and the Code of Federal Regulations. In essence, these laws and regulations define the conditions under which clinical investigational drugs may be shipped in interstate commerce and delineate the evidence for the claimed safety and efficacy of the drug, which needs to be provided prior to its marketing.<sup>4</sup> Federal regulations allow investigators to delegate these responsibilities to pharmacists and practice guidelines recommend pharmacist involvement with investigational studies.

**Investigational New Drug Applications (INDs)**

Any organization seeking to sponsor clinical trials with experimental agents must first submit an

IND to the FDA. The IND is the legal mechanism under which experimental agent research is performed in the United States. No experimental agents may be administered to patients for research in the United States without an IND. All IND sponsors have obligations, which are specified in the regulations of the FDA. The initial IND submission by the sponsor to FDA is a lengthy document that sets forth the experimental rationale for human testing, including results of animal toxicology studies, manufacturing data, purity and stability information, and an initial plan of clinical investigation. The IND is the official record at the FDA of the sponsor's clinical research with the agent.

**Phases of Clinical Drug Investigation**

The clinical investigation of a new drug is divided into 3 phases and is directed toward producing substantial proof for the safety and efficacy of the drug.<sup>5</sup> Phase 1 trials determine a safe dose for subsequent trials and define acute effects on normal tissues. In addition, these trials examine the agent's pharmacology and may reveal evidence of biologic activity. The purposes of these studies include the determination of human toxicity, absorption, metabolism, elimination, pharmacodynamics, preferred route of administration, and safe dosage range. Phase 1 studies involve a small number of persons (20 to 80) and should be conducted under carefully controlled circumstances by qualified clinical investigators. Phase 2 studies are conducted by clinicians familiar with the methods of drug evaluation, as well as the disease being treated, and drugs currently in use for this condition. These carefully supervised studies are designed to demonstrate the new drug's efficacy and relative safety. Phase 3 studies are intended to assess the drug's safety, effectiveness, and most desirable dosage in treating a specific disease in a large group of subjects. The studies should also be carefully monitored, even though they are extensive. In each phase of a clinical drug trial the FDA receives continuous reports on the progress of each phase. If the continuation of the studies appears to present an unwarranted hazard to the patients, the sponsor may be requested to modify or discontinue clinical testing until further preclinical work has been done.

**Qualifications of Investigators**

The sponsor (usually a phar-

**Table 2. Examples of Investigational Drug Storage and Control Accountabilities**

Store the agent in a secure location, accessible to only authorized personnel, preferably in the pharmacy
Maintain a careful record of the receipt, use, and final disposition of all investigational agents received
Maintain appropriate storage of the investigational agent to ensure the stability and integrity of the agent
Return any unused investigational agents to the pharmacy at the completion of the study or upon notification that an agent is being withdrawn
Each investigational agent should be stored separately by protocol. If an agent is used for more than 1 protocol, there should be separate physical storage for each protocol
Each agent should be accounted for separately by protocol. If an agent is used for more than 1 protocol, there should be a separate Drug Accountability Record Form (DARF) for each protocol
There should be a separate DARF for each agent in a multiagent protocol
Separate accountability forms should be maintained for each different strength or dosage form of a particular agent (eg, an agent with a 1- and a 5-mg vial would require different DARFs for the 1- and 5-mg vials)
The DARF has been designed for use at each location where agents are stored, eg, main pharmacy, satellite pharmacy, physician's office, or other dispensing areas
The DARF is also designed to accommodate both dispensing records and other agent transaction documentation (eg, receipt of agent, returns, broken vials)

maceutical manufacturer) of an investigational new drug will ask the clinical investigator to supply the following information before shipping the investigational drug to the investigator: a statement of his education, training, and experience as well as any information regarding the hospital or other medical institution where the investigation will be conducted; special equipment and other facilities. The training and experience required will vary, depending upon the kind of drug and the nature of the investigation. In Phase 1, the investigator must be able to evaluate human toxicology and pharmacology. In Phase 2, the investigator should be familiar with the conditions and the methods of human toxicology and pharmacology evaluation. In Phase 3, in addition to the experi-

enced clinical investigators, other physicians not regarded as specialists in any particular field of medicine may serve as investigators. At this stage, a large number of patients may be treated by different physicians to obtain a broad background of experience with the drug.

#### Obligations of Investigators

The primary responsibility for disposition of investigational drugs in a clinical study is the responsibility of the principal investigator, usually a licensed physician. As a result, the investigator is obligated to obtain patient informed consent, maintain adequate records of drug preparation and dispensing, maintain study case and progress reports, and report adverse reactions.

#### FDA Authority in the Investigational Use of Commercially Available Drugs

The FDA has no authority over the practice of medicine and cannot require a physician to prescribe a specific drug for a particular illness. Many drugs are prescribed for conditions not approved by the FDA, or in an "Off Label" manner. Physicians are encouraged to submit an IND when they use a drug regularly for purposes other than those approved by the FDA. The FDA can then accumulate data on the safety and efficacy of the drug for such treatment and can share the information with other physicians. The University of Pittsburgh Medical Center has implemented a process for intensive review of Off-Label medication use through its Pharmacy & Therapeutics (P&T) Committee and as a mechanism for providing a cost and safety check for this type of medication use.<sup>6</sup>

#### Patient Informed Consent

Each patient should complete a document referred to as informed consent. The purpose of this document is to educate patients on the known risks of each therapy or procedure. Each informed-consent document must be protocol-specific and contain the elements required by Federal regulation. These regulations do not specify the language of the document but provide a list of elements that must be addressed in the text of the consent form. The description of expected adverse events in the informed-consent document must be complete and balanced and reflective of the treatment plan to be used. Adverse events of other modalities used in the study (eg, radiotherapy, surgery) must also be described.

**Table 3. Workload Metrics for a Pharmacy-Based Investigational Drug Service**

<i>Indicators</i>	<i>Type</i>	<i>Frequency</i>	<i>Data Source</i>
Number of active clinical research studies	Operations	Monthly	Daily workload statistics
Number of studies/FTE	Operations	Monthly	Daily workload statistics
Study openings and closings	Operations	Yearly	Daily workload statistics
Doses dispensed	Operations	Monthly	Daily workload statistics
Required pharmacist and technician man-hours	Operations	Monthly	Daily workload statistics
Total IDS revenue	Financial	Monthly	Hospital finance system
Number of medication errors	Quality	Monthly	Medication Error Reporting System

FTE = full-time equivalent; IDS = Investigational Drug Service.

**Institutional Review Board (IRB) Approval**

The IRB is a standing committee of a hospital that usually reports to the hospital's board of trustees. The purpose of the IRB is to review and approve research studies based on guidelines of the Department of Health and Human Services Office of Human Research Protections (OHRP). IRB approval is required in all situations where investigational drugs are used; a hospital or commercial IRB consists of both health care professionals and lay persons whose main mission is patient protection.

**STEPS IN IMPLEMENTING A PHARMACY-BASED IDS**

A pharmacy department's role in the handling of investigational drugs depends on the type of hospital, current facilities for handling investigational drugs, and the expertise of pharmacy staff. The major steps in implementing pharmacy-based IDS include (1) determining the scope of service; (2) designing an adequate drug dispensing area; (3) developing an operational plan for the service.

**Determining the Scope of Service**

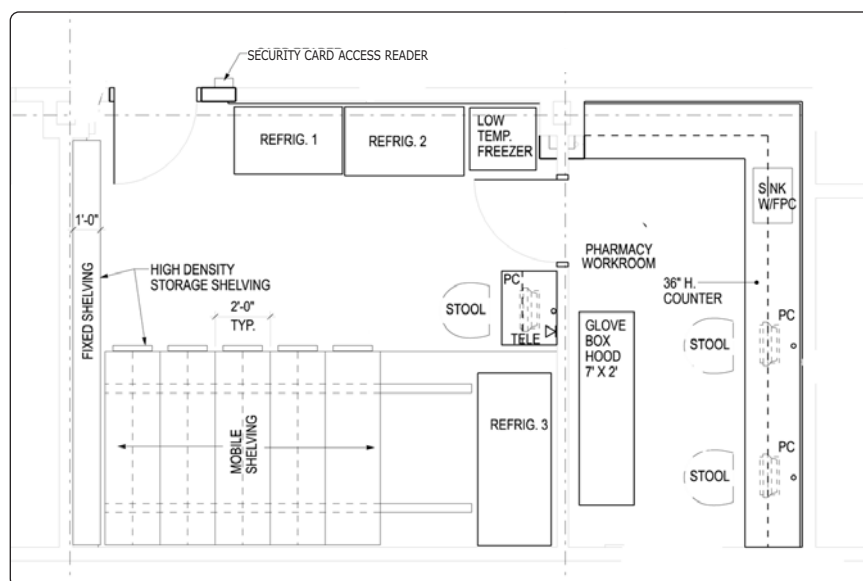
The basic role of the pharmacy in handling investigational drugs includes the registration, control, storage, dispensing, maintenance of disposition records, and drug information for these medications. Table 1 lists both basic and specialized investigational drug services that can be provided by a pharmacy department. A basis for these activities is a P&T Committee-approved investigational drug service that should also be reviewed by the pharmacy director with the hospital's medical executive committee. In order for the hospital pharmacists to carry out even this basic role, it is imperative that the hospital adopt certain policies for the use and storage of investigational drugs.

The scope of the pharmacy-based IDS is determined by understanding the hospital's strategic plan for research and or innovative medical care. For example, an organization that has a medical staff with an affiliation to a large research university will require sophisticated pharmacy services; likewise, hospitals that have established research institutes not affiliated with an academic institution

will also need a higher level of pharmaceutical service.

Some hospitals have developed innovative clinical practice committees that monitor the use of care processes that may not be totally supported by medical evidence. These processes may include medical procedures (use of devices, surgical procedures) or drug treatment (innovative off-label medication use). In this case, an intermediate form of pharmaceutical service may be required to include review and monitoring of off-label medication use or devoting part of a pharmacist full-time equivalents (FTEs) to handling investigational drugs. Finally, hospitals that do not deal with patients on investigational drugs may only need to have a policy and procedure for how to handle situations where patients are admitted to a hospital and receiving an investigational drug.

The following demonstrates a focused example of processes for investigational drug accountability and storage, and stresses that pharmacy directors must understand the full scope and detail involved in investigational drug dispensing as they plan for this service in the pharmacy department.



**Figure 1.** Example of floor plan for an investigational drug service.

Specific accountability procedures for control of investigational drugs assist the responsible principal investigator in making certain that agents received are used only for patients entered onto an approved protocol. Importantly, these processes can be delegated to the pharmacy but still remain the responsibility of the principal investigator. Table 2 lists specific accountability for investigational drug storage and control.

### Designing an Adequate Drug Dispensing Area

For hospitals offering specialized services in dispensing investigational drugs, an adequate amount of space should be designated for drug storage and preparation. Figure 1 shows an example floor plan for an investigational drug area of the pharmacy. The floor plan notes that the area is secured (using an electronic security system through a card reader) and segregates the drug stock from other stock in the pharmacy (pharmacy supply storage). The floor

plan also provides for an area for sterile compounding and other extemporaneous preparation (pharmacy workroom). In the design of the floor plan, adequate refrigeration must be considered along with data information capabilities (eg, computer, fax machines).

### Developing an Operational Plan for the Service

A significant challenge to implementing a pharmacy-based IDS is to develop an operating budget and metrics for the service. This may be difficult initially; the budgeting and staffing of the service will most likely be the result of educated assessments of new and ongoing research study volumes. These data are most easily obtained by planning a strategy with all of the stakeholders in clinical research to include research investigators, industry sponsors, and program administrators. In planning the pharmacist and technician time to operate the service, the following functions must be

considered: protocol receipt and review; protocol set-up and paperwork; developing the drug information monograph, establishing requirements for preparation, labeling and storage of medication, monitoring administration and documentation, and auditing for compliance. As a result, the department should establish a time standard for various types of investigational drug preparations, and calculate required FTEs based on volume of these investigational medication types. Table 3 lists common metrics a pharmacy director could use in monitoring the financial, operational, and quality aspects of pharmacy-based IDS.

### MISCELLANEOUS CONSIDERATIONS FOR A PHARMACY-BASED IDS

#### Retention of Records

FDA regulations require that all research records (including patient charts, case report forms, x-rays, scans that document response, IRB approvals, signed informed-consent documents, and all agent accountability records) must be kept by the investigator for at least 2 years after a New Drug Application has been approved for that indication or the study has been closed.

#### Data Management and Statistics

Since most clinical trials involve professional staff other than the protocol chair, adequate collection of clinical data is a complex task that must be integrated into the medical practices of the institution. Furthermore, data collection is best done as data are generated; this practice promotes protocol compliance and permits the protocol chair to monitor the study's progress. For these reasons, data management organized and supported at the department or institution level is usually more

efficient and reliable than that which is left to the individual investigator. The patient recruitment goals of a study should be specified in advance, with a maximum number of patients explicitly stated. Justification for the target sample size, in terms of precision of estimation or levels of type 1 and type 2 error, should be provided. The accrual rate of eligible patients that can be realistically anticipated should be given as well. Finally, mechanisms should be in place for early stopping of negative trials.

### Verification of Compliance to Study Procedures

Compliance to procedures ensures proper agent usage and is reviewed during site visits, which are conducted under a research sponsor monitoring program. Specifically, site visitors will check that the agent accountability system is being maintained and will spot-check the agent accountability records by comparing them with the patients' medical records to verify that the agents were administered to a patient entered in the recorded protocol.

### Cost Justification

Most IDSs charge fees in an attempt to recoup the costs of the IDS as well as the dispensing pharmacists' time and supplies. These fees vary from study to study and

among institutions but frequently institutions charge a study initiation fee, a quarterly maintenance fee, and a per-dose dispensing fee. Often, payment received from these charges is not sufficient to cover the cost of running the IDS. However, there may be other economic benefits. One benefit to an institution is cost avoidance, which has been defined as dollars that would have been spent to purchase medications but that were not spent because of a specific study-related intervention.

Another key benefit is regulatory and sponsor compliance. Failure to properly maintain records can place entire research programs at risk. For this reason, it is critical to outline key benefits to hospital administrators who may be hesitant to implement an IDS because the benefits are not readily apparent. Potential funding sources for the IDS include: (1) Fees charged to investigators; (2) Hospital support provided or costs absorbed; (3) Salary support provided through a research grant; (4) Fees charged to departments; (5) Designated funding provided through a research grant; and (6) Salary support obtained from a school or university.

### SUMMARY AND CONCLUSION

A pharmacy-based IDS can effectively support and establish a patient-centered focus for a hospi-

tal pharmacy department in supporting innovation and new knowledge in medication use. The director of pharmacy must use a dynamic approach in developing pharmacy-based IDS. The development and implementation involves determining the scope of service, designing an adequate drug dispensing area, and developing an effective operational plan for the service.

### REFERENCES

1. Kleinman LM, Tangrea JA, Gallelli JF. Control of investigational drugs in a research hospital. *Am J Hosp Pharm.* 1974;31(4):368-371.
2. Kleinman LM, Tangrea JA. Involvement of the hospital pharmacist in single- and double-blind studies. *Am J Hosp Pharm.* 1974;31(10):979-981.
3. Peltzman S. An evaluation of consumer protection legislation: the 1962 drug amendments. *J Polit Econ.* 1973;81(5):1049-1091.
4. LaFleur J, Tyler LS, Sharma RR. Economic benefits of investigational drug services at an academic institution. *Am J Health Syst Pharm.* 2004;61(1):27-32.
5. The Food and Drug Administration. Clinical testing for safe and effective drugs, DHEW Publication No. (FDA) 74-3015. US Government Printing Office, Washington, DC.
6. Ansani N, Sirio C, Henderson B, Smitherman T, Weber RJ, Skledar SJ, Zgheib N, Branch RA. Designing a strategy to promote safe innovative off-label use of medications. *Am J of Med Qual.* 2006;21():246-254. ■