Detailed Use Case for Drug Research

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Use Cases and Detail for Pharmaceutical Manufacturing – Drug Research

LOB: Drug Research

Critical Pain Point: Inability to organize large amounts of highly technical data from multiple platforms and databases

Key Decision Makers: VP of Research, VP of Product Development

Business Process	Scenarios/Use Cases/Solutions	System and Databases
Drug Development	**Design Protocol Management** ● Manage the design of protocols more effectively by searching through databases and identify appropriate resources and vendors **Discovery** ● Identify network of experts with similar or complementary expertise to avoid costly and redundant research ● Identify similar research and associated outcomes to accelerate research and tests ● Easily locate highly technical documents and data, such as research papers, previous drug studies, trial reports and internal notes (typically on Science Connect) **Pre-Clinical and Clinical Trials** ● Search information from drug testing to determine indications, efficacy and safety issues	**Systems** ● Science Connect (Google + type product that allows everyone to publish what they are working on and other information) ● LIMS (Lab information management systems) Clinical Data Management Systems (for the collection of data from trials) ● Document management systems (DMS) used for storing documents related to drug development **Databases** ● Compound database for chemicals (searched to help search for appropriate technical information) such as ChEMBL ● The Case Report Form, or equivalent, is the data collection tool for the clinical trial

Drug Development Overview

Drug development is an expensive process and requires approximately $1.2 billion to produce a single drug. Drug discovery falls into six key phases, which are discussed in-depth below. Some companies combine the discovery into the protocol design as well as different terminology used within the industry (e.g. clinical trials can also refer to global operations, analysis and reporting can be referred to as biometrics, etc.)

- Protocol Design: Design the protocol used for clinical testing
- Discovery: Developing potential drugs for testing

- Pre-Clinical: Small test on animals to determine indications, efficacy and safety
- Drug Development: Drugs are fully developed based on pre-clinical studies
- Clinical Tests: Full blown clinical tests (typically 3 phases)
- Post Clinical Trials: Governance and regulatory affairs

The top two levers for Client is:

- Phase I Clinical Tests: Extensive amounts of data must be gathered and analyzed; GLP indicates the use of an inter-relational database is an effective tool for storing, sorting and reviewing data. Much of this data is sifted through by researchers looking for indications and safety issues.
- Research to support discovery and protocol design (e.g. what did they previously do)

Protocol Design: Correct protocol management needs to be established, which sets the conditions and resources of the clinical trials.

Design protocol management involves extensive research on prior clinical trial protocols[1] to determine what worked, templates used, regulatory issues faced and other key issues. All study investigators are expected to strictly observe the protocol which describes the scientific rationale, objective(s), design, methodology, statistical considerations and organization of the planned trial. Details of the trial are provided in documents referenced in the protocol, such as an investigator's brochure. An enterprise search solution combines all relevant information into a secure repository that investigators can easily access at any time.

Clinical protocol requirements are matched against suppliers through a search of supplier databases (as well as internal sources) to determine the most cost effective sources for the materials to be used in the protocol. The order can be processed through an internal purchasing system or a third party system which specializes in the management of appropriate materials.

Discovery: Discovery is the act of finding new drugs or new indications for existing drugs. In this phase both external and internal data are searched to provide insights into drug development. The first step is to find a promising agent, which involves taking advantage of the advances made in understanding a disease, pharmacology, computer science and chemistry. One example is the discovery process of breaking down a disease process into its components. This will provide clues for targeting drug development. For example, if an enzyme is determined to be a key component of a disease process, a researcher might seek ways to inhibit this enzyme. Advances in basic science might help by ascertaining the active enzyme site. Numerous compounds might be synthesized and tested before a promising agent emerges. Computer modeling often helps select what compounds might be the most promising.
The typical databases that are searched are databases for compounds such as ChEMBL, and an internal system that acts much like Google + where all information related to research, milestones and significant information is posted. One of the more popular tools is Science Connect. Because there is so much information to search within Science Connect and other possible databases (such as the intranet), these are maintained by a pharmaceutical company where using GSA significantly decreases the time to discovery.

The most important use for the research staff is to locate prior research the company has done related to existing projects. The research department uses previous research documents to learn from prior

[1] Clinical Trial Protocol is a document used to define and manage the trial.

lessons and see if any applicable information can be used to lower the cost and decrease product development. Research includes highly technical documents and data, such as research papers, previous drug studies, trial reports, internal notes, emails, safety procedures, chemical MSDS[2] and other communications between researchers, which is frequently searched on Science Connect or similar systems.

To help manage the discovery process, many pharmaceutical companies use LIMS (Lab Information Management Systems), where much of the discovery data resides.

The research staff provides information to the legal department so they can file provisional applications (which are very important). The change to "first to file" for patents has created a need for an enterprise search solution, so the research staff can find all information related to new patents (i.e. materials, processes, tools, etc.) and easily submit/share with the legal department.

Pre-clinical: Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies. These involve in vitro (test tube or cell culture) and in vivo (animal) experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. Such tests assist pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug.

The preclinical phase can last up to three years, so improving this process will speed the overall drug development process significantly. This phase is followed by an application to the FDA as an investigational new drug (IND). After an IND is approved, the next steps are clinical phases 1, 2, and 3, which require approximately one, two and three years, respectively, for completion.

Clinical Trials: The length of conducting clinical trials is quite long (depending on the phase, and can last up to six years). Each of the phases is described below:

Phase 1 studies focus on the safety and pharmacology of a compound. During this stage, low doses of a compound are administered to a small group of healthy volunteers who are closely supervised. In cases of severe or life-threatening illnesses, volunteers with the disease may be used. Generally, 20 to 100 volunteers are enrolled in a phase 1 trial. These studies usually start with very low doses which are gradually increased. On average, about two thirds of phase 1 compounds will be found safe enough to progress to phase 2.

For Phase I studies, Good Laboratory Practice (GLP) compliance is useful but not mandated. However, because extensive amounts of data must be gathered and analyzed, GLP indicates the use of an inter-relational database as an effective tool for storing, sorting and reviewing data (GSA helps to solve this issue). The information collected is managed by a clinical data management system.

Phase 2 studies examine the effectiveness of a compound. To avoid unnecessarily exposing a human volunteer to a potentially harmful substance, studies are based on an analysis of the fewest volunteers needed to provide sufficient statistical power to determine efficacy. Typically, phase 2 studies involve 100 to 300 patients who suffer from the condition the new drug is intended to treat. During phase 2 studies, researchers seek to determine the effective dose, method of delivery (e.g. oral or intravenous), and the

[2] MSDS: Material Safety Data Sheet on specific chemicals (to ensure proper handling and safety).

dosing interval, as well as to reconfirm product safety.[2,7,11,12] Patients in this stage are monitored carefully and assessed continuously. A substantial number of these drug trials are discontinued during phase 2 studies. Some drugs turn out to be ineffective, while others have safety issues or intolerable side effects.

Phase 3 trials are the final step before seeking FDA approval. During phase 3, researchers try to confirm previous findings in a larger population. These studies usually last from 2 to 10 years and involve thousands of patients across multiple sites. These studies are used to demonstrate further safety and effectiveness and to determine the best dosage. Despite the intense scrutiny a product receives before undergoing expensive and extensive phase 3 testing, approximately 10% of medications fail in phase 3 trials.

Post-clinical trial research: The FDA may request post-marketing or phase 4 studies to examine the risks and benefits of the new drug in a different population, or to conduct special monitoring in a high-risk population. Alternatively, a phase 4 study might be initiated by the sponsor to assess such issues as the longer term effects of drug exposure to optimize the dose for marketing, to evaluate the effects in pediatric patients, or to examine the effectiveness of the drug for additional indications. Post marketing surveillance is important because even the most well designed phase 3 studies might not uncover every problem that could become apparent once a product is widely used. Furthermore, the new product might be more widely used by groups that might not have been well studied in the clinical trials, such as elderly patients. A crucial element in this process is that physicians report any untoward complications. The FDA has set up a medical reporting program called Medwatch to track serious adverse events (1-800-FDA-1088). The manufacturer must report adverse drug reactions at quarterly intervals for the first three years after approval.

Researchers are constantly searching for side effects from patient and doctor reports based on key words to classify and understand those side effects. GSA enables a more complete search, especially when researching potential safety issues.

Definition of Key Terms

Term	Definition
Approved Vendor List (AVL)	A list of all the vendors or suppliers approved by a company as sources from which to purchase materials.
Bill of Lading	A document generated by a shipper detailing a shipment of merchandise giving title to the goods, and requiring the carrier to release the merchandise to a named party at the destination.
Case Report Form (CRF)	Data collection tool for the clinical trial.
Clinical Trial Protocol	A document used to define and manage the trial.
Document Management Systems (DMS)	Used for storing documents related to drug development.
Food and Drug Administration (FDA)	An agency of the United States Department of Health and Human Services responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics and veterinary products.
Good Laboratory Practice (GLP)	Refers to a quality system of management controls for research laboratories and organizations to try to ensure the uniformity, consistency, reliability, reproducibility, quality, and integrity of chemical (including pharmaceuticals) non-clinical safety tests.
Investigational New Drug (IND)	Means by which a pharmaceutical company obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved.
Lab Information Management System (LIMS)	A software-based laboratory and information management system that offers a set of key features that support a modern laboratory's operations.
Material Safety Data Sheet (MSDS)	A document that provides workers and emergency personnel with procedures for handling or working with a substance in a safe manner, and includes information such as physical data, toxicity, health effects, first aid, reactivity, storage, disposal, protective equipment, and spill-handling procedures.

Standard Operating Procedure (SOP)	A written document or instruction detailing all steps and activities included in process or procedure.