Course Glossary

This glossary defines scientific terms used in the course lectures. Terms are listed alphabetically.

Absorption, distribution, metabolism and excretion (ADME) – A process through which a drug administered to a living body is absorbed and enters the systemic circulation, distributed throughout the body, metabolized in the liver and other organs, excreted into urine and bile, etc., and eliminated from the body.

Assay – A test system, used to quantitate the effects of chemical compounds on cellular, molecular or biochemical processes of interest, in drug discovery, development and toxicity testing. The primary assay is the assay used to identify biologically active chemical entities in a screening mode such as a high-throughput screen. Secondary assays are assays performed to determine whether the compounds identified from the primary screen are biologically relevant or artifacts due to assay readout interference. Secondary assays are frequently assays that confirm the activity of compounds in an orthogonal or more complex format (e.g. in cells).

Benefit-risk assessment – Broadly speaking, benefit-risk assessment in FDA's drug regulatory context is making a judgment as to whether the expected benefits (with their uncertainties) of the drug outweigh the potential risks (with their uncertainties and approaches to manage risks) associated with its expected use. Benefit-risk assessment along a product's life cycle – from development through approval and into the post-market setting – can take several forms, for different purposes. Before an investigational drug can be administered in first-in-human clinical trials, FDA must determine that the product will not pose unreasonable risks to the participants. In the context of the marketing authorization of a drug, FDA's regulatory decision-making is based on a determination that the drug is effective and that its expected benefits outweigh its potential risks to patients and to public health.

Biological target – A macromolecule or a set of macromolecules in a biochemical pathway that is hypothesized to play a role in the disease, condition, or outcome of interest. Ideally the target should be druggable so hits, lead compounds, and drug candidates can be identified and optimized to interact with the target. On-target effects refer to impact of the drug when it binds to the predetermined target, while off-target effects describes the effects that can occur when a drug binds to targets other than those for which the drug was meant to bind.

Biomarkers – Naturally occurring or endogenous factors that are objectively measured and evaluated as indicators of normal processes, pathological processes, or pharmacological responses to treatment. Biomarkers that characterize the condition and change of disease and the degree of cure are used as surrogate markers for evaluating the efficacy of new drugs in clinical studies. When clinical studies are conducted, biomarkers also can be used for patient stratification.

Body surface area conversion factor (BSA-CF) – A factor that converts a dose (mg/kg) in an animal species to the equivalent dose in humans (also known as the human equivalent dose), based on differences in body surface. A BSA-CF is the ratio of the body surface area in the tested species to that of an average human.

Chemical lead compound – A chemical compound that has pharmacological or biological activity that is likely to be therapeutically useful, but may nevertheless have a suboptimal structure-activity relationship that requires further modification or improvement. A lead could be selected from a collection of hits or could be a compound that has been optimized from a hit.

Optimization of a chemical lead compound – The optimization process involves design and synthesis steps to improve activity, selectivity, physical properties, pharmacokinetics and safety parameters. Iterative lead optimization often leads to a selected compound that is further evaluated in toxicology studies to determine its potential as a drug candidate.

Chemical library – A collection of compounds that are used in high throughput screening (HTS). Focused libraries to meet specific purposes are strategically designed and created with selected compounds. For example, the Library of Pharmacologically Active Compounds (LOPAC) contains only compounds already known or used in drugs that have already been commercialized.

Clinical trial – Medical research study involving human participants.

Phase 0 Clinical Trial – Exploratory study involving very limited human exposure to the drug, with no therapeutic or diagnostic goals (for example, screening studies, microdose studies).

Phase 1 Clinical Trial – Study that is usually conducted with healthy volunteers and that emphasizes safety and tolerability. The goal is to find out what the drug's most frequent and serious adverse events are and, often, determining what is the exposure (pharmacokinetics) of the drug and how it is absorbed, metabolized and excreted.

Phase 2 Clinical Trial – Study that gathers preliminary data on effectiveness (whether the drug works in people who have a certain disease or condition) and to identify the dose or doses for the Phase 3 studies. For example, participants receiving the drug may be compared with similar participants receiving a different treatment, usually a placebo or a different drug. Safety continues to be evaluated, and short-term adverse events are studied.

Phase 3 Clinical Trial – Pivotal study that gathers more information about safety and effectiveness by studying the drug in larger and more diverse patient populations. A Phase 3 trial may have more than one dosage and may study the drug in combination with other drugs.

Phase 4 Clinical Trial – Study occurring after FDA has approved a drug for marketing, including post-market requirement and commitment studies that are required of or agreed to by the sponsor. These studies gather additional information about a drug's safety, efficacy, or optimal use.

Compound – A substance formed from two or more elements chemically united in fixed proportions.

Control compound – A compound that is routinely run in the same manner as the test compounds in every run of the assay. This term does not refer to the plate controls used to define the maximum and minimum responses, and they may or may not be a “literature standard” or “reference” compound. The objective of using a control compound in an assay is to check if the assay activity/function is reproducible in every run.

Commercialization – The process of bringing new products or services to market. Commercialization entails product development, regulatory approvals, production, distribution, marketing, sales, customer support, and other key functions critical to achieving the commercial success of the new product or service.

De-risking – Involves *efforts* to reduce the risks, time delays and costs of advancing basic research breakthroughs into treatments. Preclinical research, which connects basic scientific discoveries with

initial testing of therapies in humans, is a particularly failure-prone stage of translation. Innovations in drug discovery and development and management of development programs can substantially reduce the risks, time delays and costs of advancing basic research breakthroughs into treatments.

Drug – (1) A substance recognized by an official pharmacopoeia or formulary; (2) A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; (3) A substance (other than food) intended to affect the structure or any function of the body; and (4) A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)

Drug candidate – A molecule among several that has been shown to have sufficient selectivity and potency toward a target, and favorable medicine-like properties, justifying further development. The drug candidate will then be subjected to a series of tests and studies. At this stage it is not yet a medicine.

Drug discovery and development – The process by which new candidate medications are discovered. Once researchers identify a promising compound for development, they conduct experiments to gather information that will enable them to develop the compound into a medication. This includes research to establish benefits; mechanisms of action; how it is absorbed, distributed, metabolized, and excreted; best means of administration; dosing regimen; toxicity; and interactions with other drugs.

Druggable target – A biological target known or predicted to be able to bind to small molecules that will regulate the function of the target. In recent years, a candidate target for drug development has been regarded as a druggable target when it is expected to bind with high affinity to an antibody drug, small molecule drug, or nucleic acid drug created by using state-of-the art technology.

First in class – An innovative drug that is highly novel and useful and may bring about a significant change to a conventional therapeutic system. Usually refers to the first product with a specific mechanism of action.

First in human (FIH) – The first study in which a study drug (candidate drug substance) is administered to humans. When there are multiple candidate indications, the disease for which efficacy and safety are first evaluated in clinical trials may be referred to as FIH indication.

Food and Drug Administration (FDA or USFDA) – A United States government agency responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription and non-prescription drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, cosmetics, animal food and feed, and veterinary products.

Freedom to Operate (FTO) – The ability of a company to commercialize a specific technology freely. It is important to obtain such Freedom to Operate when the technology is commercialized. "FTO search" refers to searching prior art or existing patents to identify if the potential exists to infringe intellectual property when a specific technology is studied, used, or commercialized.

Genotypic – Relating to an organism's collection of genes, its genotype. The genotype is expressed when the information encoded in the genes' DNA is used to make protein and RNA molecules. The expression of the genotype contributes to the individual's observable traits, called the phenotype.

Good Clinical Practice (**GCP) standards –** International quality standards for conducting clinical trials, which governments can then transpose into regulations for clinical trials involving human subjects.

Good Laboratory Practice (GLP) standards – A set of standardized practices applied when conducting non-clinical studies. This standard is also used to guarantee that safety study data (such as animal studies) comes from non-clinical studies conducted in accordance with a properly designed protocol when an application for approval is submitted to the regulatory authority. This standard applies to toxicity studies and safety pharmacological studies, which are included in non-clinical studies on the safety of a drug. Among study data to be submitted to the regulatory authority for approval, are studies called GLP-Tox studies.

Good Manufacturing Practice (GMP) standards – Overall requirements for facilities and equipment of manufacturing sites as well as manufacturing control and quality control for manufacture of drugs, etc. GMP standards often include detailed and precise record keeping with proper documentation of source and batches of chemicals, conditions, equipment, and processes used in the manufacturing process.

High throughput screening (HTS) – Throughput refers to the number of samples that can be tested at a time. HTS means many samples can be analyzed in a short period of time. HTS is a technique to evaluate a large number (hundreds of thousands to millions) of compounds in a short period of time using a mechanically controlled, automated system to identify active compounds or hits. Quantitative HTS (qHTS) refers to HTS performed in multiple concentrations to facilitate improved hit selection.

Hit – Active compound discovered during compound screening. This may include hits obtained through primary screening approaches such as HTS and compounds that have been confirmed to be active in secondary, or orthogonal assays. A hit is usually defined by its percent activity at a specific concentration in an assay relative to control compounds. Hit compounds are then chemically optimized to improve efficacy (i.e., target selectivity, ADME profile, etc.). From this process, a lead compound is identified.

Human equivalent dose (HED) – A dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose. The term HED is usually used to refer to the human equivalent dose of the NOAEL.

Human subjects research – Research that uses persons as the subjects of experiments or studies.

Intellectual property (IP) – Inventions, ideas, works of art and other products used in commerce developed through creative activities that are legally protected as patents, copyright and trademarks, enabling people to earn recognition or financial benefit from what they invent or create.

Intellectual property (IP) rights – Legal rights to IP. The first type of IP right is a patent right. The party that holds a patent right can execute it exclusively for 20 years from the application (25 years in the pharmaceutical field at the maximum). An "IP strategy" including when and where to apply for a patent and what to patent, is established to gain a competitive advantage in the market. Patent rights are country-specific.

Invention – There are four general requirements for an invention to be patentable (as a utility patent): (1) it must comprise patent eligible subject matter, (2) it must be new, (3) it must be useful, and (4) it must be non-obvious.

Investigational New Drug (IND) Application – An application submitted to the Food and Drug Administration (FDA) to obtain permission to start a clinical study on a new drug or to conduct a study to evaluate the efficacy of an already marketed drug for a new indication. An IND application and FDA's approval to proceed to clinical trial initiation are required for all drug candidates. The IND application includes information on the quality of substances being studied and their efficacy and safety.

In vitro – Research performed outside of a living organism.

In vivo – Research performed in a whole, living organism.

K – A dimensionless factor that adjusts for differences in the surface area to weight ratio of species because of their different body shapes.

K_m – Factor for converting mg/kg dose to mg/m^2 dose.

Kinase – A type of enzyme (a protein that speeds up chemical reactions in the body) that adds chemicals called phosphates to other molecules, such as sugars or proteins. This may cause other molecules in the cell to become either active or inactive. Kinases are a part of many cell processes. Human cells have many different kinases, and they help control important functions, such as cell signaling, metabolism, division, and survival. Certain kinases are more active in some types of cancer cells and blocking them may help keep the cancer cells from growing.

Lead optimization – see the definition above for "optimization of a chemical lead compound"

Licensing – Generally refers to providing access to an invention, IP, or know-how to others or permitting execution rights. A party who licenses the IP right is called a licensor, while the other party who obtains a license is a licensee.

Lowest observed adverse effect level (LOAEL) – The lowest dose tested in an animal species with adverse effects

Maximum recommended starting dose (MRSD) – The highest dose recommended as the initial dose in a clinical trial. In clinical trials of adult healthy volunteers, the MRSD is predicted to cause no adverse reactions. The units of the dose (e.g. mg/kg or mg/m^2) may vary depending on practices employed in the area being investigated

Maximum tolerated dose (MTD) – In a toxicity study, the highest dose in a single or multi-day study that does not produce unacceptable toxicity.

Medicinal chemistry – A discipline at the intersection of chemistry, biology, drug metabolism and pharmacokinetics, and other specialties, involved with the design, chemical synthesis, and evaluation of bio-active small molecules (drugs).

Metastasis – The spread of cancer cells from the place where they first formed to other parts of the body.

Milestone – A milestone is a specific point along a timeline used to manage the progress of a task. It also refers to a defined period in a project schedule or an intermediate goal point. In the pharmaceutical industry, points such as IND application, the end of a Phase I clinical trial, and the end of a Phase II clinical trial are commonly set as milestones, and many agreements provide that a certain payment (milestone fees) be made when a milestone is achieved.

National Center for Advancing Translational Sciences (NCATS) – One of the 27 Institutes and Centers that comprise the US National Institutes of Health. NCATS was created in late 2011 with the goal of transforming the translational science process so that new treatments and cures for disease can be delivered to patients faster. NCATS strives to develop innovations to reduce, remove or bypass costly and time-consuming bottlenecks in the translational research pipeline in an effort to speed the delivery of new drugs, diagnostics and medical devices to patients.

National Institutes of Health (NIH, US NIH) – The primary agency of the United States Government responsible for biomedical and public health research. NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. The NIH conducts its own scientific research and provides major biomedical research funding to non-NIH research facilities.

New drug application (NDA) – A package of documents required by the FDA before approval is granted for marketing a new drug in the U.S. When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet the FDA's requirements for marketing approval, the sponsor submits to the FDA a new drug application (NDA). The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed in the United States.

No observed adverse effect level (NOAEL) – The highest dose at which no toxic and harmful effects were seen in safety studies such as repeated-dose toxicity studies and reproductive and developmental toxicity studies using multiple dose groups.

No observed effect level (NOEL) – The highest dose at which no biological effects cause statistically significant changes in the control group in safety studies such as repeated-dose toxicity studies and reproductive and developmental toxicity studies using multiple dose groups.

Patent – The grant of a property right to the inventor(s) of an invention, issued by the United States Patent and Trademark Office. A U.S. utility patent is generally granted for 20 years from the date the patent application is filed; however, periodic fees are required to maintain the enforceability of the patent. A design patent is generally granted protection for 14 years measured from the date the design patent is granted. Patent rights are country-specific, and separate patent applications have to be filed in each country's patent office. See below for an International Treaty that somewhat simplifies this process, the Patent Cooperation Treaty (PCT).

Provisional Patent – A provisional patent application gives inventors flexibility to quickly protect an invention. **A provisional patent application allows one to file without a formal patent claim, oath or declaration, or any information disclosure (prior art) statement.** It also allows the term "Patent Pending" to be applied in connection with the description of the invention. A provisional

application for patent is valid for 12 months from the date the provisional application is filed. Therefore, an applicant who files a provisional application must file a corresponding nonprovisional application for patent during the 12-month pendency period of the provisional application in order to benefit from the earlier filing of the provisional application.

Patent Cooperation Treaty (PCT) – An international patent law treaty that provides a unified application system in which filing a single patent application allows the applicant to gain the same benefits as those obtained by filing applications in all PCT member countries at the same time. A patent application filed under the PCT is called an international application, or PCT application, and must be filed within 12 months of the provisional patent application. After the PCT application is filed, the applicant has an additional 18 months to choose individual countries where they want to file individual country specific patent applications. This is known as the National Stage.

Perinucleolar Compartment (PNC) – A subnuclear body characterized by its location to the periphery of the nucleolus. The PNC is associated with malignancy both in vitro and in vivo and its presence positively correlates with metastases.

Pharmacodynamics (PD) – The body's biological response to drugs including the drugs' reactions with and binding to cell constituents, and the biochemical and physiological consequences of these actions. PD is commonly related to drug concentration and pharmacokinetic (PK) parameters.

Pharmacokinetics (PK) – The movement of drugs through the body including the process of the uptake of drugs by the body, the biotransformation they undergo, the distribution of the drugs and their metabolites in the tissues, and the elimination of the drugs and their metabolites from the body over a period of time.

Pharmacology – The science of drugs including their origin, composition, modes of action, therapeutic value, and toxicology. The two main areas of pharmacology are pharmacodynamics and pharmacokinetics.

Pharmacologically active dose (PAD) – The lowest dose tested in an animal species with the intended pharmacologic activity.

Phenotypic – Relating to the observable characteristics of an organism, resulting from the interaction of its genotype with the environment.

Post-marketing surveillance – Surveillance conducted to confirm drug efficacy and safety after marketing has been initiated and to collect information on new effects and side effects that were not obtained in pre-marketing clinical trials.

Proof of Mechanism (**POM) –** Relates to the earliest stages of drug development, often pre-clinical. These studies are designed to show that a new medicine reaches its target organ(s), interacts with its molecular target, and affects the biology of the target cells as intended.

Reproducibility – The extent to which consistent results are obtained when an experiment is repeated, in the same lab or testing the same conditions across different laboratories.

Royalty – A payment received by a licensor who grants the licensee the right to use the patent.

Safety factor – A number by which the human equivalent dose (HED) is divided to introduce a margin of safety between the HED and the maximum recommended starting dose.

Safety margin – The ratio of the clinical dose (exposure level) in humans to the NOAEL (exposure level) obtained from animal toxicity studies, which is used as a parameter for risk assessment in humans. It is calculated as follows: NOAEL/ clinical dose (exposure level) in humans, or exposure level in NOAEL/exposure level in human clinical dose.

Science of Team Science (SciTS) – An interdisciplinary field of study that aims to develop the evidence base for effective practices in team-based science.

Target Product Profile (TPP) – A summary of expected effects, regimen, dose, dosage forms, formulation, adverse reactions etc., for a developed drug. It provides a criterion to evaluate marketability or make a Go/No-go judgment. In recent years, setting the TPP has been required from the early development stage.

Target validation – The use of a variety of approaches to determine the target that a drug or lead compound acts upon. In drug discovery, initial research may focus on a cellular characteristic (e.g. cell death or cell migration) or observable outcome (e.g. protein aggregation, organelle changes) associated with a normal or pathological process without a specific target being identified. Additional experiments are needed to determine what specific component of this process the drug or lead compound in acting upon that alters the observable outcome.

Team science – Scientific research that is conducted by a team of two or more individuals working interdependently to achieve shared scientific goals.

Technology transfer – The process by which valuable research, skills, knowledge, and/or technology is delivered from government, colleges and universities, or other research institutions into the corporate environment where it is developed into a commercial product or service.

Therapeutic index – A quantitative measurement of the relative safety of a drug. It is the ratio of the drug concentration in the blood resulting in toxicity and drug concentration in the blood resulting in efficacy. The larger the therapeutic index the safer the drug.

Therapeutic window – The range of doses achieving the greatest therapeutic benefit without resulting in unacceptable side-effects or toxicity. This range is limited by side effects and treatment effectiveness.

Toxicology – A scientific discipline focused on the study of the adverse effects of chemical substances on living organisms and the practice of diagnosing and treating exposures to toxins and toxicants. The discipline overlaps with biology, chemistry, pharmacology, and medicine.

Translational research – The process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public—from diagnostics and therapeutics to medical procedures and behavioral changes.

Translational science – The emerging field of investigation focused on understanding generalizable scientific and operational principles for translational research.

Multiple sources were consulted to develop this glossary. They included:

Assay Guidance Manual

Translational Together

NCATS Website

NCI Dictionary of Cancer Terms