OHI Deliverables # 1 (*DRAFT)*

Setting the Context: An Overview of Drug Discovery and Drug Development

Goal: Brief overview and synopsis of points in drug discovery and development from screening and target identification through to drug approval and the potential for generics.

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1. What is drug discovery?

We define drug discovery as the process whereby a drug candidate or lead compound[1] is identified and partially validated for the treatment of a specific disease. A drug or compound in this context is defined as a small molecule[2] and this briefing paper will not cover the area of larger molecules or biologics. This definition of drug discovery typically does not include preclinical studies and clinical trials, regulatory approval (e.g. FDA[3]) and sales and marketing, which are generally considered the most costly elements of the drug pipeline and are covered in the next section (see 3. What is drug development?). The first stages of drug discovery (target identification/validation) are often carried out at universities and other non-profit institutions. Some universities and non-profits are now involved in the latter drug discovery stages (lead identification and optimization) and early drug development (pre-clinical studies), which traditionally represent ground covered by biotech and pharmaceutical companies. Biotech[4] and pharmaceutical companies also carry out drug discovery, sometimes in collaboration with universities/non-profits.

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[1] Drugs have FDA-approval by definition; therefore we refer to pre-approved drugs that are determined to have potential by the drug discovery process as drug candidates or lead compounds.

[2] A small molecule is defined as simple synthetic or natural occurring organic compound.

[3] In some developed and most developing countries national approval is based on approval in other developed countries.

[4] Biotech companies originated as companies who focused on big molecules (antibodies and growth hormones), however many biotech companies are doing small molecule drug development

One way to describe drug discovery is to locate it in an overall process. In developed countries a drug is approved for a specific use by patients, often via physicians, after a sponsor (usually a company) has amassed and submitted a vast amount of information that claims to establish the safety and efficacy of the drug (with respect to one or more specific indications). A very large proportion of that submission consists of information gathered under extremely detailed rules and regulations, all of which are subject to audit by regulatory authorities (see 3. What is drug development?). The collection of rules lay out what constitute good practices, in particular, Good Laboratory, Clinical, and Manufacturing Practices, which are called GLP, GCP, and GMP and collectively as GxP. Before candidate drugs and their effects are studied under GxP conditions, the initial information about them and their effects and mechanisms is obtained usually in universities or institutes or within pharmaceutical companies. In drug discovery, most of these studies are typically pre-GxP or non-GxP studies. This is an important distinction between university based and industry based drug discovery, as pharmaceutical companies are likely to integrate GxP practices earlier in the drug discovery process.

Thus drug discovery (especially at universities) can be seen as a separate research process compared to drug development. Drug discovery has its own set of challenges, which will now be discussed.

Traditional Drug Discovery

The path to identifying and validating the drug candidate molecule is not a *one-size-fits-all-diseases* strategy. For the last twenty years researchers working in the area of drug discovery at universities, biotech and pharmaceutical companies have used a so called "reductionist target-based approach"[5], which focuses on identifying and validating small molecule compounds that have specific activity

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[5] Terstappen et al. Target deconvolution strategies in drug discovery. Nat Rev Drug Discov (2007) vol. 6 (11) pp. 891-903

against a specific target (usually a protein) whose function is thought to be essential for the disease phenotype. This process can be described in three stages: target identification and validation, lead identification and lead optimization (see Figure 1).

Target identification and validation: The first stage in this type of drug discovery process is to understand the disease mechanism, using cellular and genetic approaches, in order to identify potential drug targets. Firstly, an initial level of knowledge is developed concerning the disease etiology and whether there are certain disease characteristics or phenotypes[6] that can be targeted (e.g. HIV replication within T-cells). Secondly, a definitive understanding of the disease mechanism enables researchers to narrow down a particular target type (e.g. HIV proteases are known to be important for replication). The advent of genomics/proteomics has helped to accelerate this molecular knowledge base by providing gene sequence and gene expression data for disease tissues compared to normal tissues. Typically, genes and their protein products that are highly expressed in disease tissues, but have low expression in normal tissues become obvious potential targets for therapy. The selected disease target(s) are validated can then be prioritized for further research based on *in vitro* (usually cell-based and animal models) research that shows that modulation of target activity leads to the desired change in the behavior of diseased cells.

Lead identification: Once the disease mechanism and potential drug targets are identified and validated, assays can be designed that specifically measure the activity of compounds that can similarly effect the activity of the target, in a way that would be suggestive of and improvement of disease state
(e.g. compound X inhibits HIV protease). Once the assay/test has been designed (e.g. reduced protease activity in cell culture based assay), then screening of compounds that have activity can begin. Biotech and pharmaceutical companies have large small molecule compound libraries, which can include FDA-approved

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[6] A phenotype is any obvious trait of an organism: for example physiological, biochemical, morphological, developmental properties in either normal or disease states.

drugs, non FDA-approved drug candidates with known activity from previous screens and compounds with no known activity at all. One of the most important steps at this point is to reduce the number of compounds to test, as there can be up to 40,000 per library, and testing is expensive. Medicinal chemistry first helps to inform small molecule library classification and activity prediction. *In vitro*[7] protein-target- small molecule compound binding assays (e.g. HIV protease-protease inhibitor binding assay) were extensively used to select candidates from the small molecule libraries in order to test them in screens. However over time emphasis has shifted towards high through-put screens (HTS) that although are expensive, are able to test many compounds robustly in a short amount of time. HTS screens are often chemical and cell-based screens that can be scaled down in size and scaled up in number. Recently, cheminformatics computer algorithm modeling that predicts drug candidate-target interaction, stability and activity has been employed to reduce the number of small molecules that need to be tested with HTS (see Smart drug discovery). The aim of HTS is to achieve a number of accurate "hits" or drug candidates with the desired activity (e.g. inhibition of HIV protease). The accuracy of each hit or lead compound is then further validated with more in-depth cell-based and animal research.

Lead optimization/prioritization: Prior to clinical trials a lead compound or compounds need to be optimized for downstream development. In vivo animal and in vitro cell-based studies are used to understand the metabolism of compounds in the body and to gain some data on toxicity. This allows for the selection of lead compounds that have the greatest potential to be developed into safe and effective drugs. In addition it is determined whether the compound is chemically stable at different temperatures (for drugs in developing countries this is very important) and whether it will be feasible to manufacture. If a promising "lead" candidate is optimized, application to the FDA or relevant regulatory agency is then made for pre-clinical studies and clinical trials (see 3. What is drug development?).

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[7] In vitro is Latin for "within the glass" and refers to the method of performing a given procedure or technique in a controlled environment outside of a living organism.
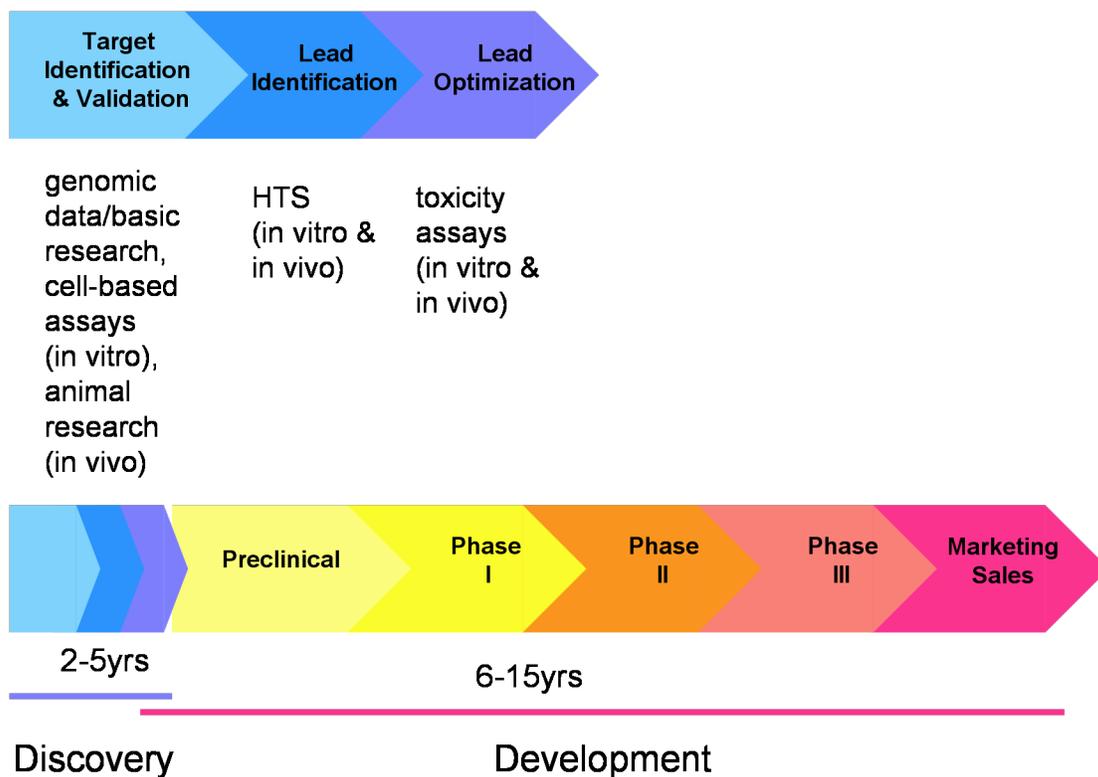
Figure 1. Traditional drug discovery

New Strategies in Drug discovery

Smart drug discovery

While pre-existing small molecule libraries represent the standard compound catalogue for pharmaceutical companies, novel drug candidate design is an important evolving component of drug discovery. The integration of in silico computer modeling and in vitro experimental methods has lead to what is known as "smart" drug design[8]. The sequencing of both the human genome (and indeed infectious disease genomes), combined with the determination the transcriptomes (gene expression) of normal and diseased tissues, has given rise

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[8] Toni Sawyer (2006) Smart drug discovery leveraging innovative technologies and predictive knowledge. Nature Chemical Biology 2(12) p646-648

to an increasing number of potential protein targets. The emerging field of structural proteomics has allowed bioinformaticians to define the shape of protein disease targets[9]. Knowledge of protein structure allows synthetic chemists and cheminformatitians to rationally design drugs using that interact to either interfere or enhance the activity of the target protein. After the drug candidates are designed and made, they are then validated in the same HTS-type screens previously described. Protein structure computer modeling can also be used to identify where known compounds (including approved drugs) might interact with protein targets. Smart drug discovery is hoped to lower costs associated with HTS, by pre-selecting in silico which compounds are likely to inhibit a particular protein target (see Figure 2).
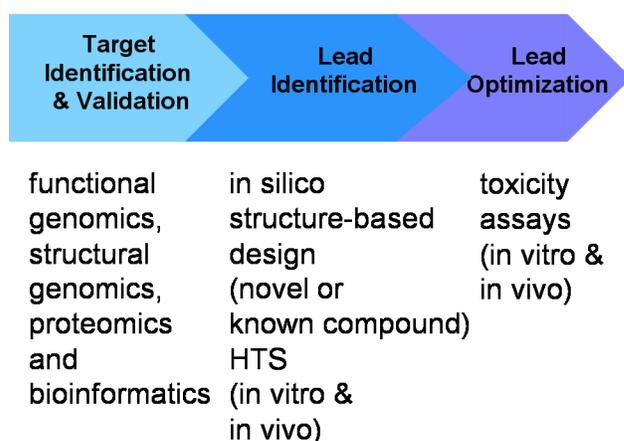
Target Identification & Validation	Lead Identification	Lead Optimization
functional genomics, structural genomics, proteomics and bioinformatics	in silico structure-based design (novel or known compound) HTS (in vitro & in vivo)	toxicity assays (in vitro & in vivo)

Figure 2. Smart drug discovery

Target deconvolution

Recently, target deconvolution[10] strategies have switched the focus to HTS drug library screens that are more phenotypic in nature rather than being protein

[9] Sleno and Emili. Proteomic methods for drug target discovery. Current Opinion in Chemical Biology 2008, 12:46–54
[10] Terstappen et al. Target deconvolution strategies in drug discovery. Nat Rev Drug Discov (2007) vol. 6 (11) pp. 891-903

target specific. These tests are carried out in mammalian cells or model organisms and once an active compound is identified by this method, its target is then elucidated (deconvolved). Target deconvolution process involves a systematic approach to understanding drug candidate mechanism of action and importantly, issues with target-specific toxicity can be identified and possibly addressed at earlier stage using this systems-based method.

Drug discovery is a continually evolving and is likely to be very different in the future. Different approaches have their own strengths and weaknesses; therefore the integration of some or all strategies seems essential to discover promising drug candidates in an efficient, timely and economically viable[11][12] manner.

2. Intellectual property related to drug discovery

Although it depends on the course of the research, an intellectual property (IP) strategy is usually determined at a relatively early stage in the drug pipeline and therefore patents are usually filed before the lead candidate enters clinical trials.

Patent claims must support the invention as being novel (new), non-obvious (inventive) and useful (utility). The most prized patent in the drug pipeline is one that covers claims on a new molecular entity (NME) (e.g. HIV protease inhibitor). A patent that covers a disease target (e.g. HIV protease) is also likely to be in the discovery IP portfolio, as are patents covering assays and methods (e.g. HTS screening methods).

3. What is Drug Development?

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[11] Drug discovery costs are difficult to estimate as most data is aggregated with drug development which represents the most costly portion of the drug pipeline. DiMasi et al, have estimated the costs of the drug pipelines as US $800million per drug, which includes lost opportunity costs and marketing & sales costs. Both sides of the debate hotly contest this number; the perceived cost of drug pipeline ranges from US $200 million to $1.7 billion.

Drug development refers to the processes involved in taking a candidate drug or biologic[13] through the stages necessary to obtain marketing approval. The end goal of drug development is to have a product that is approved by relevant regulatory authorities and can be prescribed to or otherwise made available to patients.

As a general rule, the drug development process is lengthy and expensive. There is much debate to just how expensive the process is: Merrell Goozner has written of the cost of development for a drug being around $800 million dollars. This high estimate reflects the fact that successful (or even unsuccessful) drug development, starting from the point at which an appropriate molecule/compound is identified, requires consideration and strategy on a wide range of factors including:
- identification of the disease indication to be treated,
- potential for adverse events,
- intellectual property landscape,
- regulatory requirements and hurdles,
- the ability to conduct research and trials in a regulatory compliant manner,
- potential to manufacture and deliver the drug/compound,
- willingness of payors to pay for the end product, and
- the potential market for the product.

Others dispute this figure, arguing that pharmaceutical companies fold in marketing and other administrative costs in order to create the perception that high R&D costs justify high prices for end products. For our purposes, whether the cost is $50 million or $800 million per novel candidate does not really matter; the point is that the process is, in absolute terms, expensive and risky.

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[13] U.S. Statutory Law distinguishes between a drug ("intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease") and a biologic ("any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of disease") - these definitions are intended to distinguish between small molecule products and large molecular entities produced in living cells. In the U.S. drugs and biologics are generally approved under distinct, though analogous, regulatory pathways. For purposes of this Briefing Paper, we use the term "drug" generically to include drugs and biologics.

a. Choosing a candidate for Drug Development: due diligence

Given the high price of development, the first challenge is to determine which compound should be taken forward from discovery to development. Researchers may be excited about a novel mechanism of action or early data suggesting the potential impact of a compound. However, in light of the fact that most promising candidates do not make it through the safety and efficacy hurdles toward market authorization, most potential drug sponsors will first want to undertake careful due diligence before they opt to take a candidate forward to identify the candidates that are least likely to fail. There are a range of factors that sponsors generally consider in making a decision on a candidate. These factors might include:

> (1) the pharmacology of the candidate including a characterization of how it might react with other drugs or compounds in the human body;
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> (2) regulatory considerations, including the requirements for getting approval in a particular therapeutic area (e.g., number of well-controlled large scale clinical trials required), potential for fast-track approval, possible orphan indications, etc.), whether an advisory committee might be required by regulators. Regulatory considerations may depend on whether there are competitor products and when non-inferiority or superiority may need to be demonstrated for approval;
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> (3) chemistry and manufacturing considerations, including how difficult it is to synthesize, reproduce and manufacture the compound, as well as the potential for impurities and other contaminants;
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> (4) the identifiable indication[14](s) for the compound and whether there is a medical need for the product and whether there are existing products

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[14] Drugs are approved for particular "indications" or conditions or diseases; usually the "indication" for a drug is very narrow, so a drug will be approved not for the treatment of cancer, or even for cancer in a particular organ such as the bladder. Instead it will be approved for a certain type of bladder cancer, and often for a particular stage and sub-sub-type of cancer and treatment priority such as a "second-line treatment for stage 3 superficial bladder cancer".

As far the drug regulatory authorities (Health Canada or FDA) are concerned, once approved for any particular indication, a drug may be used, on the judgment of the prescriber, for any condition whatsoever. That is, the health authorities do not regulate the practice of medicine; they are the gatekeepers for letting drugs onto the market. Physicians are constrained in their use of drugs "off-label" by their own assessments of drug safety and efficacy, plus very important considerations of liability and reimbursement.

impacting how the indication might be strategically formed; consideration of the indication will also impact how clinical studies might be designed to get the most significant efficacy result - and to minimize potential safety issues;

(5) potential toxicity issues: based on pre-clinical studies, careful consideration will be given to the types of toxicity issues that might result, how they could be controlled and whether they are the type that may pose an undue risk considering the potential benefits of the compound in light of the disease and indication being treated;

(6) Intellectual Property and potential exclusivity profile: whether the IP that exists for a compound is sufficient to protect the compound from identical or related competitor products and whether there is a sufficient incentive from IP and regulatory exclusivities together to provide an acceptable incentive for offsetting development costs.

This list is by its very nature merely an approximation of the types of considerations appropriate to any given compound, but the point should be clear: there are many complex factors that can impact the course and ultimate success of drug development. Even taking all these factors into consideration, there are no guarantees to success and issues in any of these areas may arise at any time.

b. Demonstrating Safety and Efficacy: Pre-clinical studies and Clinical Trials

Once a candidate is selected for development, the goal is to meet the regulatory requirements so that a marketing authorization will be granted. As a general rule regulators require a sponsor to demonstrate that a proposed drug (or biologic) must be safe and efficacious and that the benefits of the drug (or biologic) outweigh the risks at the specified dose and for the specified indication. This requirement, and the types of clinical trials outlined below, are fairly well harmonized amongst international regulatory authorities including the Food and Drug Administration in the

U.S., the Therapeutic Products Directorate in Health Canada, and the European Medic EMEA and other worldwide bodies.

Toward that end, the sponsor will need to conduct a barrage of standard pre-clinical studies on the identified compound in an effort to provide baseline evidence that it is safe. Most of these are conducted in animals. Pre-clinical testing is an evaluation of the drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies. All of this work must be done according to regulators' stringent "good laboratory practices" ("GLPs"), which require meticulous control and recording of processes.

In order to initiate the process and prior to being allowed to begin any trials in human beings, the sponsor will need to file an "Investigational New Drugs" (IND) application or the equivalent. The IND is aimed at demonstrating that the sponsor has conducted sufficient pre-clinical investigations to suggest that the drug will be safe in humans. Generally, at this stage the sponsor will meet with the regulator to discuss the compound and address questions that might be raised.
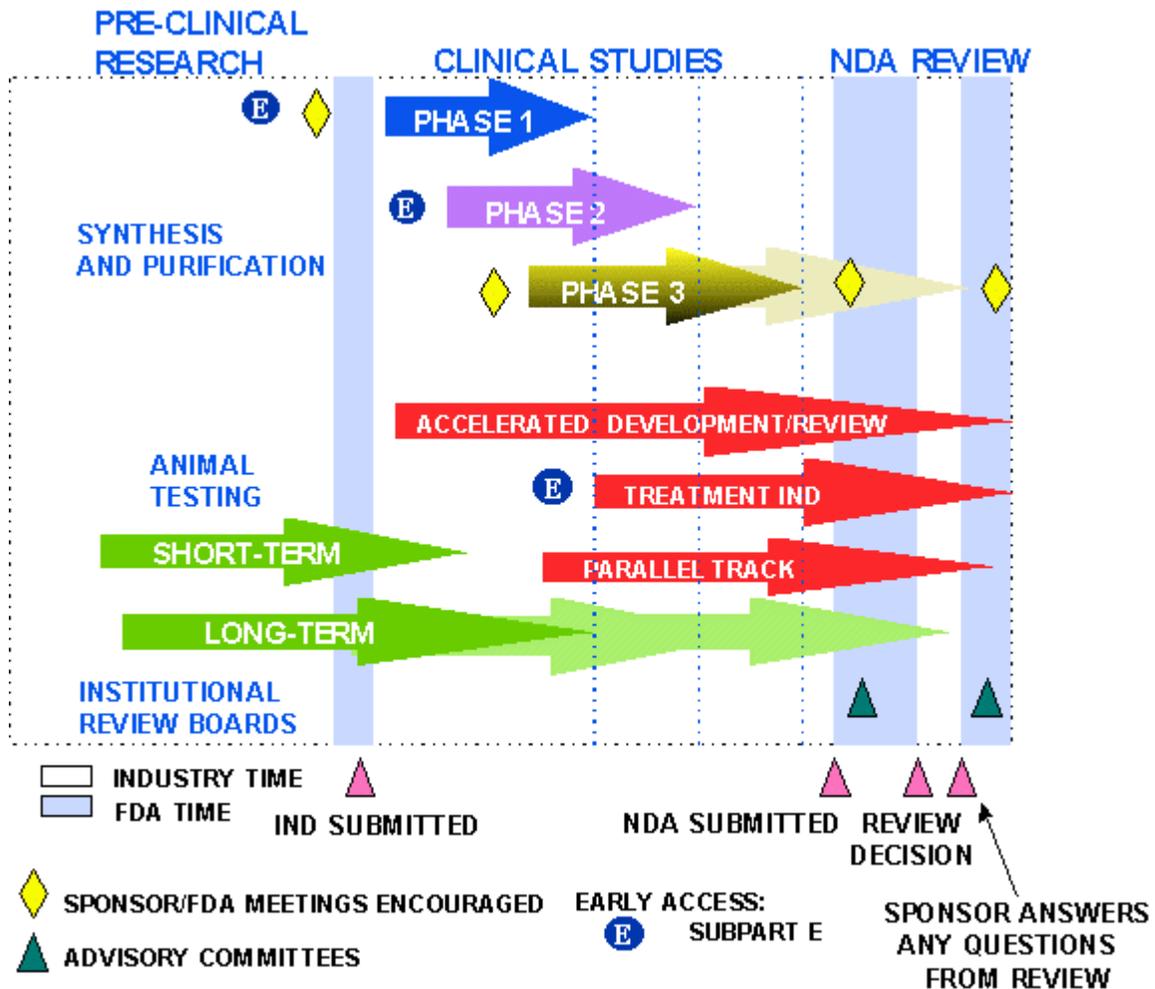
If there are no objections to the IND, the sponsor will then initiate the procession of clinical trials. The trials are typically conducted in three phases:

- Phase 1: The drug is tested in a few healthy volunteers to determine if it is acutely toxic.

- Phase 2: Various doses of the drug are tried to determine how much to give to patients.

- Phase 3: The drug is typically tested in comparative, double-blind controlled trials to demonstrate that it works.[15] Sponsors typically confer with FDA prior to starting these trials to determine what data is needed, since these trials often involve hundreds of patients and are very expensive.

- (Phase 4): These are post-approval trials that are sometimes a condition attached by the FDA to the approval.

The following chart, borrowed from FDA[16] gives an overview of this process. The red arrows refer to variations on the approval route that may be used when there is an identified unmet medical need or there is pressure to allow the drug for use, even while it is being studied. These variations have specific requirements and are only applicable in limited situations.

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[15] The comparator is required to be the "standard of care" for the indication. There are many cases where the indication is very narrow and there is no approved drug to treat that specific condition. In this case the comparator would be a placebo.
[16] http://www.fda.gov/cder/handbook/develop.htm

PRE-CLINICAL RESEARCH / CLINICAL STUDIES / NDA REVIEW

SYNTHESIS AND PURIFICATION

PHASE 1
PHASE 2
PHASE 3

ACCELERATED DEVELOPMENT/REVIEW
TREATMENT IND
PARALLEL TRACK

ANIMAL TESTING

SHORT-TERM
LONG-TERM

INSTITUTIONAL REVIEW BOARDS

INDUSTRY TIME
FDA TIME
IND SUBMITTED
NDA SUBMITTED
REVIEW DECISION

SPONSOR/FDA MEETINGS ENCOURAGED
EARLY ACCESS: SUBPART E
SPONSOR ANSWERS ANY QUESTIONS FROM REVIEW

ADVISORY COMMITTEES

All trials have to be conducted according to Good Clinical Practices ("GCPs") which are rules promulgated by regulators and designed to ensure that research is conducted in a transparent and reliable manner. The GCP obligations are not insignificant and pose an additional hurdle to organizations involved in this process. Further, it is important to recognize that carrying out the trials requires significant and varied expertise at each new stage. Phase 1 trials (or first in human) trials are themselves fraught with uncertainty and often must be carried out in special units that have the capacity to monitor and respond to dosing responses very quickly. Phase 2 trials will include first in patient testing and an assessment of relevant dosing. The extent of participation, duration, comparative arms, etc. must be chosen for each trial, in accordance with the specific characteristics of the drug, including identified potential for toxicity, potential

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reactions with other drugs, adsorbtion, metabolism and excretion characteristics as well as the mechanics of dosing and potential patient adherence.

All along this process, sponsors will confer with regulatory authorities to identify unexpected results, adverse events, potential changes to the protocol and any other unforeseen and/or significant events. It is additional important to note that once the clinical trial process begins, the sponsor is quite tightly bound to the specific compound that is being tested; innovations or changes to the compound itself or even the manufacturing process will need to be reported in to the regulators and could, hypothetically, invalidate study results generated with a prior or alternate version of the compound.

Once the entire package has been completed, the sponsor will submit a New Drug Application ("NDA") or Biologics License Application ("BLA") [or equivalent in other jurisdictions] to the regulator. The review time and process varies from country to country, but will generally involve questions to the sponsor during the review and may potentially involve the convening of an advisory board of experts in the field to advise the regulator on how to respond. In the U.S., review timeframes range from 6 months for fast track review to 10+ months for non fast-track applications.

Approval is not guaranteed even if the regulator has been involved throughout the development process. The application is generally reviewed by multiple disciplines separately, including pharmacology, toxicology, CMC (chemistry, manufacturing, controls), medical, etc.[17] Any of these groups may find issues that they feel makes the risk-benefit balance unacceptable. In recent years, the number of new drugs representing new chemical entities (NCEs, as opposed to follow-on or "me-too" versions of previously existing drugs) approved by FDA in the U.S. has declined sharply. In 2008, there were under 25 such NCEs

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[17] Health authorities that "approve" drugs are supposed to be making their determinations on the basis of scientific criteria of safety and efficacy; they do not take into consideration the costs. Costs are concerns for entirely different officials: those in governmental or private reimbursement organizations.

approved by FDA in the US. Moreover, in the wake of Vioxx and other highly publicized safety issues, regulators have implemented numerous additional controls pre-approval and post-approval that may further limit the availability and approval of new drugs.

Even after approval, there are continuing monitoring activities. As a condition of approval, regulators may require post-marketing studies (Phase IV) to track adverse events or safety issues of concern. Sponsors are required to track and report adverse events and to continually monitor and update labels as new information is made available about the safety of the drug. Further, before entering the market, the sponsor will need to interact with pricing and reimbursement administrators in multiple countries to determine the actual availability of the drug to patients. Depending on the sponsor's aims, post-marketing will also require attention to IP and regulatory exclusivities to ensure that monopoly rights are not being infringed. This in itself can be a labor intensive and costly undertaking.

c. Generics

The generic pathway offers an abbreviated route for completing the regulatory requirements discussed above and as such is cheaper and less burdensome to complete.[18] It is important to realize, however, that approval of a generic version of a drug is *not* automatic once there is an approved brand version of a drug. First, generic approval is only available once relevant patent terms and exclusivities have expired and so there is generally some period before an application for approval of a generic can be submitted. Second, generic versions of drugs must be individually approved by relevant regulatory authorities based on GLP, GCP and GMP compliant evidence of bioequivalence, as well as clinical

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[18] This discussion has merged drugs and biologics in the discussion of drug development. Importantly, however, for purposes of generics, there are very different regulatory approval mechanisms because of the nature of the substances themselves. It is much more straightforward to copy small molecule drugs based on chemical formulae and conformation information. Biologics, by their nature, are very large complex molecules and are produced in cells - rather than being synthesized. As a result, very minor variations in production conditions can have drastic impacts on safety and efficacy.

support for any differences between the proposed generic version and the approved drug. For the remaining issues related to the drug, the generic applicant is allowed to rely on data in the brand drug's original application. Thus, generics get a "shortcut" to marketing authorization.

Nonetheless, generics are subject to the same regulatory parameters as their brand counterparts. Generic manufacturers also have post-marketing safety reporting obligations and are subject the similarly tight controls on ingredient quality, sourcing and other manufacturing issues. The net result is that while it is less burdensome to obtain regulatory approval of a generic drug, it is still a costly process with strict controls and follow up that must be maintained.

d. Patent Terms and Exclusivities

It is worth noting briefly the basis for drug market exclusivity, once they are approved. In essence, there are two types of exclusivity: (1) that conferred by patent; and (2) that conferred by regulators - also known as regulatory exclusivity or data exclusivity.

Patent exclusivity reflects the IP landscape of the drug. For the term of the relevant patent(s) on a drug, competitors are precluded from using that protected information. Generally, the strongest patent for a drug is a "composition of matter" patent, that protects the molecule/compound representing the active ingredient in the drug. As long as that molecule/compound is under patent protection, no one can market a copy of the drug.

Regulatory exclusivity is conferred by regulators, in effect, as an incentive for submitting certain types of applications. Regulatory exclusivity effectively protects the data submitted for approval. Thus, during the term of regulatory exclusivity, no competitor can rely on the data for a brand name drug to obtain approval for a generic or copy of that drug. Thus, the generic pathway is not available, and

approval can only be based on submission of a full regulatory package (as described above).

Regulatory exclusivities are generally run concurrently with patent terms and for the most part are awarded for successful approval of new chemical entities or new indications, for which significant clinical studies were required. Often times, pharmaceutical companies submit data for new indications to get the 3 year exclusivity period at a time when their patent on a drug is close to expiration. The added regulatory exclusivity effectively prolongs the period of market exclusivity and is often referred to by critics as "evergreening."

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