Perspective

Drug discovery and development: Role of basic biological research

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Abstract　　This article provides a brief overview of the processes of drug discovery and development. Our aim is to help scientists whose research may be relevant to drug discovery and/or development to frame their research report in a way that appropriately places their findings within the drug discovery and development process and thereby support effective translation of preclinical research to humans. One overall theme of our article is that the process is sufficiently long, complex, and expensive so that many biological targets must be considered for every new medicine eventually approved for clinical use and new research tools may be needed to investigate each new target. Studies that contribute to solving any of the many scientific and operational issues involved in the development process can improve the efficiency of the process. An awareness of these issues allows the early implementation of measures to increase the opportunity for success. As editors of the journal, we encourage submission of research reports that provide data relevant to the issues presented.
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1. The process: Many years, many failures, much uncertainty

Most often, the development of a new medicine starts when basic scientists learn of a biological target (e.g., a receptor, enzyme, protein, gene, etc.) that is involved in a biological process thought to be dysfunctional in patients with a disease such as Alzheimer's disease (AD). Here, we are considering the discovery and development of entirely new medicines, those with a mode of action different from already approved medicines and intended for a clinical indication that is not addressed by approved medicines. Better medicines that are iterative improvements on current medications are valuable as they may offer benefits over existing medications in terms of potency, safety, tolerability, or convenience, but they usually do not involve the manipulation of biological targets different from those directly affected by existing medications.

Analyses across all therapeutic areas indicate that the development of a new medicine, from target identification through approval for marketing, takes over 12 years and often much longer [1]. The cost to develop a New Molecular Entity (NME; a small molecule compound) or New Biological Entity (NBE; an antibody, protein, gene therapy, or other biological medicine) is certainly over $1 billion and, on average, has been estimated to be about $2.6 billion [2]. Fig. 1, adapted from Paul et al. [3], shows a schematic of the stages involved in developing a new medicine along with average times required for each stage and the approximate cost (in 2010 dollars) for each phase of development. Importantly, Fig. 1 also depicts the number of molecules that must be entered into each stage of development to, eventually, produce one new approved medicine. This figure is based on analyses across several therapeutic areas and includes data from development programs that are new iterations of existing medicines as well as those seeking medicines based on completely new targets or that aim for completely unprecedented therapeutic indications. It seems highly likely that the numbers in Fig. 1 greatly underestimate the numbers of molecules needed at each stage of development to produce a new medicine to treat a disease for which no therapy currently exists. Separate figures for AD drug

The Drug Development Process: It's Long, Expensive and Risky

	Target to Hit	Hit to Lead	Lead Optim	Non-Clinical	Phase 1	Phase 2	Phase 3	Sub to Launch
# per Launch	24.3	19.4	14.6	12.4	8.6	4.6	1.6	1.1
P(TS)	80%	75%	85%	69%	54%	34%	70%	91%
Cycle time (yrs)	1.0	1.5	2.0	1.0	1.5	2.5	2.5	1.5
Cost/launch ($mil)	$94	$166	$414	$150	$273	$319	$314	$48
P(TS)AD[1]					28%	8%	1.8%	100%

Adapted from: SM Paul et al. Nature Reviews: Drug Discovery, 2010.
Costs are capitalized based on 11% cost of capital and in 2010 dollars.

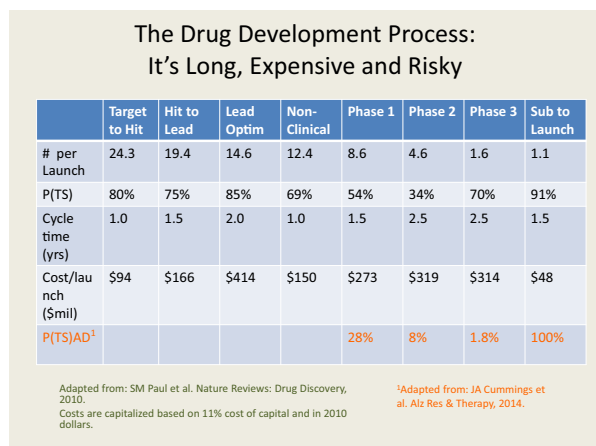[1]Adapted from: JA Cummings et al. Alz Res & Therapy, 2014.

Fig. 1. A diagram of the stages of drug discovery and development with estimates of cost and duration. Adapted from [3] and [4].

development programs are not available, but the last line of Fig. 1 shows clinical transition probabilities calculated by Cummings et al. [4], who reviewed all of the 244 unique compounds studied in clinical trials for AD from 2002 through 2012. It is evident that the likelihood of advancing an AD drug candidate has been very low when compared with those for development programs across a broad range of therapeutic areas. Stated another way, the probability is very low that any new biological target or molecule identified as potentially relevant to the modification of AD will result in an approved new medicine. We should anticipate that a very large number of biological targets will need to be discovered and interrogated pharmacologically and genetically to achieve a single new disease-modifying medicine for AD.

In accordance with this, central nervous system (CNS) drugs have lower success rates and take a longer time to develop, than do other drug classes. Specifically, the success rate of neuropsychiatric drug candidates who enter into human testing to effectively reach the marketplace is dramatically lower (8.2%) than for all drugs combined (15%) [5,6]. In the case of drugs focused toward AD progression, of the numerous evaluated clinically, the attrition rate has thus far been 100%. Furthermore, the average clinical development time for neuropsychiatric drugs is in the order of 8.7 years, as compared with 5.9 years for antiviral agents, almost 50% longer. The time required to gain regulatory approval is also longer for neurological drugs, 1.9 years as opposed to an average of 1.2 years for all drugs. Taking into account the approximately 6 to 10 years that drugs generally are in the preclinical phase of development, neurological drugs can take up to 18 years to run the gauntlet from initial laboratory evaluation to regulatory approval and use [5,6]—a long duration in relation to the current 20-year patent protection rights. The drug development process is set up, particularly at the stage of clinical

development, to "fail fast, fail early" in a strategy to eliminate key risks before making a expensive late-stage investment [7,8]. Nevertheless, neurological agents tend to fail later during the clinical development process—in phase 3 clinical trials [5,6], particularly for recent AD experimental therapeutics, thereby making CNS drugs among the most expensive to develop. It is hence important to optimize each piece of the preclinical and clinical development process.

2. Discovery: From target to clinical candidate

The goal of a preclinical drug discovery program is to deliver one or more clinical candidate molecules, each of which has sufficient evidence of biologic activity at a target relevant to a disease as well as sufficient safety and drug-like properties so that it can be entered into human testing. Most discovery programs seek to produce more than one candidate molecule because, as is shown in Fig. 1, many molecules do not move through the entire process because of problems with safety, kinetics, potency, intellectual property protection, or other factors. There is no simple formula for producing a viable clinical candidate molecule, although extensive collaboration of chemistry, biology, toxicology, and pharmacokinetics is almost universally the norm in modern drug discovery programs [9]; small molecule drug discovery programs typically produce massive amounts of data using high-throughput screening techniques that evaluate many compounds at many doses against many assays [9].

Some of the information that should be developed during discovery studies for a clinical candidate molecule is shown in Fig. 2. All of the topics listed in this figure will need to be addressed before deciding whether a molecule is suitable for testing in humans. There are no perfect discovery programs, and some of the desired information listed in Fig. 2 may be missing; however, gaps in

Information to be Developed for a Potential Clinical Candidate Molecule

- Clarity about target validation – relation to human disease
  - Target similar to other effective drugs
  - Genetic data from humans
  - Targets physiology affected by disease
  - Effective in animal "model" of disease - what evidence supports relevance to human disease?
- Reliability of findings – across multiple assays, labs, doses, populations and conditions as appropriate
- Specificity of molecule against target
- Kinetics of molecule(s)
- Potency of Molecule(s)
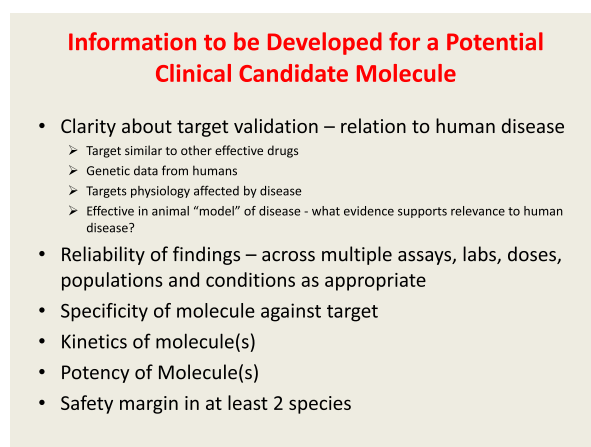- Safety margin in at least 2 species

Fig. 2. A summary of the information to be developed before the selection of a clinical candidate molecule proposed for testing in humans.

knowledge at this stage often lead to difficulties in interpreting later studies. Critical to moving any molecule forward will be an assessment of target validity; that is, does the molecule target an aspect of biology that is relevant to the disease of interest? And, is the target expressed in the human brain during the disease process that allows a window of opportunity for treatment? Target validation has no uniformly accepted definition, although data from humans showing some relationship of the proposed target to the disease, such as AD, are essential. For potential medicines that are designed to be improved iterations on already approved medicines, the validating data are usually quite compelling and derive from the fact that other medicines with similar mechanism of action have shown efficacy. For AD, where there is no disease-modifying medicine, such validation is not available. In the search for medicines directed toward completely novel targets, advances in genetics, such as the Human Genome Project, have produced many potential new pharmacological targets and genetic "validation" is often cited as a reason for pursuing a novel drug target [10]. However, mechanistic targets such as receptors and enzymes that are well understood biologically have led to many of the medicines currently used; in addition, whole animal models that reproduce some physiological aspects of human disease such as abnormal activity in a specific neural circuit have also been used successfully [10]. None of these approaches to target validation are a guarantee of success in screening for potential new medicines, but it is important to be very explicit about the data supporting the pursuit of a target and the kinds of screening tools available for identifying potential clinical candidates. This explicit understanding will help insure that results obtained with one molecule can be used to help inform the development program for the next molecule.

Drug developers seeking medicines for diseases, such as AD, cancer, or other difficult to treat diseases, are very eager to learn about new targets that might be the focus of a new drug discovery program. At the same time, they are often very skeptical of new findings in the scientific literature that claim to have identified a NBE or process that could be a target of interest. The investment in time and money needed to pursue a new biological target is very large so that drug developers nearly always attempt to reproduce reported findings before engaging in screening against novel targets; such efforts to reproduce even findings reported in the most reputable journals find that most, maybe even as many as 90%, cannot be reproduced [11]. The reasons for this high failure rate are a matter of some discussion; for present purposes, it is important to note that investigators proposing that a new finding is relevant to drug discovery should expect a high level of skepticism and, even if industry investigators show interest, it is almost certain that there will be attempts to replicate the findings and explore their reproducibility with other animal models, cell lines, and physiological conditions [12].

3. Development: Kinetics, drug disposition, safety, biomarkers, and efficacy

A biological target, even one with validating data, will only be useful for drug development if it is possible to make molecules that affect the target in a way that could be well tolerated and therapeutically useful. Furthermore, those molecules must be shown to have properties enabling them to act like a medicine when given to people. The molecules must have pharmacokinetic (PK) properties that enable there to be a predictable and consistent relationship between the dose of the drug given, exposure of the drug at the proposed site of action, and the binding of the drug to the target of therapeutic interest. The preclinical and later clinical studies needed to determine these PK properties of a proposed medicine are extensive [13] and are particularly complex for CNS targets because of the blood-brain barrier. Fortunately, advances in medicinal chemistry and biological PK modeling have reduced the number of molecules entering clinical development with unsatisfactory PK properties [13]. Indeed, this represents an area in which the identification of a problem, unsatisfactory PK/bioavailability, has resulted in implementation of effective strategies to remedy a significant cause of drug development failures. During 1991, unsatisfactory PK/bioavailability properties of experimental drugs represented the most significant cause of attrition, accounting for approximately 40% of drug development failures. By 2000, however, this cause of attrition had fallen to less than 10% [14]. The appreciation that previously successful drugs typically have physicochemical and structural properties within certain ranges, and the application of this knowledge when considering the synthesis of new chemical entities, as proposed by Chis Lipinski in his "rule of five" [15], has positively impacted the development of both systemic and CNS drugs.

The range of potentially safe and tolerable doses of a molecule must be determined before human testing. Toxicology studies in at least two nonhuman species are usually used to determine a projected safe dose range and to provide information about compound distribution, organ-specific toxicity, and metabolism [16]. These studies should provide information on the emergence of adverse effects as compound dose is increased and provide guidance on compound-specific monitoring that might be needed in early clinical studies. Serious, irreversible adverse effects observed in these studies within some multiples of the projected efficacious dose are likely to prevent further development of the compound. Compound failure rates due to toxicity before human testing are relatively high [7], and account for as much as 30% of drug attrition occurring during the clinical stage of development [14], emphasizing the need to have backup compounds for targets that are well validated and of high strategic importance. The other key cause of attrition is a lack of efficacy, accounting for some 30% of drug development failures [14] and quite possibly more for CNS drugs in which animal models of efficacy are

indisputably unpredictive—likely consequent to the complexity of the human brain in comparison with rodent animal models and the complex etiology of neurological disorders.

As indicated in Fig. 1, only about 1 in 8 compounds entering clinical development in the pharmaceutical industry is eventually approved for marketing. As noted, the success rate is much lower for diseases such as AD. The recent review mentioned previously [4] found that 244 compounds entered clinical development for AD between 2002 and 2012 with only one of them (memantine—an N-methyl-D-aspartate receptor antagonist and symptomatic, rather than disease progression, drug) achieving regulatory approval; this is a failure rate of 99.6%. Even with the extraordinarily high failure rate in this disease, companies have continued to invest because the unmet medical need is great and there are scientifically plausible targets to pursue. Most (78%) of the 413 clinical trials (244 unique molecules) conducted of potential medicines for AD between 2002 and 2012 were supported by the pharmaceutical industry [4].

While investment in AD therapeutics continues, the high cost of failures means that scientists proposing new targets or molecules for development should examine carefully the characteristics associated with successful development programs. In an indication where failure is the norm, it is far better if those failures occur earlier rather than late in development. Also, it is best if each study in the development program yields data that provide a compelling basis for termination, continuation, or specific modification of the compound development program; data that are difficult to interpret scientifically can lead to more studies and delayed decision-making with no prospect for better studies in the future. Even programs that are terminated can be "good failures" if the termination has convincingly tested a proposed therapeutic mechanism, a soundly based scientific hypothesis, or provides clear direction for future studies [7]. Some key elements needed for highly informative phase 2 programs have been identified [17] and are summarized in Fig. 3. The first essential element is clear evidence that the molecule being tested has adequate exposure at the proposed site of action. For AD therapeutics, this usually means somewhere in brain; CSF studies in humans are often used as indirect measures of CNS target exposure. The second key element is evidence for binding to the therapeutic target, such as a receptor, enzyme, protein, or specific brain structure. Brain imaging technology, particularly positron emission tomography, has enabled target engagement studies for many CNS molecules; such studies may also help inform the most likely clinically efficacious dose [18]. The third essential element for success in phase 2 is evidence for a pharmacodynamic (PD) or downstream biological effect of the drug—best associated with its proposed mechanism of action or underpinning the scientific hypothesis being tested. Measures of amyloid β concentrations in blood and CSF have provided useful

> ### Phase 2: The Tree Pillars of Survival
>
> ➤ Evidence of **exposure** and its relationship to dose, frequency of administration, patient characteristics (weight, organ function, etc.) For CNS drugs this is often done with plasma/CSF studies.
>
> ➤ Evidence of **target engagement** and its relationship to drug PK. Done thru PET RO, biochemical assays or other. Needed to show that an agent binds to the expected target given it's proposed mode of action
>
> ➤ Evidence of target related **pharmacodynamic effect** and its relationship to dose and drug PK. Pharmacological activity is demonstrated thru evidence on downstream biological measure or clinical efficacy. This is used to set dose and dosing regimen for phase 3.
>
> From: P Morgan et al. Drug Discovery Today, 2012.

Fig. 3. A summary of the critical compound-related information needed from phase 2 to improve the likelihood of moving to phase 3. Adapted from [12].

measures of the PD effects of amyloid β lowering compounds such as the γ- and β-secretase inhibitors [19]. The recent development of techniques to sample the contents of extracellular vesicles (exosomes) enriched for neuronal origin from peripheral blood and to use them as a biomarker discovery platform for neurological disorders [20] has the potential to provide a window into disease progression within the brain and its response to drugs. Drug development scientists in the pharmaceutical industry often look to academic laboratories for leadership and partnership in developing the tools needed to assess PD effects of drugs, as the technology for making these assessments (e.g. biochemical assays, imaging procedures, positron emission tomography ligands, evaluating the cargo of exosomes) is often not compound specific and may require scientific knowledge not readily available in a company.

Clear measures of exposure, target engagement, and downstream biological effects do not assure clinical efficacy, but they do insure that the studies in the clinical development program are testing the therapeutic value of a proposed biological target and intervention strategy. The viability of a new biological finding as a therapeutic target can be markedly enhanced by technologies that enable measurement of exposure, target engagement, and PD effects. If such measures are available, the proposed target will have a much better chance of being followed up with a well-funded discovery and development program. When such measures are ignored, it is difficult to interpret data showing that a drug is ineffective because of flaws in the drug development and design process (e.g., inadequate exposure of the target to the drug), rather from lack of efficacy. In the former case that can potentially be remedied, the proposed mechanism of action and/or scientific hypothesis has not been evaluated under appropriate conditions optimized to expect drug action; resulting in a type 2 error and the waste of resources [21].

4. Essential elements: Linking and cross-validating studies as one progresses through the preclinical/clinical process, early proof of mechanism studies, check lists to help avoid hidden errors

Collaboration across disciplines and between preclinical and clinical studies is almost essential for a successful drug discovery and development program. Activities contributing to the eventual approval and use of new medicines come from academic laboratories, large and small pharmaceutical companies, and multiple contract research organizations. Fig. 4 lists many of the kinds of research activities that are needed to produce a new medicine; to be done effectively, they should be done with some recognition of how these pieces fit together and with the recognition that the results from one activity must be communicated effectively to scientists involved in each of the other activities. No single type of research provides the entire key to success.

Linking and cross-validating studies, whether undertaken within the same laboratory or across laboratories, is an essential component to a successful drug development program—particularly when such studies relate to the mechanism of action of the experimental drug of interest and/or fundamental hypothesis being evaluated. All too often drug development uses approaches that are intended to minimize the time to regulatory approval and focus too exclusively on obtaining evidence of drug efficacy, rather than understanding drug action and testing the founding hypothesis. Evaluations of regulatory efficacy measures alone, albeit necessary steps to successfully develop drugs, are too frequently insufficient within themselves to support the scientifically rigorous translation of discoveries into clinical practice benefits and advances in scientific knowledge and methods. The simultaneous evaluation of measures associated with drug mechanism/hypothesis can open new avenues of research as well as close them, and advance our knowledge of the brain and its targets for intervention. To ensure against errors, often hidden ones, a "check list" is valuable (indeed, crucial) to optimize the translation of a drug candidate through the nonclinical and clinical stages of the drug development process and, thereby, maximize the potential for success [22]. The publication of positive and negative drug development studies and clinical trials, likewise, is essential as when such information goes unreported, the predictive value of preclinical models cannot be evaluated, and investigators cannot not learn from earlier failures how to improve methods and practices [23,24].

5. Additional uncertainty: Regulations, manufacturing, finding the right patients

The discovery, design, and synthesis of one or more good molecules directed toward validated targets and informed by well-designed and well-executed clinical and nonclinical studies will eventually lead to a submission package for regulatory approval. In planning a development program, it is important to determine whether the proposed studies will satisfy regulatory requirements for evaluating safety and efficacy and enable development of an informative label for the new medicine. Although few medicines have been approved for AD, regulators in the United States and other countries have been very proactive in developing regulatory guidance on new medicines in this area [25]. However, it is possible that a proposed new medicine is envisioned to work in a way that is not covered by published regulatory guidance; in such a case, the developers must work interactively with regulatory officials to come up with a plan that does justice to the mechanism proposed and that will satisfy regulatory needs.

Once a molecule is approved, it must be manufactured according to high standards of purity and stability as prescribed by regulations [26]. Although manufacturing is not usually a concern for discovery biologists, the process of manufacturing a new medicine can be complex and expensive, particularly for biological products (NBEs). The complexity of manufacturing may play a role in determining the financial viability of investment in a specific biological target. Finally, a new medicine must find acceptance in the medical community so that physicians and patients can be assured that the medicine can be given to the right patients, at the right doses at the right time. This is essentially what is meant by the term "personalized medicine" [27]. For new medicines designed to be used in a group of patients already identified by widely used diagnostic practices, finding the right patients may not be too difficult. If the appropriate patient population is not one identified by current diagnostic practice, then efforts must be taken to enable clinicians to identify the right patients before product launch. Recent studies in AD therapeutics geared toward prodromal and preclinical AD, if successful, require new diagnostic approaches in clinical practice [28].

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Individual Laboratory Contributions to Drug Discovery and Development

- Target identification – new receptor, enzyme, pathway, protein, other.
- Target validation – data linking target to human disease
- Finding new molecule – chemical or biological
- Screening assays – cell lines, animal models, others.
- Data on drug-like characteristics – PK, toxicology
- Development tools – PD Biomarkers including biochemical assays, PET ligands, electophysiological measures, others.
- Efficacy measures – clinical scales, cognitive tests, functional measures, self reported outcomes, electronic health recording
- Technologies to improve efficiency of trial completion – recruiting technologies, electronic data capture and tracking, trial simulation, safety monitoring, other.

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Fig. 4. A partial list of the kinds of data and research tools that contribute to a successful drug discovery and development program.

6. If at first you don't succeed (and you won't), learn, then try again

Fig. 5 provides a schematic of many of the activities that occur during the drug discovery and development process. Note that many molecules, both NMEs and NBEs are considered in the discovery phase at the left to yield a single approved medicine. The flow of new information from basic science, through preclinical and clinical development, to Food and Drug Administration filing along with critical activities at each stage is depicted. Also critical, however, are the reverse arrows at the bottom showing that later preclinical and clinical data identifying deficiencies (failures) in some molecular approaches provide feedback to inform the conduct of studies at earlier stages of discovery and development that are more likely to yield successful medicines. With long time lines for drug discovery and development, and high failure rates, many investigators will work in a therapeutic area such as AD for years without seeing a new generation of medicines. This can be frustrating but other therapeutic areas such as cancer and heart disease have also gone through long periods of incremental scientific advances before the introduction of markedly more effective therapeutic agents. Analyses that take the long-term view of the drug development process indicate that incremental learning shared across the various disciplines involved in the process and across the stages of drug development is key to the delivery of new medicines [29]. Sharing of precompetitive data and clinical trial results by commercial sponsors is also important for the advance of science and contributes toward the more rapid introduction of new medicines [29,30]. Incentives that provide intellectual property protections for investment in expensive, high-risk research directed toward areas of high unmet medical need can encourage both investment and data sharing by commercial sponsors [31]. In spite of the lack of new AD medicines in recent years, the drug discovery and development process has improved as a result of more precise diagnosis, information on natural history of AD and measurement of clinical progression, better biomarkers, genetic findings, and knowledge of pathophysiology. Such knowledge, combined with a focus on good molecules and efficient development plans will ultimately produce better medicines.
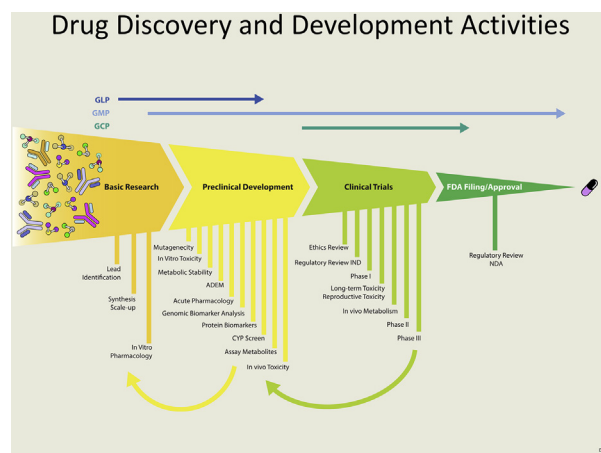
Fig. 5. A schematic of the activities involved in the drug discovery and development process. At the left are shown icons depicting small molecules (NMEs) and biological molecules (NBEs) being considered for development. At the top are the time lines for quality assurance guides governing the process; they are good laboratory practice (GLP), good manufacturing practice (GMP), and good clinical practice (GCP). Specific activities in the stages of development are shown at the bottom; they include studies of absorption, distribution, excretion and metabolism (ADEM), screening for activity at cytochrome P450 (CYP) liver enzymes, and regulatory filings for Investigational New Drug (IND) and New Drug Application (NDA). Abbreviations: NBE, New Biological Entity; NME, New Molecular Entity.

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