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Introductory Chapter

Overview of Current Drug Discovery and Development with an Eye Towards the Future

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1. Introduction

Drug discovery and development process aims to make available new pharmacological interventions to prevent, treat, mitigate, or cure disease in a safe and effective manner. It is a slow, complex, multi disciplinary and costly process. Drug development starts with a target identification and validation, followed by drug candidates (hits) discovery, and lead drug (compound with favorable pharmaceutical, safety, efficacy, and pharmacokinetic profile) selection and optimization. Preclinical (non clinical) efficacy, pharmacology, toxicology, and mechanistic studies may include *in silico* (computational) methods, use of *in vitro* animal or human tissues (including cells and subcellular fractions), and *in vivo* animals. The studies rely on models that are thought to be predictive of the subsequent preclinical or clinical effects. Guidances (government-regulated standards of normal expectations) for different steps are readily available from the regulatory agencies (<http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm>). The required toxicology studies must be performed according to the Good Laboratory Practice (GLP) guidelines. Medicinal chemistry and pharmaceuticals also play a crucial role from the beginning of the drug discovery and development process, involving chemical synthesis (including compliance with current Good Manufacturing Practice, cGMP), characterization, purification, chemical alteration, stability determination, and formulation of the drug candidate. The first-in-human (FIH) doses are based on the No-Observed-Adverse-Event-Level (NOAEL) values obtained in the relevant and more sensitive toxicology species (rodent and non-rodent, commonly rat and dog), interspecies dose extrapolation, and a selection of an appropriate safety factor. Subsequent to preclinical evaluation, an Investigational New Drug (IND) application is submitted to the regulatory agency (e.g. United States Food and Drug Administration, FDA or European Medicine Agency, EMEA) summarizing all preclinical data (chemical, pharmaceutical, efficacy, toxicology and other) along with a rationale for the proposed clinical study and a clinical study protocol. Clinical drug development can commence after review of the IND by the regulatory agency and a clinical study approval by a local Institutional Review Board (IRB, a committee of scientists and non-scientists overseeing the clinical research). Phase 1 studies commonly use human volunteers to determine human safety and pharmacokinetics. Frequently, these studies also include biomarkers of efficacy as secondary endpoints. Drugs with acceptable safety profiles then enter Phase 2 for efficacy evaluations. These include the proof-of-principle studies to demonstrate effects on disease-relevant biomarkers and the proof-of-concept studies to

demonstrate direct effects on the target disease in a small patient sampling. Controlled trials are commonly designed to compare effects of the new drug to a placebo or to a standard of care treatment (for ethical reasons). Drugs showing promising efficacy continue to Phase 3, much larger trials examining efficacy as well as safety. Drugs emerging from these trials with appropriate evidence of safety and efficacy are submitted for marketing approval via a New Drug Application (NDA). Following a review and approval by the regulatory agency, the drug can then be marketed and enters Phase 4 or post-marketing monitoring.

Recent estimates suggest that it takes up to 13.5 years and 1.8 billion U.S. dollars to bring a new drug to the market [17]. There are rising concerns over the diminished productivity (number of new medical entities approved) in face of the escalating cost (R&D spending). In view of this, there is a growing effort and urgency to find new approaches aiming to decrease attrition and increase success in drug development [8, 10, 11, 17]. This is at times when number of drug blockbusters is coming off patent, large personnel layoffs and pharmaceutical consolidation (buying and merging in an effort to shore up pharmaceutical company pipelines). There are strong beliefs that pharmaceutical industry needs to find means of improving efficiency and effectiveness in order to sustain itself. Two independent studies, one by the FDA and the other by the European Federation of Pharmaceutical Industries and Associations (EFPIA), examined the causes behind the decreasing productivity. Based on these studies, improvements in predictivity of safety and efficacy were deemed to have the greatest potential for reversing the trend of diminished productivity and success [10]. This led to formation of public-private initiatives aiming to accelerate the development of better and safer medicines, the Innovative Medicines Initiative, IMI (<http://imi.europa.eu>) and the Critical Path Institute, C-PATH (<http://www.c-path.org/>). In 2004, FDA launched the Critical Path Initiative (CPI) as described in its white paper *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (<http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm>):

“Sounding the alarm on the increasing difficulty and unpredictability of medical product development, the report concluded that collective action was needed to modernize scientific and technical tools as well as harness information technology to evaluate and predict the safety, effectiveness, and manufacturability of medical products. The report called for a national effort to identify specific activities all along the critical path of medical product development and use, which, if undertaken, would help transform the critical path sciences.”

This was echoed in subsequent C-PATH reports (<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/UCM186110.pdf>; <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm>). Dr. Raymond Woosley, the president and CEO of the C-PATH is quoted on the C-PATH's website that it presently takes 15 years for drug development and 95% of drug candidate fail along the way. The very ambitious goal cited by the Institute is to shorten the time to 3 years and improve the success to 95%.

Major reasons cited for drug attrition are lack of efficacy, presence of toxicity, and commercial concerns [12]. It was reported that only 5% of the compounds entering the first-in-human studies in oncology achieve successful registration [12]. Majority of failures occurred in Phase 3 and were attributed to the lack of efficacy proof of concept, lack of objective and robust biomarkers, inadequate predictivity and poor translation of scientific discoveries and preclinical information to clinical settings. Innovation was commonly

viewed as one of the most needed approaches to reversing the situation [8, 11, 17, 24]. A recent Science editorial by the current FDA commissioner [6] echoed these viewpoints. Commonly cited areas for potential and fruitful innovations include the development process itself, identification, validation and qualification of relevant biomarkers, predictive modeling, clinical trial subject selection, clinical trial design, and collaborative efforts involving pharmaceutical companies, academia, government, and public.

“Fail fast, fail cheap” is a common mantra in the pharmaceutical industry. This is intended to minimize losses of time, resources, and expenses. There are number of go/no-go decision gates along the common drug development path. Earlier an appropriate no-go decision is made, lesser the possibility for waste. Drug developers strive to identify the most effective and efficient means of bringing safe and effective products to the market. Success along the development path hinges on using appropriate and robust models and biomarkers, which are relevant and predictive of a disease process of interest. One frequently proposed solution is to move the clinical proof-of-concept phase to an earlier point on the drug development timeline and in a bidirectional manner with the preclinical development [17]. It's expected that this would result in a lesser number of drug candidates entering later clinical testing phases but with increasing probability of their success.

In an effort to decrease the development time and improve drug development efficiency, the regulatory agencies have recently introduced the Exploratory Phase (also known as Phase 0) option(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078933.pdf>). The regulatory requirements for Exploratory Phase are lesser than those for Phase 1 but the doses and scope of the former are also more limited. The Exploratory Phase has no therapeutic or diagnostic intent. Its purpose is to obtain pharmacokinetic and/or pharmacodynamic data and thereby provide an opportunity to obtain the necessary information for an early decision whether to continue the development or to select the optimum candidate or formulation for development [22].

One of the major initiatives in an effort to improve the efficiency and success in drug development deals with identification and validation of robust and predictive biomarkers. Biomarkers play a pivotal role throughout the drug discovery and development process, from the beginning through post-marketing. Biomarker Consortium, composed of the National Institutes of Health, the FDA, the Center for Medicare and Medicaid Services, Pharmaceutical Research and Manufacturers of America (PhRMA), Biotechnology Industry Association (BIO), pharmaceutical companies, academia, and patient groups, was formed in the United States to accelerate development in this area. Present and future perspectives by FDA on molecular biomarkers have been summarized in a recent publication [7]. The Predictive Safety Testing Consortium, PSTC (<http://www.c-path.org/pstc.cfm>) represents an example of one successful collaborative effort stemming from some of these initiatives. In collaboration with the regulatory agencies (FDA and EMEA), the PSTC worked on defining methodologies and validations for new safety biomarkers and presented an initial path and outline for regulatory qualification of biomarkers [5, 21]). In addition through the efforts of the Nephrotoxicity Working Group, seven renal biomarkers have been qualified for limited use in nonclinical and clinical drug development as a measure of drug safety. These efforts were highlighted in a special issue of Nature Biotechnology (<http://www.nature.com/nbt/journal/v28/n5/index.html>).

Advances in hardware and software computational power and sophistication are fueling the rapidly growing reliance on computers and computational modeling in an attempt to

improve the efficiency and effectiveness in the drug discovery and development process [9]. It's not uncommon to hear statements at drug development conferences that computational modeling will play the major role in drug design and development in not too distant future, similar to its role presently in the automotive and airplane industries. Computational modeling addresses the key critical element in all aspects of the drug discovery and development process, the prediction [13]. This *in silico* approach is thought to obviate some disadvantages of the more traditional approaches (need for large amounts of test agent for *in vivo* testing, poor predictability of *in vivo* animal and *in vitro* models for human toxicity and efficacy, lack of reliable high-throughput *in vitro* assays and a lack of animal models for some common adverse events seen in humans, e.g. headache, nausea, dizziness) [16]. There are also increasing legal requirements, especially in Europe, for use of alternative, non-animal models in the regulatory safety assessment of chemicals and urging development, independent assessment and application of computational methods. [15]. As stated in the *Science* editorial: "The FDA is also working to eventually replace animal testing with a combination of *in silico* and *in vitro* approaches" [6]. In 2007, the National Academy of Sciences also proposed a shift away from the current animal toxicology testing to use of emerging technologies i.e., *in vitro* assays using human cells, non-mammalian model organisms, high throughput testing, imaging technologies, omics technologies, systems biology, and computational modeling. Some of the advantages and disadvantages of these approaches were recently discussed by van Vliet [23]. In order to address the great complexity of the biological systems, extensive computational power is required and there are several major virtual screening efforts utilizing grid or distributed computing (e.g. <http://www.worldcommunitygrid.org/research/hdc/overview.do>). *PriceWaterhouse Coopers Pharma 2005: An Industrial Revolution in R&D* report emphasized the growth and value of *in silico* approaches and projected that *in silico* methods will become dominant from drug discovery through marketing (http://www.pwc.com/en_GX/gx/pharma-lifesciences/pdf/industrial_revolution.pdf). Furthermore, the report suggested that we are in a transitional period where the roles of primary (laboratory and clinical studies) and secondary (computational) science are in process of reversal. In a more recent report, *PriceWaterhouseCoopers Pharma 2020: Virtual R&D*, it was stated that pharmaceutical innovation and productivity could be improved significantly via enhanced and more complete molecular understanding of the human body and a more complete knowledge of human disease pathophysiology, thereby enabling development of more predictive computational models (<http://www.pwc.be/en/pharma/pdf/Pharma-2020-virtual-rd-PwC-09.pdf>). This was envisioned as a path towards predictive biosimulation in form of a "virtual man" and a "virtual patient" in some not too distant future with some of the effort along these lines already in progress.

The rapid growth in scientific knowledge and computational capabilities is also providing means for integrating and analyzing disparate chemical, biochemical, physiological, pathological, and clinical data in a parallel as opposed to a sequential fashion. Systems biology applies principles and mathematical tools of electrical engineering and networks to dynamic modeling and simulation of complex biological systems in a holistic manner. This is facilitating a change in drug discovery and development paradigm away from the reductionist approach. It's becoming more recognized that a commonly utilized reductionist approach may not be well suited for complex human disease processes and that the old magic bullet paradigm needs to be replaced by a magic shotgun for many of the diseases

[19]. Human physiology and pathology are very complex involving multi-factorial and heterogenous processes with dynamic, redundant and interactive networks and signaling pathways [1-4, 14, 18, 20]. In fact, the term “Network Medicine” and what it entails is growing in recognition [2]. Furthermore, one size doesn’t fit all and the targets may also change as the disease progresses. In many cases, it’s more relevant to understand the system and how to apply and interpret its perturbations in order to achieve desired efficacy and safety as opposed to concentrating on a single target. In fact, a partial modification of several targets may be more effective and safer than a complete modification of a single target. Based on the above overview, it is clear that changes and innovations in drug discovery and development are needed and that there are ongoing efforts in this area on several fronts. Ultimately, the success hinges on improving the predictivity of efficacy and toxicity, which in turn depends on innovations and having reliable and robust biomarkers and using appropriate tools and methodologies.

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Drug discovery and development process aims to make available medications that are safe and effective in improving the length and quality of life and relieving pain and suffering. However, the process is very complex, time consuming, resource intensive, requiring multi-disciplinary expertise and innovative approaches. There is a growing urgency to identify and develop more effective, efficient, and expedient ways to bring safe and effective products to the market. The drug discovery and development process relies on the utilization of relevant and robust tools, methods, models, and validated biomarkers that are predictive of clinical effects in terms of diagnosis, prevention, therapy, and prognosis. There is a growing emphasis on translational research, a bidirectional bench to the bedside approach, in an effort to improve the process efficiency and the need for further innovations. The authors in the book discuss the current and evolving state of drug discovery and development.

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