COMMENTARY

Advancing Drug Discovery: A Pharmaceutics Perspective

ELIZABETH KWONG

Kwong Eureka Solutions, Quebec, Canada

Received 9 July 2014; revised 25 September 2014; accepted 4 November 2014

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24294

ABSTRACT: Current industry perspective of how discovery is conducted seems to be fragmented and does not have a unified overall outlook of how discovery challenges are being addressed. Consequently, well-defined processes and drug-likeness criteria are being viewed as "broken" and will not maintain future R&D productivity. In this commentary, an analysis of existing practices for defining successful development candidates resulted in a 5 "must do" list to help advance Drug Discovery as presented from a Pharmaceutics perspective. The 5 "must do" list includes: what an ideal discovery team model should look like, what criteria should be considered for the desired development candidate profile, what the building blocks of the development candidate should look like, and how to assess the development risks of the candidate. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: drug-like properties; operating models in discovery; physicochemical properties; Drug Design; ADMET properties; *in-silico* modeling; *in-vitro* models;target therapeutic profile (TPP); developability risk assessment; MAD; rule of five

INTRODUCTION

Despite today's challenging environment, pharmaceutical industry players continue to strive to deliver scientific excellence, meet unmet medical needs, and drive state-of-the-art innovation. At the same time, the industry and its stakeholders are cognizant that the current model is not sustainable for long term. To fix this situation, one of the analyses on R&D productivity[1] has pointed toward the reduction of costs and cycle time. At the same time, shifting compound attrition to earlier during lead optimization before the first-in-human stage of clinical development will be a part of the cost-saving features of this enhanced productivity. In other words, the "preclinical stage" investment is now becoming the new "Phase IIb proof-of-concept study" for key "go/no-go" decisions. By their estimation, this paradigm shift will increase the overall probability of technical success in late-stage phases II and III. This analysis therefore suggests a refocus of resources to discovery research and early translational medicine. Finally, for any successful R&D, there is no substitute for good people and good science. Investment in talent and getting the right people at the bench and in decision-making roles is critical.[1]

Since the publication from Paul et al.,[1] there has been a long-range planning in the pharmaceutical industry to focus on process efficiencies in the preclinical stage. This has been achieved by optimizing decision-making in discovery research, which includes faster "go/no-go" decisions about progressing programs into clinical development. In addition, improvements have been implemented in research capabilities based on the newest scientific insights and the optimal use of resources to balance multiple projects, cost, priorities, and productivity. It will be increasingly important for scientists to not only think from the left or right side of their brain but rather thinking using one brain. As a consequence, a conscious effort to re-organize discovery groups evolved, which included the integration of the preclinical/development functions such as drug metabolism and pharmacokinetics, pharmaceutics, process chemistry research, and toxicology into drug discovery,[2,3] in hopes of improving the efficiency of generating candidates for the development. At the same time, this shift of resources from early development to the discovery space allowed integrated teams such as Developability Assessment Groups[4] to help drive the optimization of well-balanced "drug-like" properties of the candidate. Continued improvement on this holistic approach and reorganization of discovery team resulted in identifying liabilities early, and enabled more rationale candidate selection decisions.

It was also suggested that drug delivery studies, drug–drug interaction assessment, and safety pharmacology assays can be used to provide preclinical information necessary to select a drug candidate with the best overall pharmaceutical profile. Higher sample throughput screens, better *in vitro* cell models, and computational models have been employed to manage resources, costs, and time.[3]

It is also worth noting that in the Discovery space, medicinal chemists are usually the leads and the drivers of the program. This element of discovery programs include many fields of research such as biology, pharmacology, biomarker identification, functional genomics, metabolism, pharmacokinetics, toxicology, pharmaceutics, and so forth and most often chemists in partnership with the biologists are at the heart of the team and will progress the program based on structural–activity relationship (SAR). The success of the discovery program will depend in part on how well the different cross-functional scientific information and historical data are captured to ensure the delivery of an effective and safe drug candidate. For example, medicinal chemists from Hoffmann-La Roche had developed ROCK, which is a wiki-based application to capture, browse, and search information, key discoveries, and property effects related to a chemical structure to aid their drug design.[5] These types of tools help Discovery scientists to avoid reinvention, but rather learn from the past experience and historical data to save time and innovate new ideas. Furthermore, it is important for the Development scientists who are tasked to interface with the chemists and discovery scientists to learn this area of

Correspondence to: Elizabeth Kwong (Telephone: +514-694-6475; E-mail: ec_kwong@videotron.ca)

Journal of Pharmaceutical Sciences

expertise because this will be very different from how development projects are managed and progressed.

More recently Ritchie and Macdonald[6] and Bickerton et al.[7] suggested the use of quantitative estimate of drug-likeness score based on the calculated physicochemical properties. However, this score is not able to discriminate drugs with respect to metabolic profile and route of elimination. On the contrary, Braggio et al.[8] introduced a drug efficiency concept that they claimed as the key lead optimization parameter that can select the best molecule with high *in vivo* potency with potentially lower therapeutic doses. They claimed that changes in physicochemical properties of a molecule or the effect of *in vitro* Absorption, distribution, metabolism and excretion (ADME) or changes in a chemical structure contribute less to drug efficiency. For example, an increase in lipophilicity can decrease aqueous solubility and increase metabolic clearance that reduces systemic exposure, whereas, in many cases, increasing lipophilicity can also increase permeability, favoring absorption and penetration into the target compartment.[9] Perhaps the complement of these two approaches will be needed to allow for a realistic lead optimization.

With all these process enhancements and streamlined well-defined drug-likeness criteria for improved candidate selection described so far in the literature, what else can be done? With the infrastructure supportable by upper management in place, it will be the science and innovations that will be needed to bring this to the next level.

DRUG DISCOVERY OVERVIEW

In 1997, Lipinski et al.[9] had published the "rule of 5" (RO5) physical property guidelines for drug absorption. This paper became the leading measure of drug-likeness, with more than 1500 literature citations. They stated that based on database from clinical candidates reaching phase II, poor absorption are more likely when clog $P > 5$; molecular mass is >500 Da, the number of H-bond donors >5, and number of H-acceptor is >10. Since then, an increasing number of papers have emerged highlighting the importance of lipophilicity, which is measured by log of octanol–water partition coefficient (log P) on individual absorption, distribution, metabolism, elimination, and toxicology parameters and on overall compound developability during the lead optimization.[10–12] However, several expert opinions have cautioned following these rules rigidly[13,14] because it was recognized that many valuable marketed drugs were made at the margins or even outside the boundaries of these proposed drug's rigid properties.[15]

It was reported recently that most marketed drugs have become increasingly larger in size and more lipophilic.[10,16,17] Some reasons for this increase were: advances in synthetic chemistry-related methodologies, improvements in biological assays, an unhealthy preoccupation with high potency (where *in vitro* potency is normally sitting at the top of the screening cascade and is viewed as a filter for compound progression)[18] and the introduction of more challenging drug discovery targets with shallow, lipophilic, or hydrophilic binding pockets.[19] For example, "Best-in-Class" like the follow-on statins have higher molecular weights than their "First-in-Class" predecessors but they possess higher oral bioavailability, which goes against the convention of RO5 and would have been rejected if RO5 had been strictly enforced as a filter. Many more examples have been cited in the literature that showed that drug-likeness does not correlate well with the fate of marketed drugs.[19]

Figure 1. The ideal Discovery team makeup.

WHAT CAN WE DO BETTER?

Based on what has been shared in the last few decades on success and pitfalls in discovery, the rest of this commentary will be based on my 5 "must do" list for success from a pharmaceutical scientist's perspective.

Operating Model

As part of the entrepreneurial activities in drug discovery, it is important to consider the implication of the makeup of the discovery team as discussed earlier (Fig. 1). The team has to be cross-functional and less hierarchical, with the authority to decide what scientific data are required to make the right decision to go forward or not. Team members must understand the background and history of the target and candidates such that there is no "tossing of projects over the fence." Ownership has to be from beginning to end. For small pharmaceutical companies that will have limited internal resources, the discovery team will consist of consultants or contractors or CROs that will represent these functional areas. This may not be a new concept with all the changes and re-shaping occurring in the enterprise; it is still worthwhile to compare this model to existing ones to make sure that teams are identified appropriately.

A truly integrated team and not just an "on-call participant" is required for Discovery to be successful. The team has to function like a separate business unit by itself. They should concentrate on big picture evaluation and not functional silos. Infrastructure to support this team will also be needed, for example, information technology group that can help consolidate the information that will become the database for follow-on activities or the development of *in silico* or modeling tools. Collaboration with CRO to help manage the resources is also the key to success. Additional collaboration with top academic thinkers combined with expertise in industry will improve science and innovation in discovery. The team should be able to leverage other functional areas if more resources are needed.

To be a nimble discovery functional team, each team member requires the following competencies:

 DOI 10.1002/jps.24294