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Scientific Risk Assessment Strategies for Managing the Transition from Discovery to Development

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This white paper is a rendition of an article presented in AAPS in the July 2010 AAPS News Edition by By Annette Bak Ph.D., associate director, Phase Definition & Materials Science; Caroline McGregor Ph.D., associate director, Basic Pharmaceutical Sciences; Allen Templeton Ph.D., senior director, Basic Pharmaceutical Sciences, Merck & Co.

Making the correct lead selection early in the preformulation development stages for new chemical entities (NCEs) has become increasingly important in the pharmaceutical industry. Of note, the price tag for a newly marketed drug has increased from $138 *million in* 1975 *to over $250 million in 2000 after adjusting for inflation, which includes the high cost associated with developing those candidates that have failed throughout the process*

As is well known throughout our industry, the probability of a new chemical entity (NCE) making it to market is very low. As shown in Figure 1, only 5 out of every 10,000 NCEs from discovery make it into phase I clinical trials, and only 1 out of these 5 is approved for the marketplace.[1] The underlying scientific causes of attrition are primarily related to a lack of efficacy, toxicity, or pharmacokinetic (PK)/formulation related events[2]; however, as shown in Figure 2, there are differences as a function of clinical stage. According to Figure 2, a significant part of the attrition in phase I and II studies is because of PK and ADME issues. Effectively managing risks related to compound physicochemical properties, formulation, and oral absorption is critical prior to significant investment in a molecule. Figure 2 only takes actual absolute failures into account. It has been estimated that approximately 40 percent of the world's top oral drugs are classified as Biopharmaceutical Classification System (BCS) **II** and IV compounds, which have low solubility[4], and that the problem is even worse in current discovery pipelines.[5] Many of these compounds may require heroic formulation efforts to avoid failure yet still have commercial limitations that can lead to additional costs and timeline delays in an era of frugal resource management. The goal of effective portfolio management is to prioritize and, if needed, fail candidates early to avoid the sharp increase in costs as drug development progresses (illustrated in Figure 1) and to do this at a stage where the number of candidates are sufficiently small to enable generation of a fail thorough in vitro and in vivo dataset to identify risk and pick the best candidates. Typically, a thorough evaluation of candidate quality is done immediately prior to the candidate nomination stage through a developability or a risk assessment package within the discovery pharmaceutics disciplines.[6, 7]

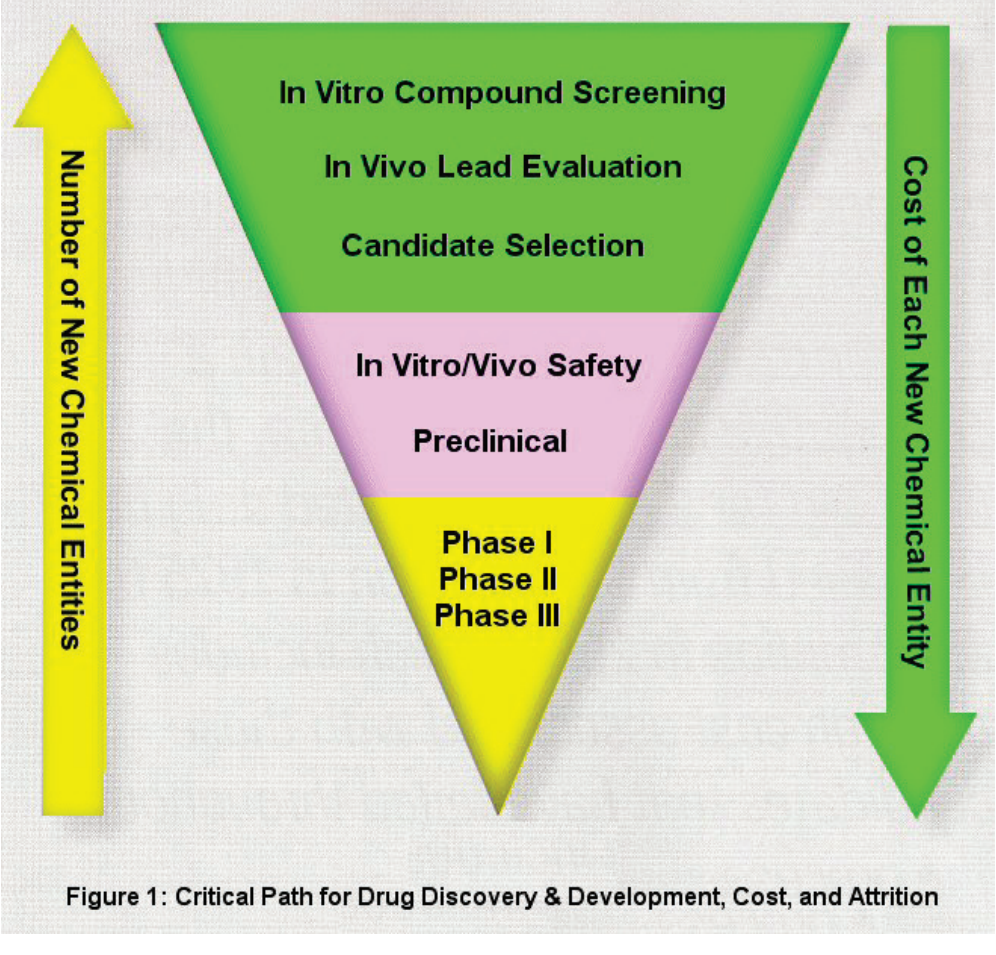

Figure 1: Critical Path for Drug Discovery & Development, Cost, and Attrition

DISCOVERY PHARMACEUTICS RISK ASSESSMENT

Usually a key exploratory toxicology study acts as the gatekeeper to differentiate between the leading three to four potential drug development candidate molecules. It also serves as a natural juncture for initiation of a serious evaluation of the physicochemical properties of these candidates. While timescale of activity will vary substantially from one corporate institution to the next, the generation of the physicochemical data sets typically will commence approximately three to six months prior to candidate nomination for development. The key physiochemical datasets that can be used to assess the overall quality of drug development candidates fall into two general types. The first type is a generic set of physicochemical data that varies little from one therapeutic target to the next and serves as the basis for a more general risk prediction. The most important types of general properties to understand

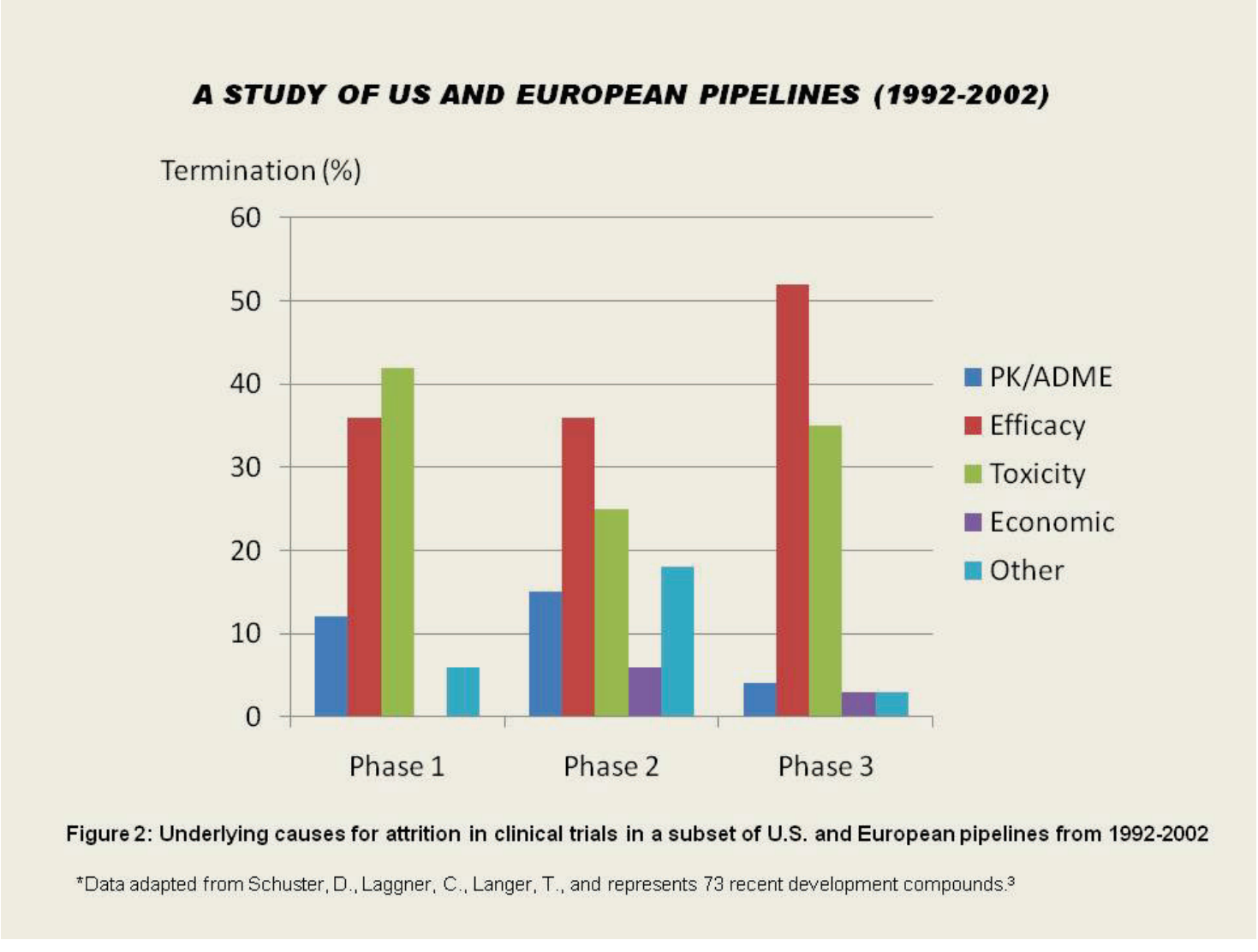

Figure 2: Underlying causes for attrition in clinical trials in a subset of U.S. and European pipelines from 1992-2002

*Data adapted from Schuster, D., Laggner, C., Langer, T., and represents 73 recent development compounds.[3]

include solubility, chemical and physical stability, drug physical form, and biopharmaceutical characteristics.[5,7] From these general categories comes a considerable amount of information that can vary considerably (e.g., the systems in which solubility is tested) in terms of detail and depth of understanding. It is important to note that there are a number of measurements typically conducted at the interface between discovery and development that do not fall neatly into these categories yet are critical to understanding risk.

The solubility of a compound in a variety of media speaks volumes to the overall risk for pharmaceutical development. Not surprising, molecules with high aqueous solubility can be developed most readily using simple and well-understood formulation approaches for both toxicology studies and clinical study. New drug development candidates have trended toward poorer solubility in recent years, which has necessitated utilization of stabilized amorphous formulation systems or other enabled formulation technologies to obtain sufficient absorption. The chemical and physical stability of the drug molecule is also important to understand to avoid potential pitfalls and challenges in development such as failure of clinical formulations because of stability issues. Oxidative, hydrolytic, or photo-driven drug degradation pathways are most commonly in need of evaluation. Drug physical form is often not well understood at the time of transition of a molecule from discovery to development since this is typically not the focus of medicinal

chemistry groups. A thorough selection and characterization of potential salt and polymorphic forms of potential development candidates is advocated to determine solubility and stability challenges so as to better appreciate the risks of molecule development. And last, an assessment of the actual biopharmaceutical characteristics of the potential candidate, such as measurement of dose proportionality, is very important to gain a sense of absorption (or exposures) that can be obtained from the relevant drug form and vehicle system. A different, yet important second set of physicochemical data that should be generated are those therapeutic area or molecule-specific data sets viewed as key to progress the molecule from a commercial perspective. Examples include feasibility studies to support a specific drug delivery modality, such as respiratory or dermal, evaluation of lifecycle management opportunities, or a specific set of studies to understand the viability of a prodrug candidate molecule. Consideration of both data sets are critical components and vital to more fully appreciate the overall pharmaceutical development risks of a potential candidate. There are various means by which these data can be assembled, and many companies have adopted numeric or color-coded risk assessment tools to assess the overall risks of discovery candidates and make decisions on whether to progress a candidate forward, turn it back, or invest resources in a scaled manner. Physicochemical properties are usually just one component of the overall evaluation of risks. In the most ideal of circumstances, a proactive understanding of potential risks has been factored into the drug discovery process, and that active pharmaceutical science collaboration has addressed many of the key risks prior to the drug discovery funnel, narrowing to a few key candidates.

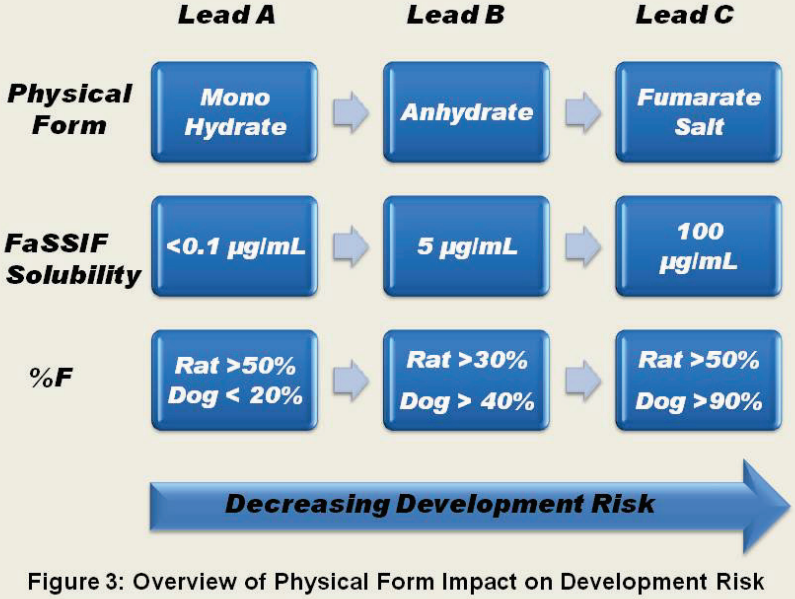

Figure 3: Overview of Physical Form Impact on Development Risk

Since identification of an ideal candidate is rare, compromises are necessary, a candidate with less-than-ideal physicochemical properties is often presented, and key development risks are then highlighted as part of the overall trade-offs inherent to the drug development process. As a result, the key data sets previously mentioned allow for derisking in terms of commitment to the necessary scientific investments to enable compound progression to good laboratory practices (GLP) toxicology studies and early clinical studies. These datasets can also become the focus of additional discovery efforts to find a more optimal candidate based on the severity of the limitation(s) presented.

THE IMPACT

The following case study illustrates the importance of these key physicochemical property datasets in understanding the development risks associated with promising lead candidates. Lead-A was an early candidate evaluated using less formal risk assessment methodology prior to the transition from discovery to early development. Lead-A was evaluated as a highly crystalline monohydrate of the neutral (free base) form that showed excellent physical and chemical stability. The compound was practically insoluble across the physiologically relevant pH range with only 3 µg/mL solubility in simulated gastric fluid (SGF) at pH 1.4 and <0.10 µg/mL and in fasted state simulated intestinal fluid (FaSSIF) at pH 6.5. The pKa was 7.5, and salt formation was feasible as a means to increase solubility. The predicted human efficacious dose was in the range 400-2,000 mg for an estimated dose

number[8] (Do) in the range of 190-940. The compound also exhibited high permeability (>50 x 10-6 cm/s) and this combined with the solubility afforded a preliminary BCS II classification. The bioavailability of Lead-A was noted to be species, gender, and formulation dependent. The highest exposures were achieved with a nonaqueous solution formulation with bioavailabilities of >50 percent in rats, yet <20 percent in dogs (10 mg/kg dose). An enabling formulation approach (e.g., nanocolloidal dispersion formulation) was unable to increase exposures further. The compound also showed a less-than-proportional increase in exposure with increasing dose. Based on the available data, significant challenges were expected for the development of formulations, which would provide adequate exposures for both toxicology and clinical studies that demonstrated that this compound had higher risk relative to a molecule with optimum physicochemical properties. And this proved to be the case. A complex self-emulsifying drug delivery system formulation was required to establish the necessary exposures in toxicology studies. However, for the clinical formulation, the high predicted dose, poor solubility in suitable nonaqueous vehicles, and the propensity for the compound to precipitate from solution both in vivo and in vitro eliminated the possibility of a liquid filled capsule formulation. Ultimately, the fumarate salt coupled with a polymer-stabilized amorphous solid dispersion formulation was selected for early clinical studies, because this was the only approach that afforded acceptable exposures in preclinical species. This formulation approach consumes significantly more resources prior to first-in-human clinical studies than a more conventional formulation approach. In addition, a significant positive food effect was observed with this formulation in a dog model

Drug Property	Required Tests	Toxicology Formulation	Clinical Formulation
Solubility	Aqueous buffers and simulated gastrointestinal fluid solubility "fed" and "unfed"	Conventional solution/suspension v. amorphous/nano technology/hot melt extrusion	Conventional tablet v. amorphous/nano technology/hot melt extrusion
Stability	Solution and solid state stress testing (forced degradation). Excipient compatability	Stability of formulation and storage temperature	Stable formulation and storage conditions for clinical trial
Physical Form	Abbreviated high-throughput or manual screening with high level of solids characterization	Avoid form changes for non solution formulations	Avoid form changes and/or bioequivalence studies or repeat PK
Chemical Form	Stereoisomers; reference standards, isomerization, synthesis purity	Batch analysis, qualify isomers & potential isomers	Formulate for long-term stability
Impurities	Genotoxic impurity route of synthesis analysis, Process and degradation, HPLC & validation	Batch analysis, qualify impurties	Formulate for long-term stability. API and excipient compatability

Table 1: Pre-Formulation and Formulation Development Activities of NCEs

Given the significant interspecies variability, this preclinical model could not be considered fully representative of human exposure, and early clinical studies further confirmed that the exposure of Lead-A is significantly limited by absorption. Because it was not possible to achieve sufficient exposures in human at a commercially viable dose, even with the amorphous formulation, development was ultimately terminated. Based on the preclinical and clinical data with Lead-A, it was deemed that the primary differentiating factor in any back-up molecule would be increased probability of achieving the targeted human exposure with a commercially viable dose, ideally using a more conventional formulation approach. Attainment of this goal could be achieved through improvements in one or more of the characteristics that impact the human dose prediction, namely in vivo potency, clearance, and bioavailability. It will also be important to address the key factor (poor aqueous solubility) that contributed to the limited absorption. Specific criteria were established for the back-up molecule that provided improved solubility in biorelevant media sufficient to solubilize the target dose from a conventional formulation as well as a specific requirement for acceptable oral bioavailability when dosed as an aqueous suspension. Ultimately Lead-C was selected to fulfill these criteria. The solubility as the crystalline salt form was dramatically increased over that of Lead-A via introduction of appropriate structural moieties, in this case a basic aromatic group that could be converted to a salt. Over a tenfold increase in FaSSIF and a >500-fold increase in SGF solubility were achieved. The projected human efficacious dose for Lead-C was significantly lower at 50-80 mg, and this combined with the significant increase in solubility allowed for a Do in the range of 3-6. The permeability was still high (>30 x 10-6 cm/sl. and based on this and the solubility, the preliminary BCS class was II. Oral bioavailability was determined for the crystalline salt form as an aqueous suspension at 10mg/kg and was found to be >50 percent and 90 percent in a rat and a dog, respectively. The exposures did not increase in a dose proportional manner; however, significant margins over the target efficacious exposure were achieved in both species from this suspension formulation (25x in a rat at 100 mg/kg and 15x in a dog at 50 mg/kg). Based on this data, it was predicted that this molecule would achieve acceptable exposures from a more conventional solid oral dosage form in the clinic. The solubility was also expected to support dose proportionality in humans up to doses of ca. 700 mg, thus addressing another major issue with Lead-A. By understanding the risks associated with key physicochemical data sets and the impact that these can have on the progression of a drug molecule through development, it was possible to focus efforts on the design of a back-up molecule that clearly addresses the key problems associated with the lead compound. As noted earlier, proactive involvement of pharmaceutical scientists in the discovery phase can help identify issues early and either work to resolve them or direct efforts to address the challenges presented. The key data sets for Lead-A,B, and C are summarized in Figure 3. In this case, Lead-C was predicted to have low risk with typical resource requirements for toxicology and clinical studies, as compared to the high risk and resulting resource implications associated with Leads A and B.

LEVEL OF RISK ACCEPTABLE

As illustrated in the preceding case study, to fully capitalize on a risk assessment, it is important to power it with the right experiments. This is intimately related to the level of risk acceptable. Determining an acceptable level of risk can be difficult since, in addition to the science, it is also related to company culture and current trends. In the most extreme sense, risk tolerance can vary from 0 to 100 percent. In the discovery paradigm prevalent in the early 1990s, the risk tolerance was high and discovery scientists concentrated on optimizing pharmacological potency. It was then left up to development scientists to mitigate the resulting poor physiochemical properties. This was especially true after the launch of high-throughput screening, where compounds were solubilized in dimethyl sulfoxide. Not surprising, development scientists were not successful in all cases or the candidates required costly and heroic formulation efforts[9]. Consequently, the paradigm changed in the late 1990s, the level of risk tolerance decreased, and the focus of pharmaceutical scientists changed to include proactive assessment of developability, such as physicochemical properties in the discovery setting.[10] Bringing the risk to 0 percent as part of a discovery risk assessment is obviously not feasible, since it would essentially require a full set of development activities on all discovery candidates considered. The latter would be too costly in terms of resources because it would not take advantage of the candidate attrition rates utilized currently and would strand resources on programs that will ultimately fail for unrelated reasons. The data-driven risk assessment tools used should, however, speak to the various challenges anticipated across the pharmaceutical development space, progressing with higher accuracy to lesser accuracy in terms of prediction as a function of time. For example, whereas the pharmaceutical risks associated with the achievement of requisite exposure

multiples in GLP toxicology studies should be well understood, the risks associated with the ultimate commercial product cannot be fully articulated at the discovery development interface. Table 1 summarizes the properties discussed in this article along with the line-of-sight or qualitative risk prediction they provide to development formulation activities (toxicology and clinical). Although variation in the types of in vitro physicochemical experiments and animal PK studies across pharmaceutical companies (see Huang and Tong[6] and Saxena et al.[7] for developability assessment reviews) is expected, the case study included in this article indicates the benefits that may be derived from a thorough risk assessment. Such approaches have much potential in helping aid portfolio management and creating success around this key topic.

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