Developability Assessment in Pharmaceutical Industry: An Integrated Group Approach for Selecting Developable Candidates

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Received 16 May 2008; accepted 20 August 2008

Published online 14 October 2008 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21592

ABSTRACT: This article describes the role and responsibilities of the Developability Assessment Group (DAG), a pharmaceutical Research and Development (R&D) subgroup, which supports drug discovery and development scientists with screening, developability assessment, and selection of new molecular entities (NMEs) for clinical studies. A strong collaboration between discovery group and DAG is essential for selecting the right NMEs for late-stage development, and consequently decreasing the NME attrition rate in late-stage development as well as in bringing down the associated cost and timelines. The investigations performed by DAG for evaluating research leads as well as the significance of these investigations in the developability assessment, the value of cutting edge tools and technologies, and the usefulness of the data in the decision making process are discussed in this review. Developability assessment of NMEs often includes physicochemical and biopharmaceutical characterization, development of suitable formulations for pharmacokinetic (PK), efficacy, and toxicity studies, selection of suitable physical form (salt, polymorph, etc.), and formulation development for phase I clinical studies. Overall DAG activities not only contribute to streamlining efficacy–toxicology evaluation, but also in building developability screens, which allow pharmacologically effective, minimally toxic, and developable candidates to reach the clinic and eventually to the market. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:1962–1979, 2009

Keywords: developability assessment; early drug development; preformulation; formulation; pharmacokinetics; solid dosage forms

INTRODUCTION

With increasing development costs, long development and approval times, fewer new product launches, lack of rich pipelines, and loss of revenues to generics due to patent expiration, the pharmaceutical industry is seeing insufficient revenue and profit growth.[1–5] High attrition rates are commonly observed during development of new molecular entities (NMEs) mainly due to lack of desirable physicochemical and biopharmaceutical attributes, unacceptable toxicity, and poor efficacy in preclinical and clinical studies, all of which contribute to increasing drug development

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Journal of Pharmaceutical Sciences, Vol. 98, 1962–1979 (2009)

costs.[3,4,6] As a result, there is an enormous pressure on the pharmaceutical industry to cut cost and streamline development.[7] While different pharmaceutical companies are dealing with these challenges differently, it has been observed in the last two decades that the industry has benefited substantially by nurturing and strengthening the discovery–development interface by addition of a developability screen.[8–14] This screen has been accomplished by conducting sufficient preclinical studies during the candidate selection phase to assess risks involved with the development of each molecule and to optimize candidate selection. An added benefit of implementing the developability screen is that the knowledge gained during the candidate selection phase is useful for rapid development of optimal formulation and clinical strategies, and consequently, it is helpful in shortening the development timeline for an NME and reducing the risk of failure during development. This approach has not only benefited the industry, but also has benefited the society as new and better life saving drugs are reaching patients sooner and are cost effective.[5]

While the developability screening of NMEs, has been reviewed and covered earlier under various headings and details by several authors, the focus of this article is on the sequence of events and decision-making process at the discovery–development interface. Most of these events and sequences are already being practiced in the industry under different R&D settings. This article offers a comprehensive review of these activities under one heading which can serve as a useful reference not only for scientists who have been involved in NME developability assessment for a while but also as a valuable tool for pharmaceutical scientists new to developability assessment activities, students, pharmacists and for those who are new to drug development process.

While discussing the developability assessment activities in this article, the authors have described a group known as the Developability Assessment Group (DAG) working at the discovery–development interface. It is commonly observed that the organizational structure of the function performing developability assessment varies significantly from one pharmaceutical company to another.[8–14] While the authors based on their experience at Novartis believe that the most optimal organizational structure is to have a DAG integrated within the discovery organization, several other organizational models can function equally well as long as all group members work closely together with a common objective. The emphasis in this article is not on the organizational structure, but on the valuable information that a group/function responsible for developability assessment can generate at various stages of the drug discovery process to identify potential drug candidates and to select the optimal candidates for transitioning from discovery to development.

PLACE AND FOCUS OF DAG IN CURRENT R&D SETTING

Traditionally, in brand pharmaceutical companies, R&D is comprised of "discovery–research" and "development" functions.[15,16] The role of discovery–research is to discover and characterize NMEs for various diseases which involve efforts from various discovery functions such as chemistry, biology, pharmacology, biomarker, functional genomics, metabolism and pharmacokinetics (PK), safety and toxicology, etc. The goal of every discovery–research program is to identify NMEs with the desired PK, efficacy, and safety as efficiently as possible and handover selected NMEs to the development functions for clinical studies. The goal of development is physiochemical evaluation of NMEs forwarded by discovery–research along with physical form selection, synthesis evaluation, and formulation development strategies for moving the compound to the clinic. On achieving positive outcome from the clinical studies, the NME moves to late-stage development where it is transformed into the final market product and the long term safety and efficacy studies are conducted to satisfy the health agency requirements for approval and launch. As reflected above, the discovery–research and development functions have different goals and priorities, which at times allow passage of NMEs with unsatisfactory developability characteristics to development phase. Such NMEs present increased probability of failure during development and contribute to high attrition rates.

In such a scenario, DAG plays an important role in managing the interface between discovery–research and development. DAG generates valuable information that is critical for determining if the NME should be advanced (from discovery–research) for proof of concept studies (to late-stage development).

ROLE OF DAG

The major roles of DAG are described in Figure 1. DAG activities can be classified mainly in following three categories: evaluation of physiochemical properties of the compounds, formulation development for biopharmaceutical studies, and biopharmaceutical evaluation and decision-making. All of these studies are interrelated, impact each other's outcome and play a major role in determining fate of an NME. Figure 1 also shows how DAG activities contribute towards development screen, which along with efficacy and toxicity screens plays a vital role in selection of an NME for clinical studies.

Physiochemical Characterization

A very significant role of DAG is to evaluate the physiochemical properties of the lead candidates from discovery. The goal is to assess the developability of the candidate with just a few milligrams to a few hundred milligrams of a compound using the state of art high throughput, automation, miniaturization, and simulation technologies. If the parent molecules do not yield satisfactory physical/chemical stability (or biopharmaceutical attributes), DAG evaluates various physical forms (salts and polymorphs) to achieve the above and recommends the dosage form strategy for clinical studies and for late-stage development. In addition, DAG provides input into potential development issues and risk factors, which might surface during product development and scale-up based on the physical and chemical properties of the candidates. The following headings discuss the physiochemical characterization in detail.

Physical Characterization

The original neutral or ionizable (free acid/base) compound and all the possible salt forms obtained from salt profiling of ionizable molecules are characterized for their physical properties. The physical evaluation consists of five key studies as shown in Table 1. The first study is X-ray powder diffraction (XRPD) analysis, which provides information about the crystallinity of the physical form. The second study is thermo gravimetric analysis (TGA), which provides information on weight loss as a function of temperature and gives an idea about decomposition temperature. The observed weight loss could be because of the adsorbed volatile impurities, solvates, hydrates, and/or loss of counter ions from the salt of a compound. These data in conjunction with the differential scanning calorimetry (DSC) data can reflect weight loss during heat transitions leading to identification of hydrates, solvates, etc. The third study is DSC analysis to obtain information such as melting point(s) of a crystalline compound, glass transition temperature of an amorphous compound, and heat transitions at particular temperatures reflecting change in forms. The

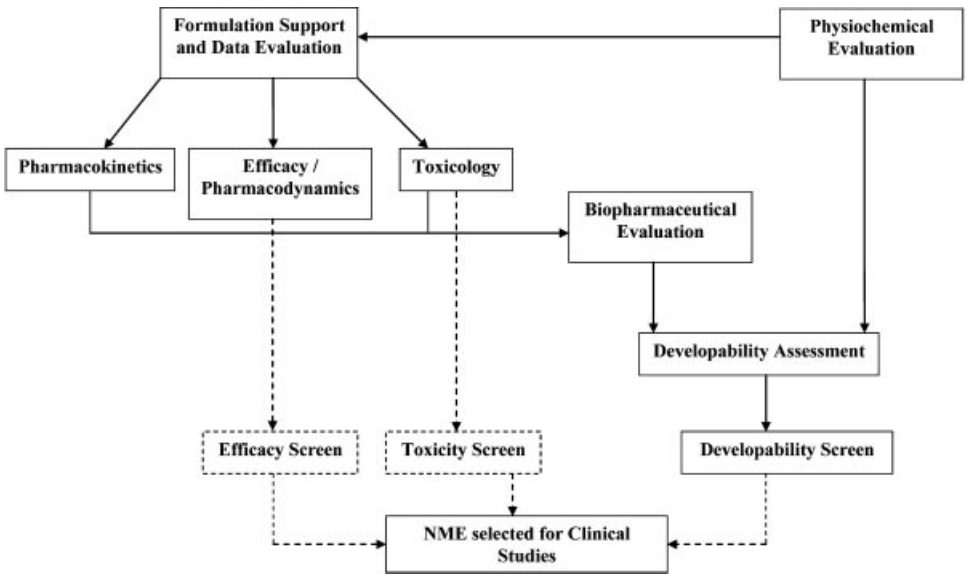

Figure 1. Major roles of DAG in pharmaceutical R&D.

Table 1. Studies for Physical Characterization of the Compound

S. No.	Study	Factors Evaluated	Desirable Properties for Development
1.	X-ray powder diffraction (XRPD)	Crystallinity	Crystalline
2.	Thermo gravimetric analysis (TGA)	Weight loss associated with heat transitions, hydrates, and solvates	Minimum/absence of hydrates or solvates
3.	Differential scanning calorimetry (DSC)	Melting point, heat transitions, and glass transition temperatures	High melting point (90–150°C)[a]
4.	Dynamic vapor sorption (DVS)	Hygroscopicity	Minimum hygroscopic nature
5.	Raman spectroscopy	Raman shift for ionizable groups	Confirmation of salt formation

[a]Melting point range: 90–150°C—Recommended for development.

fourth study is the dynamic vapor sorption analysis, which determines the hygroscopic nature of the compound. Hygroscopicity is another critical compound attribute, as it can lead to significant physical and chemical transformation to render the product unacceptable. The fifth study is Raman spectrometry. It confirms whether the compound indeed exists as a salt. The desirable physical characteristics of a salt form for development are listed in Table 1. A crystalline form is the preferred physical form for conventional oral solid dosage forms. Crystalline compounds are more pure and are stable during storage and processing than the amorphous form. An amorphous form (being a high-energy form) tends to revert back to a more thermodynamically stable physical form during storage and processing. Crystalline compounds with melting points >150°C are preferred for development. Lower melting point compounds may cause difficulty due to melting, sticking, and picking during processing (for a solid dosage form) and/or storage. However, some of these limitations may be overcome by other means such as customized processing conditions, using special excipients, etc. There are a number of marketed products, which contain drugs with melting points <100°C. With the advances in manufacturing, storage, and formulation technologies, difficulties during handling, processing, and storage can be overcome. It is better to avoid solvates or hydrates due to potential chemical instability and dissolution issues during storage. If hydrates are selected for development, it's desirable to have stable hydrates as unstable hydrates can undergo transformation into other forms, which may impact compound's dissolution rate, bioavailability, and chemical instability.

Solubility and Dissolution Testing

The absorption of a compound can be limited by solubility and/or dissolution rate. Thus, solubility is an important physiochemical property of an NME and its salt forms. The solubility evaluation for a physical form is done by DAG in various types of media such as water, different pH buffers, simulated physiological fluids, different surfactant solutions, complexing agents, and organic solvents. Solubility in water is important for development of solution formulations. Information on pH dependent solubility of a compound can be useful for selection of an appropriate pH, which can be used in formulations for preclinical studies. Solubility data in various physiological buffers may reflect how a compound may dissolve and behave in the gastrointestinal tract. Solubility data in various aqueous surfactant solutions can provide information regarding the role of wettability on dissolution and this information can be useful for developing formulation and dissolution medium. Also these data might be helpful in assessing the potential for food effect. Solubility data also helps analytical chemists to develop an appropriate dissolution media for compounds with poor aqueous solubility and stability. Finally, the solubility information in different organic solvents is useful in selection of suitable solvents for formulation, processing, and cleaning.

Depending on the physical forms of a compound and its pH dependent solubility, the compound might precipitate out in stomach fluids (pH ~2) or in small intestine fluids (pH ~5–7) during its transit in gastrointestinal tract. The precipitated compound may dissolve differently in the gastrointestinal fluids than the original form. Occasionally, for compounds with pH dependent solubility,

certain forms/salts of a compound may dissolve in the stomach fluids, and upon gastric emptying in the intestine may remain dissolved, thus yielding supersaturated solutions. In such cases, the compound may show much higher bioavailability. Thus, it is critical to evaluate dissolution characteristics of various physical forms before selecting one for further evaluation. Dissolution studies should be conducted either with suspension formulations or with compounds filled in capsule with or without formulation excipients. The physiological conditions can be simulated by using pH 1, 2, 4.5, and 6.8 buffers at 37°C as the dissolution media. The presence of formulation excipients could help simulate a solid dosage form and can reflect the effects of formulation excipients on dissolution rate. For compounds with poor solubility, dissolutions studies should be conducted in the simulated gastric and intestinal media to determine the potential for food effect.

Solubility Enhancement

Some of the solubility enhancement options available to the DAG scientist are described in Table 2.[17,18] As shown in Figure 2, the most commonly employed option for a compound (i.e., a free acid, free base, or zwitterions) is to change the physical form of the compound to a new form (salt), which is physiochemically stable and is more soluble than the original form. Alternatively, drug delivery systems such as nanoparticles, solid dispersions, and lipid-based systems can be employed for enhancing solubility.

Stability Evaluation

For a NME, DAG evaluates all physical forms of interest for physical and chemical stability at various accelerated storage conditions. The physical stability in solid state and chemical stability in both solid and solution forms are evaluated at elevated temperatures (80°C) and relative humidity (RH) conditions (75% RH/50°C) for a period of 2–4 weeks. These data provide an assessment of potential changes in physical characteristics (e.g., crystallinity, hygroscopicity, etc.) and an estimate of chemical degradation during processing, storage, and product shelf life. Chemical stability is an important attribute for a compound to be selected for development. Photo stability is also evaluated for both solid and solution form of the compound as per ICH guidelines.[19] Once the physical form and formulation principle has been selected, both drug substance and drug products are subjected to 40°C/75% RH for 3–12 months and 25°C/ 60% RH 3–12 months for stability evaluation and calculation of shelf life.

While crystalline compounds with melting points >150°C are preferred, sometimes the only option available may be a compound/form with melting points in the range of 60–100°C. In such cases, there is a possibility that the compound might melt during processing of solid dosage form development, and therefore, for such compounds it is critical to evaluate impact of milling and compression on physical and chemical stability. To assess the impact of milling, the compound can be ground with mortar and pestle or milled, and the XRPD and DSC pattern are compared with the similar data for the ungrounded material. If there are any changes in the physical form, the product should be evaluated for chemical stability under accelerated conditions. Similarly, for assessing the impact of compression, the compound can be compressed using a carver press at various pressures to make a pellet and the XRPD and DSC pattern are compared with similar data for the material before compression. Such comparisons

Table 2. Commonly Applied Solubility Enhancement Techniques for Oral Delivery

S. No.	Solubility Enhancement Approach	Techniques
1.	Change in particle size	(1) Size reduction
2.	Complexation	(1) Complexing agent
3.	Change of physical form	(1) Salt synthesis
		(2) Polymorph selection
4.	Use of delivery systems	(1) Solid dispersions
		(a) Spray drying
		(b) Hot melt-extrusion
		(2) Lipid based systems
5.	Prodrug	(1) Chemical modification

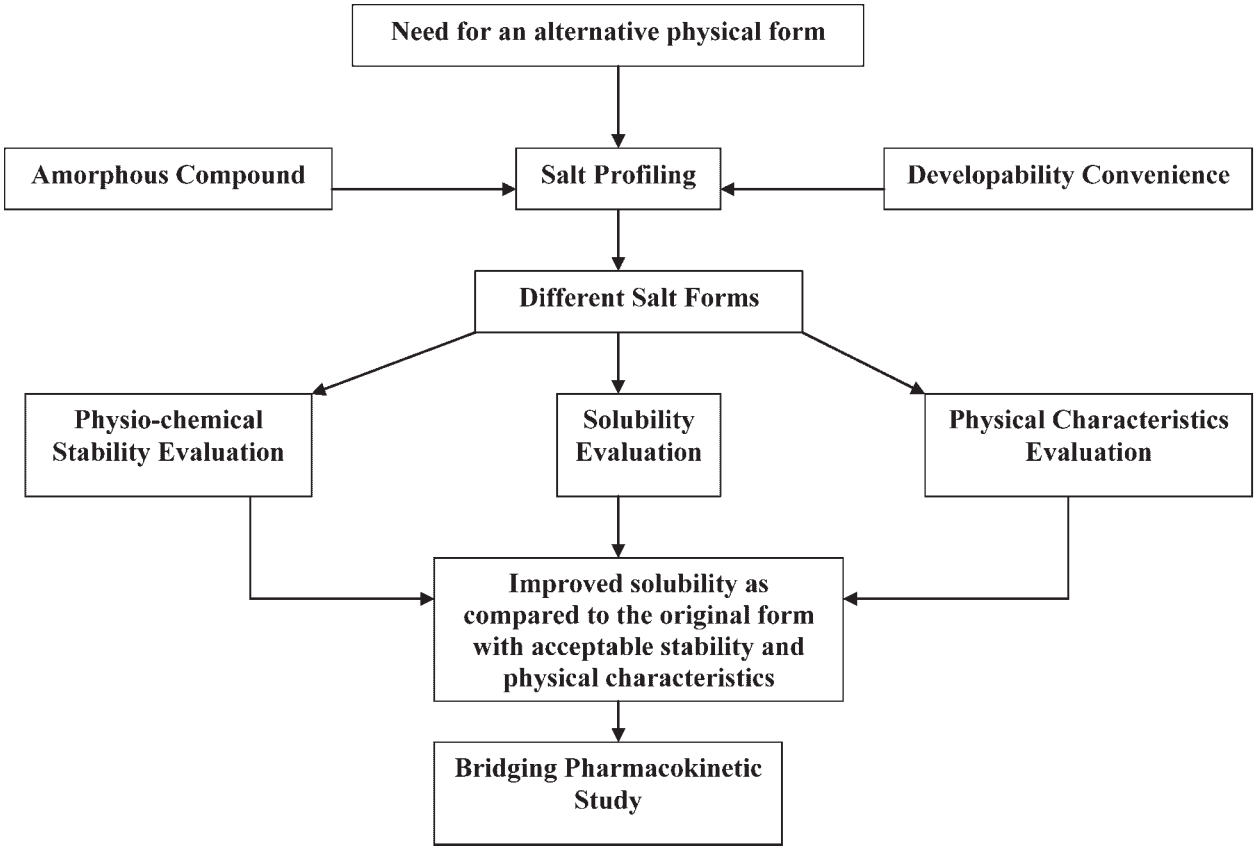

Figure 2. Physicochemical and biopharmaceutical evaluations of alternate physical form after salt profiling.

give an early indication of potential issues, which might surface during the late stage formulation development and manufacturing.

Formulation Development for Biopharmaceutical Studies

Another major role of DAG is the development of formulations for early PK studies, PD (pharmacodynamics) studies, efficacy, and toxicity screens. Selection of adequate formulation principles is critical for obtaining reliable information during efficacy and toxicity screening, especially for drugs with poor solubility with potential for variable exposure. For such drugs, an inadequate formulation principle may limit exposure through limited solubilization or precipitation in the gastrointestinal tract of a drug presented in the solubilized form, and thus leading to low and variable exposure and false safety and toxicity interpretation. Some of the examples of misleading results from the formulation errors are shown in Table 3. Additionally, inadequate exposure may also lead to poor efficacy, and thus could lead to rejection of a potential blockbuster. Cyclosporine, a Novartis blockbuster drug, is an excellent example of a poor solubility drug, whose success was driven by an adequate formulation principle such as Sandimmune® and Neoral®.[20,21] Thus, success of such efficacy/toxicity screens depends a lot on proper selection of suitable formulations, which lead to an objective go–no go decision for a compound. The proper understanding of the formulation principles and formulation optimization is critical to obtaining meaningful data for decision-making. The following sections discuss some suitable formulation principles in detail.

Solution Formulation

The most common formulations developed by DAG scientists are liquid solutions and suspensions. The solution formulations comprise of simple solutions with compound dissolved in aqueous media with or without buffers, surfac-

Table 3. Examples of Errors During Formulation Development for Preclinical Studies

S. No.	Formulation Error	Effect on *In Vivo* Studies
1.	Compound's physical form change and /or chemical degradation in formulation	Misleading results in bioavailability, efficacy, and toxicology studies
2.	Precipitation of compound from solution *in vivo*	Misleading results in Bioavailability, efficacy, and toxicology studies
3.	Stability (a) Physical (b) Chemical	Misleading results in bioavailability, efficacy, and toxicology studies
4.	Use of amorphous drug substance (which has potential to convert into less soluble crystalline form)	Change of amorphous form to crystalline form of less solubility in formulation, on standing, leads to error in doses for animal studies
5.	Undefined particle size	Low exposure from suspension formulations misleads to wrong physical form selection
6.	Excipients (a) non-GRAS (b) Above LD50	Toxicity due to excipients misleads to compound related toxicity

tants, or complexing agents. If the compound is not soluble in aqueous medium, a combination with a suitable nonaqueous solvent, or simply a nonaqueous medium with one or more suitable solvents may be selected to obtain the desired solubility. As the compound advances to the next level for assessment in higher rodent and non-rodent species, the solutions have minimal or no organic components. This avoids toxic effects and palatability issues associated with organic components. In such cases other solubilization techniques such as change of pH, complexation, micellization, *in situ* salt formation, particle size reduction, etc., are utilized.[14]

Some important factors involved in developing solution formulations are listed in Table 4. The choice of excipients and their levels depend on the route of administration, for example, oral or i.v. A dilution study in relevant media is very crucial for formulation optimization to limit or avoid compound precipitation upon dosing.[14] These formulations should be tested for stability under physiological pH conditions to predict *in vivo* stability of compounds used and for chemical/physical stability under refrigerated and room temperature conditions to qualify appropriate storage conditions.

Suspension Formulation

In case of a suspension formulation, often the crystalline compound is suspended in an aqueous medium by using a suspending agent. Depending on the necessity and animal species to be dosed, a surfactant is incorporated to increase the wetting of the suspended compound. Increased wettability in turn helps increasing the dissolution rate of the compound. In development of suspension formulations, one must evaluate physical stability of the suspension to ensure uniform dosing of the drug from suspension. In addition, if an unstable polymorph or physical form of a compound is used in the suspension formulation, the compound may convert into a stable physical form. Since biopharmaceutical behavior of a suspension can be seriously impacted by these changes, it is critical to ensure content uniformity of the suspension and form stability during storage prior to

Table 4. Factors to be Considered While Developing Solution Formulations

S. No.	Key factors for solution formulations	Recommendation
1.	Choice of excipients	Based on route of administration
2.	Dilution effect *in vivo,* physical stability	Check gradual 10–100-fold dilution in physiological buffers
3.	Chemical stability in solution	Check at physiological buffers or buffers simulating the pH *in vivo* at 37°C

dosing. The content uniformity may be achieved simply by shaking the suspension before dosing. However, the physical form may have to be assured through other means such as X-ray powder diffraction techniques.

The average particle size for suspensions for PK studies is preferred to be less than 10 μm to avoid any dissolution issues due to size. This size is attainable by probe sonication under laboratory settings and can be achieved by milling during scale-up and drug substance development. In some cases where solubility/dissolution is highly limited by particle surface area, nanomilling could be used to get the average particle size in nanometer range. These suspensions are known as nanosuspensions. Nanomilling is usually performed on a slurry of the compound in water, thus can only be used with compounds stable in water. At laboratory scale, nanomilling could be achieved by using high-pressure homogenizers.

For amorphous compounds, suspensions are not recommended for PK studies. Amorphous forms are more soluble than the crystalline compounds and have much of the compound in solution form, which defeat the purpose of suspension PK studies.

Salt Forms Profiling

The main reason for DAG to conduct salt profiling for a lead compound is the poor exposure of the original free form (more than twofold lower) from suspension as compared to solution (Figs. 2 and 3). Salts usually exhibit higher solubility/dissolution rates than the original free acid or base form, leading to improved exposure. Another important reason for identifying a salt form is to improve physiochemical properties of the original form. This leads to lower likelihood of encountering complications during their processing, manufacturing, and storage and thus providing convenience/suitability for development purposes (Fig. 2).

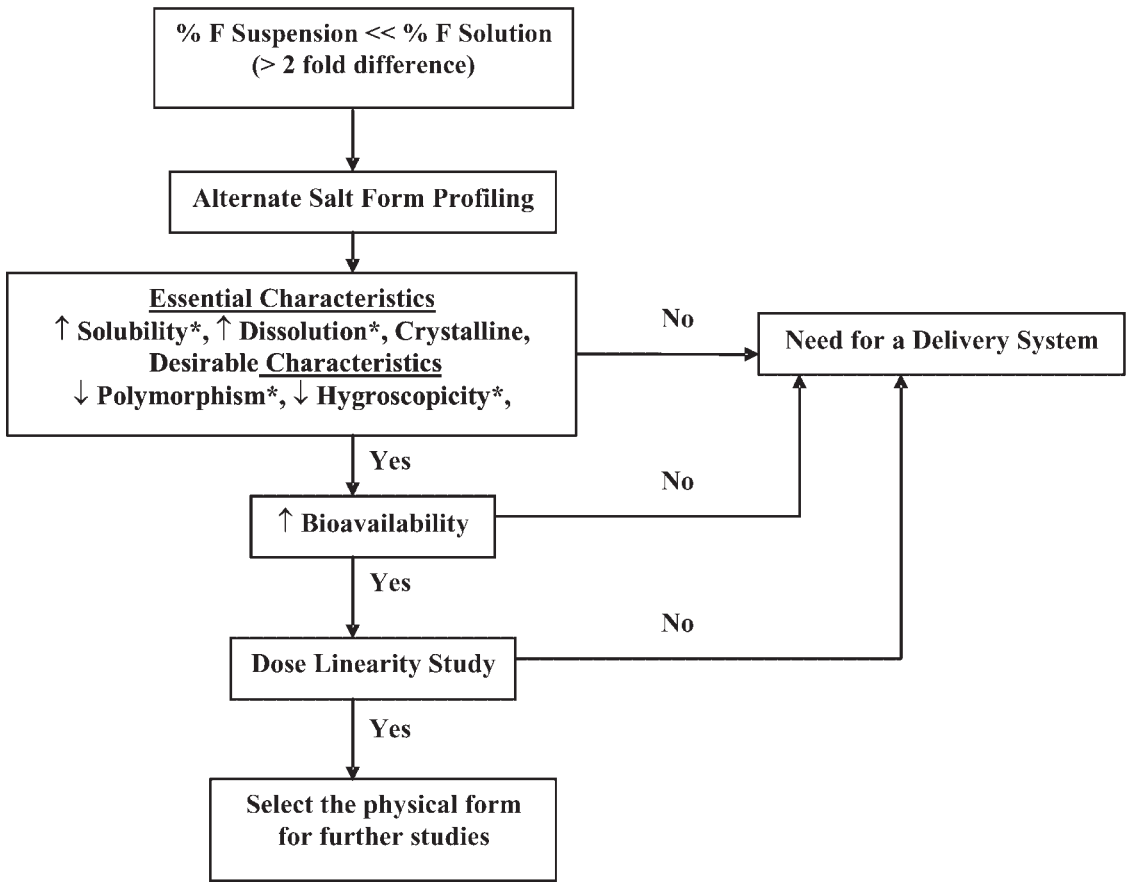

Figure 3. Selection of an alternative salt form of a compound. *As compared to the original form.

An early profiling of the alternative salt forms for lead compounds is done using a few common acidic or basic counter ions selected based on the pK_a of the compound.[22] The goal is to achieve a salt form, which is more soluble and dissolves more rapidly in the physiological pH environment, crystalline, less hygroscopic, and more stable under accelerated degradation conditions than the original form of the compound.[23] Once the different salt forms of a compound are obtained, they are evaluated for solubility, stability, and physical characterization as shown in Figure 2. The salt that shows the most desired physical characteristics, increased solubility/dissolution rate, and stability is moved forward for PK evaluation as shown in Figure 3. Salts are evaluated for % F from oral suspensions (at high dose) as compared to parent form, followed by dose linearity study. If two or more salt forms have similar attributes, a bridging PK study may be done for comparing exposure from oral suspension to select the best salt. The physical form, which gives dose linear exposure and is scalable and physicochemically stable, is selected for development.

Alternate Delivery Systems

For NMEs with poor solubility profile, if reduction in particle size and alternative salt forms fails to increase solubility/dissolution rate, solid dispersions and lipid-based delivery systems offer excellent alternatives for low dose drugs. Increased solubility/dissolution helps to enhance bioavailability of such poorly soluble compounds. The sequence of activities for selecting a delivery system is shown in Figure 4. The main goal is to evaluate an optimal delivery system to enhance solubility, bioavailability, and dose linearity. Once such delivery system is identified for an NME and evaluated for stability and processing limitations, it can progress to dose linearity study. On positive outcomes from dose linearity study these delivery systems are used as formulations for PK, efficacy, and toxicity studies.

For oral strategy, the two most evaluated alternate delivery systems are solid dispersions and lipid based systems. Solid dispersions consist of molecular dispersion of the compound in polymers and surfactants.[24] The physical form of the compound in the solid dispersions is mostly amorphous.[24] Since the dissolution of the compound is facilitated by its amorphous state, it is critical that these formulations have adequate

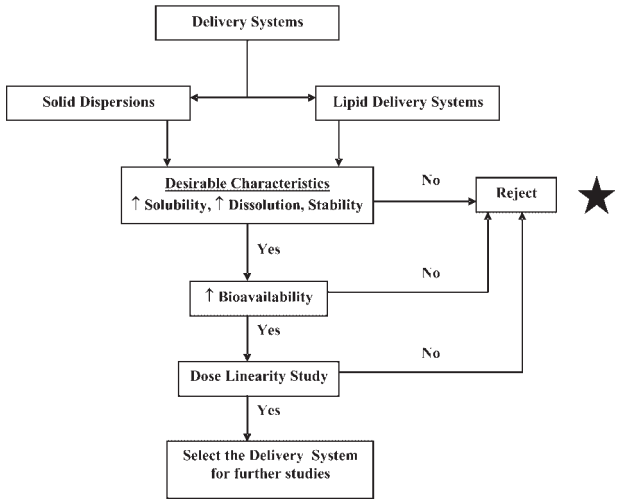

Figure 4. Selection of delivery systems for poorly soluble compounds (★ indicates go–no go decision).

physical stability, as the crystallization of the compound may lead to much slower dissolution, and consequently, lower bioavailability. The lipid-based formulations mainly consists of lipids, surfactants, or self-emulsifying vehicles, which help to enhance the aqueous miscibility/solubility and dissolution of lipophillic or amphiphillic molecules by entrapping the molecule in a lipid phase or between lipid–water interface.[25,26] However, both of these nonconventional formulation strategies could suffer from stability issues and complications during scale-up and manufacturing.

If the delivery system fails to achieve the desired solubility, stability, and bioavailability, the NME should be rejected. It is the authors' experience that poor solubility/bioavailability compounds consume enormous resources. Such compounds should be easy to reject, however, in reality it is the quest for improving solubility and bioavailability with drug delivery systems that keeps such compounds alive much longer than they should. A careful assessment of the solubility, bioavailability, form choices, and dose should lead to a meaningful go–no go decision for a compound.

Moreover, while some of these delivery systems may be used in preclinical studies (i.e., PK, efficacy, and toxicity), one should keep in mind that developing stable and manufacturable solid dispersion and lipid-based systems is quite complicated and may not be successfully achieved at clinical or commercially relevant scales with adequate product stability. Therefore, it is not

surprising that even with extensive research efforts by many pharmaceutical companies, only a very few solid dispersion and lipid based products are on the market. Thus, for a compound that requires such delivery systems, one should be very careful in promoting such compounds forward. It is the authors' recommendation that such compounds should be promoted only if the efficacy is seen at low doses along with a broad safety margin. For all such compounds considered for promotion into development, it is critical to assess the food effect and the impact of variability in systemic exposure on the probability of successful development.

Another alternative for enhancing solubility of NMEs to improve oral bioavailability is the prodrug approach.[27] Prodrug is made by modification in chemical structure of an active compound. A prodrug metabolize back into the original active compound *in vivo*. Addition of polar functionalities to hydrophobic molecules, addition of ionizable groups to unionizable molecules, or addition of lipophillic group to highly polar molecules are some of the strategies used for solubility enhancement by prodrug approach. DAG support the efforts made by medicinal chemists to evaluate physiochemical properties and stability of the prodrugs. However, its authors' experience that many times, prodrugs are chemically unstable both as drug substance and in drug products. For this reason a permanent chemical modification in the structure of a compound is preferred to improve its solubility instead of a prodrug strategy.

Biopharmaceutical Evaluation and Decision Making

Biopharmaceutical assessment is of critical importance in determining the suitability of a compound for development and is conducted by discovery–research (biopharmaceutics subgroup) with formulations provided by DAG. However, a very close collaboration exists between discovery and DAG in developing experimental protocols, analyzing data, and decision-making. Multiple animal studies in several species such as rodents, dogs, monkeys, etc., may be performed on each compound to determine if the desired exposure and PK profile is attained. Upon successfully achieving the biopharmaceutical exposure, the compounds are advanced for PD efficacy and/or toxicology assessment in different animal species. The early PK helps to screen the hits based on bioavailability (exposure to plasma). In addition, the PK studies are useful for determining the right physical forms (e.g., salts, hydrates, cocrystals, etc.) and the formulation principles. Figure 5 represents a general sequence of the studies during early development phase of a compound. The following sections discuss in detail some of the studies performed for evaluating biopharma-

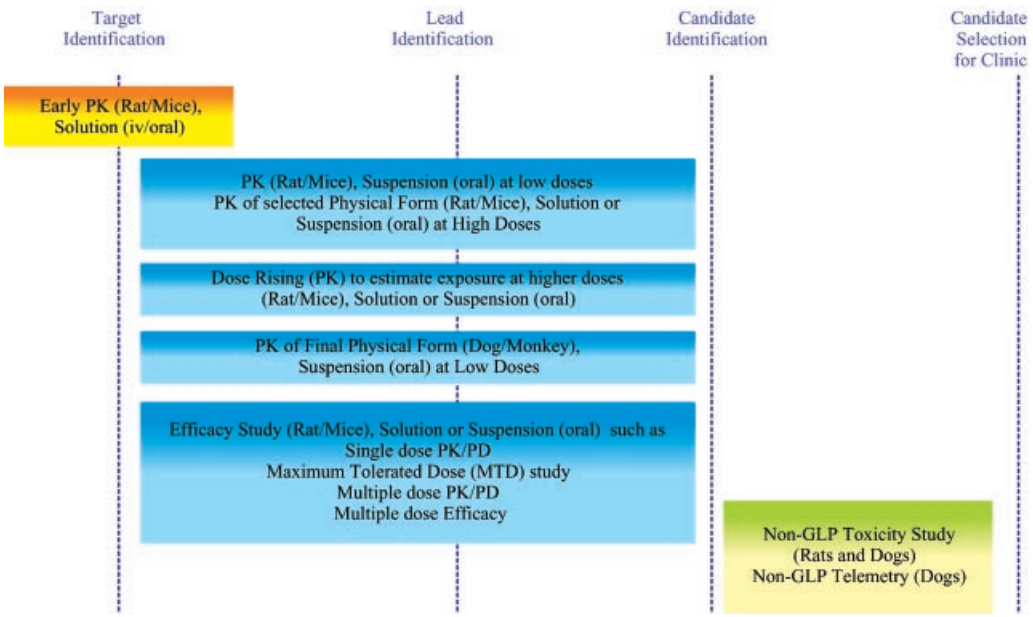

Figure 5. Sequence of biopharmaceutical studies during early development phase.

ceutical properties of NMEs, in the order in which these studies are conducted. It is to be noted here that the workflow and decision making described in the following sections represents a general scenario of screening based on PK properties of NMEs. Before starting the PK studies on NMEs, it is very important to review some *in vitro* data sets (available from discovery–research) such as *in vitro* metabolism (by liver microsomes in mice, rat, dog, monkey, and human) and *in vitro* potency (efficacy) data. The *in vitro* metabolism data set can prove to be very useful in identifying early on potential species-specific difference (due to in *in vivo* metabolism of compounds). If such species-specific differences are observed, then species for PK screening should be selected accordingly and impact of metabolism on *in vivo* exposure should be explored further. On the other hand the *in vitro* potency data set might be useful to move forward some NMEs with poor PK profiles but very high potencies.

PK in Rats/mice Using Solution Formulation

The rationale for performing these early PK studies is to screen the compounds (from a series) based on *in vivo* exposure to obtain hits as represented in Figures 6 and 7. In these studies, an i.v. and oral dose of 1 and 1–10 mg/kg, respectively, are evaluated. The key data of interest from these studies are the plasma half-life ($t_{1/2}$), plasma clearance (CL), percent bioavailability (*%F*), and exposure, which is measured by area under the curve (AUC). In these studies, the $t_{1/2}$ and CL values can serve as useful screens to select better candidates. This data is available from i.v. dosing of the compounds. All candidates, which have the $t_{1/2}$ greater than 1 h and CL less than the hepatic blood flow, are moved forward. From rest of the candidates with poor PK profiles, the compounds, which show very high potency from *in vitro* data sets are also moved forward. The third important piece of information is the oral bioavailability of the compound preferably from a solution formulation. As shown in Figure 8, drug in solution represents the form in which the drug is absorbed from the gastrointestinal tract after oral administration. Thus, bioavailability from oral solution along with permeability data from Caco-2, Parallel Artificial Membrane Permeability Assay (PAMPA), and metabolism assays provide critical information on the compound's

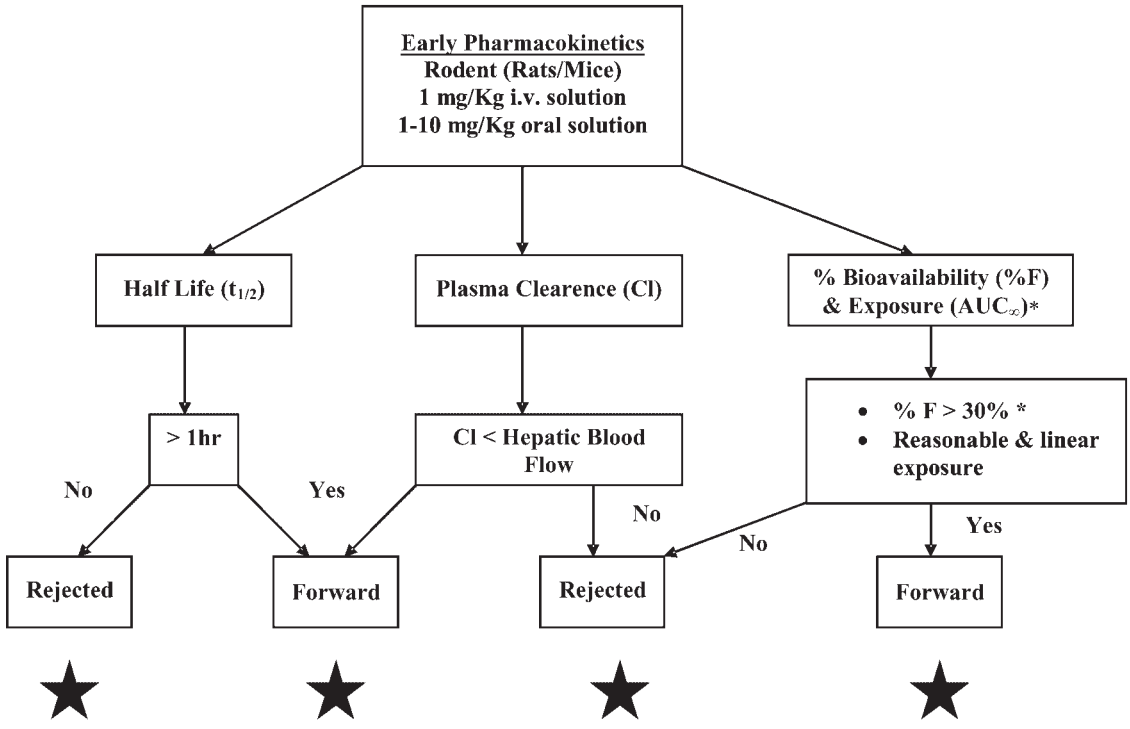

Figure 6. Screening of NMEs based on early PK studies in rodent species (★ indicates go–no go decision). *Oral bioavailability >30% in mice is advisable, however these values might differ based on disease areas and in case of highly potent molecules. *AUC∞–Area under the curve (till infinite time point).

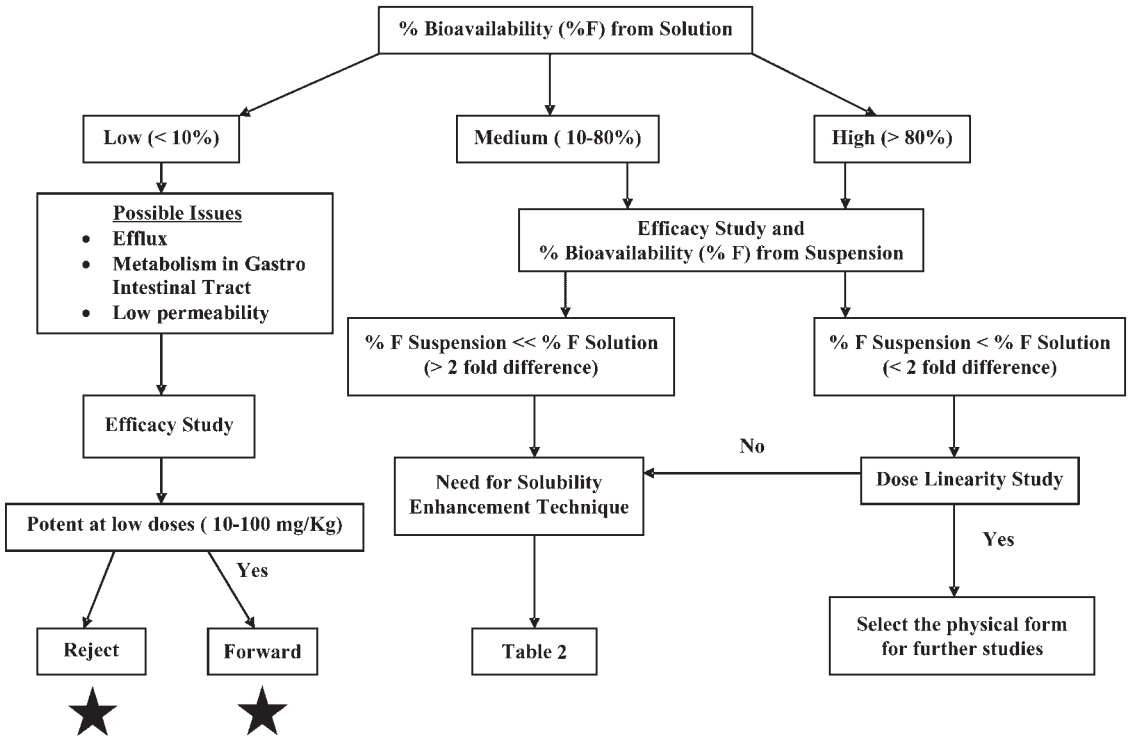

Figure 7. Role of bioavailability from solution and suspension in selecting a potential developable compound (★ indicates go–no go decision).

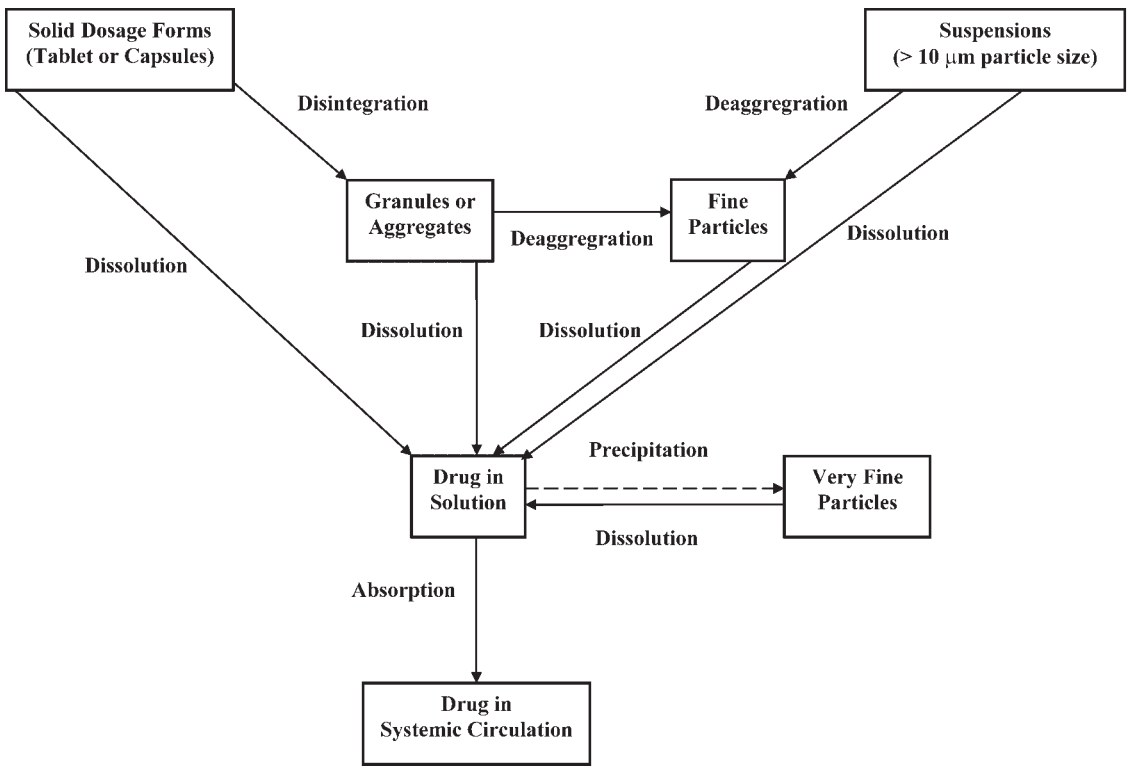

Figure 8. Fate of solid dosage forms and suspension formulations in gastrointestinal tract before drug absorption.

in vivo exposure. Caco-2, PAMPA, and metabolism assays are *in vitro* assays done early on by research to characterize hits and provide very valuable information when used along with the *in vivo* PK data. For example, if at a particular dose the $\%F < 10\%$ and the Caco-2 assay indicate tendency for efflux with normal metabolism, it might be important to determine if the drug is primarily eliminated in the feces. It may also be important to determine bioavailability as a function of dose to assess if the efflux mechanism can be saturated. Thus, *in vivo* bioavailability and *in vitro* Caco-2 assay data may provide valuable information on the *in vivo* behavior of a compound. Along with the bioavailability, the exposure (AUC) obtained by the compound is also very important. Many times a compound can have adequate bioavailability, but could lacks sufficient exposure needed for reasonable efficacy, if efficacy is driven by AUC. Early evaluation of compound's exposure, required for sufficient efficacy, could serve as a screening tool for selecting potential compounds.

For early PK studies, rat is the species of choice because of ease of dosing and sampling. But in cases where the efficacy model is mice or in cases where rat shows specific metabolism, mice are used as early PK species. Figure 7 represents a decision tree, which is very useful in deciding the next steps using the valuable information obtained from the %F data. Initially, the %F from oral solution is analyzed and classified as low, medium, or high based on %F being <10%, 10–80%, and >80%, respectively. All compounds possessing medium to high %F are moved forward towards the efficacy study. Low %F from solution could be due to issues in absorption (e.g., permeability, efflux, etc.) and/or metabolism of the compound in the liver or gut. In these cases, the %F is independent of the physical form of the compound. Usually, only the compounds with low clearance (less than hepatic blood flow), low to medium volume of distribution and higher half-life (>1 h) in rats or mice are moved forward to the efficacy study.

PK in Rats Using Suspension Formulation

The rationale for performing these studies is to select the physical form and/or formulation strategy for compounds showing medium to high %F from solution formulations in rats. Suspensions are commonly used for screening of crystalline compounds in preclinical studies. Suspension consists of fine particles and/or particle aggregates of a crystalline compound suspended in water using suspending agents/surfactants. Suspension formulation used for PK studies should be of known particle size and physical form (polymorph, salt, etc). Less than 10 μ particle size suspensions should be used to avoid dissolution issues due to particle size. As depicted in Figure 8, solid dosage forms (tablets and capsules) also disintegrate into particle aggregates and fine particles in the gastrointestinal tract, leading to formation of suspension of these aggregates and fine particles in the physiological fluids. Thus, $\%F$ from oral suspension formulations is representative of the $\%F$ from oral solid dosage forms in majority of the cases and could provide us valuable information to predict the exposure and bioavailability of compounds from a solid dosage form.

As depicted in Figure 3, the $\%F$ from oral suspension is compared to $\%F$ from oral solution. If, the difference between $\%F$ from suspension and solution is less than twofold, the compound moves forward to dose linearity study. Dose linearity studies are performed in rats, but the actual animal species may vary from one compound to another. The objective of the dose linearity study is to determine if a compound shows linear exposure as a function of dose from the selected physical form and formulation. This linear range helps the pharmacologist/toxicologist to identify the appropriate dose for the toxicity studies. On the other hand, if the difference in $\%F$ between oral solution versus suspension is more than twofold, it is recommended that mechanisms for solubility and exposure enhancement be evaluated to bridge the gap between the exposures from solution and suspension.

PK in Dogs/monkeys Using Solution and Suspension Formulation

For a lead NME, it is important to understand the PK behavior in nonrodent species. Secondly, it is required to have toxicity evaluated in a rodent and a nonrodent species. Thus, a PK study in the nonrodent species such as dogs or monkeys is performed, to understand the PKs. In these studies, i.v. and oral solution formulations of 2 and 10 mg/kg, respectively, and 10 mg/kg suspension are evaluated. Apart from $t_{1/2}$ and CL values, the main purpose of these studies is to determine $\%F$ from solution versus suspension

(Fig. 3). This comparative bioavailability information from oral formulations enables the DAG scientists to determine if the *%F* from a solid dosage form will be enough to get adequate exposure (i.e., 5–10-folds "above efficacy concentration"). In case of inadequate exposure, solubility enhancement techniques are needed to improve the exposure.

Sometimes, the comparison of exposures between rodent and nonrodent species helps in determining the most suitable efficacy model, which can predict exposures and drug effects closer to humans and could be useful later for assessing and optimizing formulations or life cycle management.

In case of highly soluble and permeable compounds, in which *in vitro* assays predict similar metabolism and distribution patterns among different species (rodent, nonrodent, and human), the exposure in higher species can be predictive of exposure in humans. For compounds with poor solubility, poor permeability, or both, due to number of other factors effecting absorption, distribution, metabolism, and elimination of the compound, the prediction of exposure in human based on exposure in higher species is much more complicated.

Efficacy and Toxicity Studies

Upon selection of the species for the efficacy model and following the proper selection of the physical forms, formulations, or delivery systems, the compound is moved forward to the efficacy study. Efficacy studies serve as important screens to filter out subefficacious molecules and move forward the efficacious candidates. The sequences of evaluations performed after completion of efficacy screen are shown in Figure 9. Potency from the efficacy screens then determines the fate of all compounds, as often the most potent compounds are preferred over less potent compounds. Compounds that require doses of >150 mg/kg for efficacy in animal model are often rejected during preclinical efficacy screen. For such compounds the required human efficacy doses could reach above 1 g/day (assuming same human efficacy doses as in animal model and dosing an adult human being with 70 kg average body weight), which presents a dosing issue in terms of patient acceptability and compliance. However, if a compound is first in its class with favorable safety and developability profile, it could be of strategic interest to move the compound to the clinic for proof of concept, mean while keep screening/

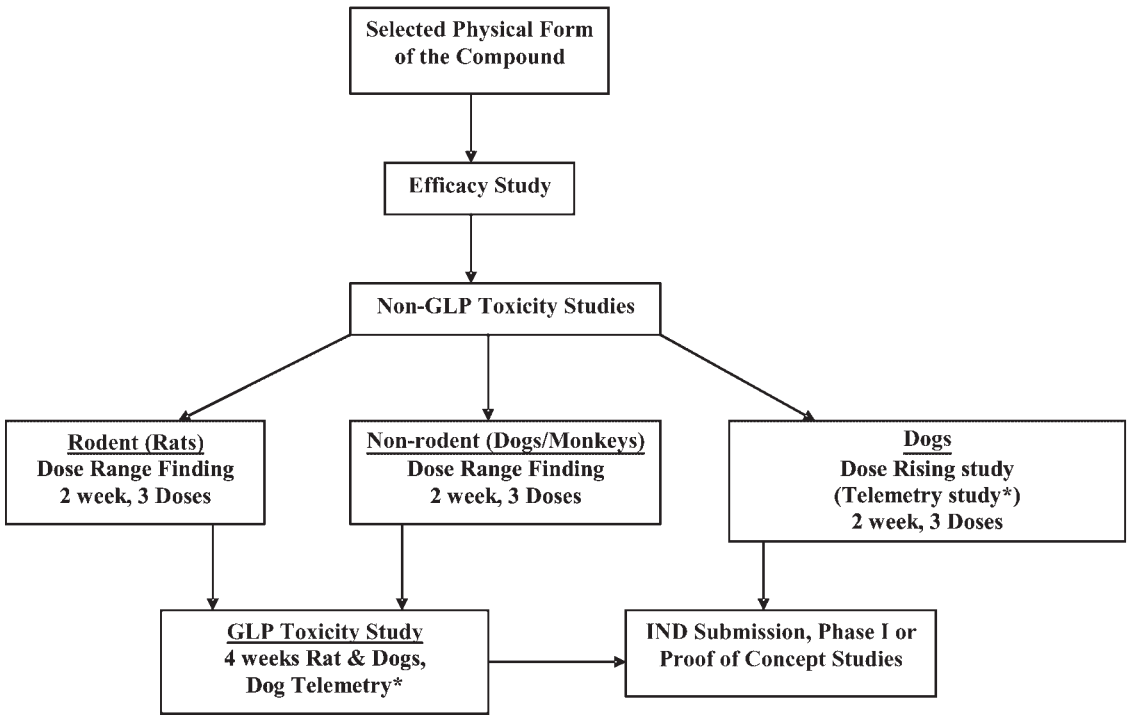

Figure 9. Toxicity screening studies for efficacious compounds. *Required if compounds shows activity in *in vitro* hERG (human Ether-a-go-go Related Gene) assay.

developing backups exhibiting high potency (50–100 times than the compound in clinic).

Once the efficacy study criteria are met, NMEs are screened for toxicity in both rodent and nonrodent species. Telemetry study in dogs to evaluate cardiovascular toxicity is also performed for compounds, which shows activity in *in vitro* hERG (human Ether-a-go-go Related Gene) assay. A 2-week non-Good Laboratory Practices (GLP) toxicity study is conducted first in both rodent and nonrodent species, and if the results are satisfactory, a 4-week GLP toxicity studies in rodents or nonrodents is performed next. The 2-week non-GLP toxicity studies are also known as dose range finding studies as they provide information on the toxicity assessment at various doses. Some tissue histology is performed during these studies to understand the acute toxicity of administered doses and then based on these results an estimate of doses for a 4-week toxicity study is made. Additionally, a dose rising study is done in dog/monkey to estimate the maximum tolerable dose (MTD) for a telemetry study. Once MTD dose is known, the compound is moved forward for dog/monkey-telemetry study at or below that dose.

On receiving the positive outcomes from the toxicology studies, the compound is moved forward for the next phase that is proof of concept study in humans/phase I clinical trails. Occasionally, there are several compounds, which cannot be differentiated during the preclinical evaluation. In such cases, two or more compounds may be selected for evaluation in humans to identify the most suitable compound for development. Such human studies are most commonly referred to as exploratory investigational new drug applications (Exploratory IND). Depending on positive outcome during exploratory IND studies, the most promising compound with maximum possibility of success during phase II or market launch is selected for full development. DAG plays very important role in candidate selection and formulation support during exploratory IND studies.

DAG TOOLS

A pharmaceutical company with significant drug discovery commitment and latest technological advances in high throughput screening (HTS) and combinatorial chemistry can produce a large number of hits and subsequent leads in a short period for each program.[28] Therefore, to cope up with a large number of molecules and very limited supply of material, DAG must maintain a high level of productivity and efficiency by utilizing HTS, automation, miniaturization, and simulation technologies.[10]

High Throughput Screening, Automation, Miniaturization

Several fast pace HTS along with state of art analytical tools allow DAG to provide valuable information with only small amounts of material. Some of the examples, where HTS can be applied include screening for crystallinity, solubility, salt, and polymorph selection, and formulation development. Use of robots in conjunction with solid and liquid dispensers can add to the efficiency/productivity of DAG by enabling automation. HTS with use of 96-well plates can be utilized for salt and formulation screening with less than 100 mg of material. Some suppliers for liquid and solid handling are Zinsser Analytics, Tecan, Emerald Biosystems, Biodot, etc. The example of analytical equipment miniaturization used by DAG is microdissolution apparatus (from pION, Woburn, MA), which reduces the amount of material needed for assessment of how a compound will dissolve in the gastrointestinal environment.

In Silico Simulation and Modeling

With advancement in simulation/modeling softwares, DAG can simulate the physiochemical properties based on chemical structure and *in vivo* absorption/exposure in humans based on solubility, permeability, dissolution, and PK data in animals. These are prophylactic approaches, which could save a lot of time and valuable resources spent in actual experimentation. Moreover, these techniques could help identify the potential issues early on. An example of such simulation software is GastroPlus™ which is useful in predicting the effect of particle size on absorption as a function of dose.[29] This could be useful specially for compounds with poor solubility and high permeability, in which size reduction could lead to enhanced solubility and oral bioavailability. Thus such simulation tools could prove to be useful in guiding the formulator in evaluating the right candidate for particle size reduction techniques such as nanomilling. Presently, several important simulation software are at different stages of their evolution and validation. Constant use and understanding of

simulation techniques can eventually lead to higher productivity, better utilization of resources, faster screening, and better prediction of possible issues in humans.

While HTS automation, miniaturization or *in silico* simulation technologies increase screening throughput and/or expedite the selection process, they come with drawbacks that must be effectively managed. Some of the problems in HTS are dispensing low volumes of volatile or viscous organic solvents using liquid dispenser, dispensing very small amounts of solids of varying bulk density using solid dispensers. Filtering the contents on 96-well plates, time to set-up the process and reproducibility of results specially when dealing with few milligram compound. Similarly miniaturization often leads to difference in equipment set-up/components as compared to parent equipment, which makes data correlation between both equipments challenging. Similarly, *in silico* simulation and modeling software's are still new to the industry and are currently in validation stages. Thus the data generated by these needs to be supported by *in vitro*/*in vivo* studies.

Its authors' view that even with the current limitations HTS, automation, miniaturization, and simulation technologies will be the way forward for the pharmaceutical companies in order to be efficient and productive in R&D and especially in activities at discovery–development interface. As these technologies are evolved, used, validated, understood, and developed even further, these will offer accurate prediction and enhanced efficiency. Continuous feedback and innovative ideas from the end users and financial support from the pharmaceutical companies are the driving factors for the success of such technologies.

DEVELOPABILITY ASSESSMENT REPORT

The outcome of DAG's activities on each lead candidate is presented in form of a detailed report known as "Developability Assessment Report." This report provides a critical assessment of the candidate developability, and the risks involved in further development of the candidate concerning manufacturability, physical/chemical stability, biopharmaceutical delivery, adequacy of PK profile, and potential for food effect, metabolism, and drug–drug interactions. Additionally, this report provides recommendation for physical form for late stage development, dosage form strategy for clinical studies and estimated human doses.

Overall the critical assessment of candidates developability includes the physiochemical and the biopharmaceutical data of the lead compound which includes physical form characterization, salt and polymorph screening, preformulation data, formulation development (including the need for delivery systems), dosage form attributes, preclinical exposure (PK and toxicokinetics with original and other developable salt forms). Moreover, it also includes information on the NME's pharmacology, mode of action, chemistry, pK_a, kinetic solubility, *in vitro* permeability (from PAMPA and Caco-2 assay), *in vitro* enzyme induction and *in vitro* liver microsome stability, *in silico* clearance.

DAG'S FEEDBACK TO DISCOVERY AND DEVELOPMENT GROUPS

Each NME passes through DAG during its journey from discovery–research to development phase. This means DAG scientists get opportunity to experience and study different projects from different disease areas, different targets within same disease areas, different chemical series within same targets, and different molecules within same chemical series. This kind of exposure enables DAG scientists to provide valuable feedback in both discovery and development areas.

In discovery, DAGs often provide feedback/suggestions to discovery chemists. These suggestions are focused on obtaining the desired the solid state properties, solubility, lipophilicity, and physicochemical stability by modifications in the chemical structure of the compounds without altering the desired efficacy, selectivity, specificity, and toxicity profiles. Example of some common suggestions are, (a) by minimizing the number of rotational bonds in the molecule, the polymorphism associated with that molecule may be reduced, (b) by incorporation of hydrophilic, H-bond donating groups in poorly soluble molecule the aqueous solubility may be enhanced, (c) by including electron withdrawing group next to ionizable group, the affinity of ionic bond formation with a counter ion during salt synthesis may be enhanced, and (d) by addition of hydrophilic groups in a lipophilic molecule, a log$p$ value of <5 may be achieved. Such feedback is very important to the discovery chemist during the

lead identification phase and may improve the chances of success of these NMEs, thereby reducing attrition down the road.

Similarly, DAG provides feedback to the drug substance and drug product development scientists. Information like recommendation for final physical form, salt and polymorph screening, hygroscopicity, physical and chemical stability of bulk substance, etc., gives chemists valuable information on possible hurdles and risk factors, and other potential opportunities. On other hand, information like proposed formulation strategy for clinic, dissolution, major interactions with excipients, physical stability during grinding and compression, solubility in various media, and effect of solubility enhancers such as surfactants, wetting agents, etc., provides the drug product development scientist great help in formulation development, selection of excipients, processing, and storage conditions. Thus, overall DAG plays a key role in saving time and resources during development as a lot of necessary information is generated early on by DAG during candidate selection phase.

Another important input of DAG to drug development process is recommending abbreviated developability assessments for some compounds. In such cases some logical correlations and extrapolations from *in vitro* and preliminary *in vivo* data could help in reducing some *in vivo* experiments. Based on authors' experience, for the compounds which can be classified as highly soluble and highly permeable (based on early *in vitro* and PK studies) or highly potent in animal models (low predicted human doses), an abbreviated developability assessment could expedite the compounds time to reach the clinic. Similarly for first in class compounds sometimes its beneficial to reach the clinic for proof of concept with suboptimal properties rather than spending time on optimizing the compound properties.

CONCLUDING REMARKS

The ability of a pharmaceutical company to benefit from a rich pipeline critically depends on the success it achieves in selecting the right molecules for development and taking them efficiently through the various development phases to approval. While a thorough and significant effort during discovery stage may lead to longer time in selection of development candidates, it is the authors' opinion that such an approach would not only increase the likelihood of success in development, but would improve the likelihood of a more sustained success in the end. Thus in order to reach a meaningful go–no go decision for moving a compound to development, a careful assessment of the solubility, bioavailability, physical form, and dose is essential. In addition, if compound is first in class and life saving, it is worth to put enormous efforts and resources for its success during development.

Serving as an interface between discovery and development, DAG plays a critical role in selecting the right molecules and advancing them efficiently from discovery through the proof of concept. In fulfilling its obligation, DAG conducts an *in silico* assessment during lead identification/optimization and performs a series of experiments using high throughput tools and technologies along with conventional manual experiment setups, to provide input on physicochemical and biopharmaceutical attributes of discovery candidates during lead optimization through candidate selection. The information generated is not only useful for advancing the right candidates during various discovery phases, but is also essential for the rapid development of sound product strategy for supporting proof of concept clinical studies.

The success of the DAG depends greatly on the academic training, experience and expertise of DAG scientist. They need strong understanding of organic chemistry and salt synthesis, solid-state characterization, formulation principles, biopharmaceutics, and PK. They also need a broad understanding of the whole drug discovery and development process. Strong communication and leadership skills are equally important due to a large number of interfaces involved. DAG provides much-needed interface between discovery and development function for smooth and efficient transition of compounds from discovery to development. Despite the critical academic training and experience needed for success of DAG scientists, much of the training is accomplished from the industry with exposure and support in many different areas.

ACKNOWLEDGMENTS

The authors are very grateful to Dr. Abu T. M. Serajuddin and Dr. Wei-Qin (Tony) Tong, Technical Research and Development, Novartis Pharmaceuticals Corporation, One Health Plaza,

East Hanover, NJ for their scientific inputs, valuable discussions, and help in reviewing this manuscript.

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