1

FACTORS THAT IMPACT THE DEVELOPABILITY OF DRUG CANDIDATES

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1.1 CHALLENGES FACING THE PHARMACEUTICAL INDUSTRY

Drug discovery and development is a long, arduous, and expensive journey. It was estimated that the total cost of developing a new drug in the US pharmaceutical industries was well over a billion dollars in the 2000s, and this figure has been increasing [1, 2]. This figure may be slightly better for biotechnology-based research and development (R&D) [1]. The entire process may take up to 14 years [1, 3]! Yet, only 2 out of 10 marketed drugs would return revenues that match or exceed R&D costs according to a recent analysis [4]. There has been a tremendous amount of pressure on the industry to maximize efficiency, shorten development time, and reduce the cost during discovery and development. In order to accomplish such objectives, one needs to analyze the entire drug discovery and development process so as to identify steps where changes can be made to increase efficiency.

The entire endeavor of developing a new drug from an idea to the market is generally divided into several stages: target identification, hit identification/discovery, hits’ optimization, lead selection and further optimization, candidate identification, and preclinical and clinical development [5]. Among these, each stage has
many interrelated aspects and components. A target is identified in early discovery when there is sufficient evidence to suggest a relationship between the intervention of a target and treatment of the disease or conditions. Tens of thousands new molecules are then synthesized and screened against the target to identify a few molecules (hits) with desired biological activities. Analogs of these selected molecules are then made and screened further for improved activities and drug-like properties. Optimization results in identifying a small number of compounds for testing in pharmacological and other models. Those active compounds (leads) are further optimized for their biopharmaceutical properties, and the most drug-like compound(s) (drug candidates, only 1–2 in most cases) are then selected for further preclinical and clinical development. The drug discovery and development path with an emphasis on the discovery stages is schematically illustrated in Figure 1.1.

Having been through the screening and optimization processes, however, of those drug candidates with most drug-like properties, only about 40% successfully make their way into the evaluations in humans (first-in-human or FIH clinical trial) [6]. Unfortunately, data from historical average reveals an almost 90% overall attrition rate in clinical development [6]. In another word, only one molecule successfully makes into the market from 10 compounds tested in humans. Results from another statistical analysis gave a similar success rates for new chemical entities or new molecular entities (NCEs/NMEs) for which an investigational new drug (IND) application or a biologic license application (BLA) was filed in almost four decades [7], and the figure has not changed much [8]. This high attrition rate obviously does not meet the needs of long-term success desired by both the pharmaceutical industry and health care system.

![Diagram of drug discovery and development process](image)

**FIGURE 1.1** A schematic illustration of the drug discovery and development process with the estimated number of compounds shown for each step.
Prentis et al. [9] analyzed many factors that potentially were attributable for such a high attrition rate based on the data from seven UK-based pharmaceutical companies from 1964 through 1985. The results from this statistical analysis revealed that a 39% failure was due to poor pharmacokinetic properties in man, 29% was due to a lack of clinical efficacy, 21% was due to toxicity and adverse effects, and about 6% was due to commercial limitations. Although not enough information was available in a great detail, it is believed that some intrinsic relations of these factors existed. For instance, toxicity or lack of efficacy can be precipitated by undesired drug metabolism and pharmacokinetic (DMPK) properties of the molecule. Based on the assumptions that most failures was not due to the lack of “biologic activities” per se as defined by *in vitro* testing, there has been a drive to incorporate the evaluation of drug delivery properties, which may potentially precipitate developmental failures, into the early drug discovery and candidate selection processes with the intention of reducing the proportion of late stage failures, which is obviously most costly.

Rapid development in biology, and in rational and structure-based chemical design in addition to new technologies such as generation of diversity libraries, automation in high throughput screening, and advanced instrumentation in bioanalysis have significantly accelerated lead identification and discovery process [10, 11] for a given target. In light of these scientific and technical advances and under the pressure to reduce the cost and shorten the time of discovery and development, many major organizations in the pharmaceutical industry went through rapid and drastic changes from the late 1990s to early 2000s. A conference entitled “Opportunities for integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development” [12] was a landmark of this fundamental change in the pharmaceutical industry [13]. The developability concept was introduced to pharmaceutical R&D with an organizational and functional integration in early drug discovery and development [14]—optimization of DMPK properties of drug candidates in conjunction with toxicology and pharmaceutical development. These changes were successful in addressing some of the specific causes of the attrition. Early investment in optimizing absorption, distribution, metabolism, and elimination (ADME) in drug discovery [15] has successfully reduced attrition rate due to poor human pharmacokinetics from about 39% in the previous survey [9] to approximately 10% in the year of 1991–2000 [16]. A top cause of failures appeared to have shifted to toxicology related. Furthermore, failures due to other reasons, such as the lack of clinical efficacy, remain to be a major issue.

Being encouraged by the successes in addressing ADME issues early on in the discovery and preclinical development, R&D in pharmaceutical industry bolstered the number of drug candidates entering into clinical trials during the early 2000s. Unfortunately, this did not make the expected positive impact on the output in terms of the number of new medicines into the market. The success rate, instead, fell to approximate 5% in the year of 2006–2008 [17]. Thus there is a need of improved understanding of disease mechanism(s) and issues in drug delivery. It shouldn’t be forgotten that waves of mergers and acquisitions aim at boosting R&D performance in the pharmaceutical industry apparently failed to effectively address the issues either [18].
FACTORS THAT IMPACT THE DEVELOPABILITY OF DRUG CANDIDATES

Nevertheless, the march goes on. A fairly recent analysis indicated that the number of approved new drugs from pharmaceutical companies has essentially been relatively constant during the past 60 years [19]. Over a thousand new drugs had been approved by the US Food and Drug Administration (FDA) in this period of time. There is no doubt that these medicines helped enormously in treating diseases, managing health conditions, and improving the quality of life. Indeed, life expectancy and cancer survival rate improved due to new treatments [20, 21]. Death rates in cardiovascular diseases decreased significantly [22]. Average cholesterol level in adults in the United States fell to the ideal level—below 200 mg/dl [23, 24]. The most striking example was the dramatic drop in HIV/AIDS death rate since the approvals of anti-retroviral treatments [25]. These testimonial facts are the demonstration of the value of pharmaceutical R&D of new medicine.

Since the first therapeutic monoclonal antibody—muromonab-CD3 (Orthoclone OKT3®)—was approved by the US FDA in 1986 [26], more than 30 therapeutic monoclonal antibodies have been approved, and probably hundreds based on the same platform of therapeutics are under clinical development. This class of molecules mimics the human immune system and very specifically intervene cell membrane-bound or soluble targets by antagonizing (a few agonists too) the pathway or neutralizing the ligand [27]. Monoclonal antibody therapeutics along with other biologics such as recombinant or fusion proteins are commonly referred as large molecule to differentiate from synthetic drugs or small molecules. Based on an analysis [8] of the data up to 2004, clinical approval success rate for large molecule therapeutics more than doubled that for small molecules. An in-depth survey on only monoclonal antibody-based therapeutics reveals similar encouraging trend [28]. The discovery and development of biologics are seeing rapid growth. It is expected that the top list of sales will be dominated by biologics in a few years according to Slatko’s analysis based on the observations made in 2010 [29].

Taking advantage of the high specificity of a monoclonal antibody as a guided carrier to deliver chemotherapeutic agent specifically to the tumor cells was truly an innovation in drug delivery. This class of coupled molecules is commonly referred as antibody–drug conjugate (ADC) (for a thorough review, see Zolot et al. [30]). The very first ADC was approved for acute myeloid leukemia in 2000 (although it was withdrawn in 2010 based on US FDA’s recommendations) [31]. Shortly in the next few years a CD30-specific ADC, brentuximab vedotin, was approved by the US FDA in 2011. Trastuzumab emtansine was approved in 2013. Through conjugation of anti-human HER2 receptor antibody with mertansine, a tubulin inhibitor, Trastuzumab was created as a unique ADC [32]. Because the monoclonal antibody targets HER2, and HER2 is over-expressed in certain cancer cells, the cytotoxic toxin is delivered specifically to tumor cells such as in breast cancer [33]. It has been proven to be a very successful drug delivery strategy for cancer therapies.

Over the past several decades, the never-ending endeavors conjointly by pharmaceutical, academic, and regulatory scientists and researchers have been devoted to finding more effective and safer medicines for treating variety of diseases. The journey has been focused more closely on understanding the biology, learning the etiology, finding the right
molecule, and delivering the molecule to the right target. Many successful stories and
good lessons learned undoubtedly demonstrate that drug delivery has been playing a criti-
cal role. The developability of drug candidates is an assemblage of assessments that pro-
grammatically ensure and optimize drug delivery. The concept has not changed although
the domains of developability have been continuously extending along with the
development of technologies and advance in sciences. The evaluation of developability
mostly involves the integration of research activities in functional areas such as DMPK,
pharmaceutical development, safety assessment, and process chemistry into drug dis-
covery and development process in very early stages of discovery. The inputs from other
functional areas as well as those from clinical, regulatory, commercial, and marketing
groups in the early stage help to minimize costly mistakes in late stages of development
and have become more and more important to the success of the drug discovery and
development process. Developability is an overall evaluation of the drug-like properties
of an NCE/NME. Many of the changes in the pharmaceutical industry have been driven
by the concept of ensuring developability. These changes, in other words, the integration
of the sciences and strategies in multifunctional areas in drug discovery and development,
are to ensure that the NCEs/NMEs of interest will have the best possibility of success in
every step toward the final goal.

In the next few sections, examples of some factors that are often examined for
developability and their intrinsic relationship are briefly discussed. This is, of course,
not a comprehensive coverage of the developability. However, we do hope that this
section will put various chapters in perspective and allow readers to see individual
sections in the context of an integrated drug discovery and developmental process.

1.2 FACTORS THAT IMPACT DEVELOPABILITY

In most pharmaceutical companies, many efforts have been made to create a clear
framework for selecting compound(s) with minimal ambiguity for further progres-
sion. Such a framework is not a simple list of the factors that impact the quality of a
drug-like molecule and can vary from company to company [34]. This framework,
which is more often referred as “developability criteria,” is a comprehensive sum-
mary of the characteristics, properties, and qualities of the NCE/NME(s) of interest,
which normally consist of preferred profiles with a minimally acceptable range.
A preferred profile describes the optimal goal for selection and further progression
of a candidate, whereas the minimum range gives the acceptable properties for a
compound that is not ideal but may succeed. Molecules that do not meet the criteria
will not be further progressed. Such criteria cover all the functional areas in drug
development. Some of the major developability considerations are briefly described
as examples in the following paragraphs.

1.2.1 Commercial Goal

It is self-evident that we are in a business world! Generally speaking a product needs
to bring value to the health care system and be profitable to the manufacturer to be
viable. Therefore, early input from commercial, marketing, and medical outcome
professionals is very important for setting up a projective product profile, which profoundly affects the development of the developability criteria for intended therapeutics. In general, this portfolio documents the best possible properties of the product and minimum acceptable ranges that may succeed based on the studies of market desires. These studies should be suggestive based on the results from professional analyses of health care needs, potential market, and existing leading products for the same, similar, or related indications. The following aspects need to be well thought out and fully justified before the commencement of a project: (i) therapeutic strategy, (ii) dose form and regimen, and (iii) the best possible safety profile such as therapeutic window, potential drug–drug interactions, and any other potential adverse effects. Using the development of an anticancer agent, as an example, for therapeutic strategy selection, one may consider the choice of developing a chemotherapeutic (directly attacking the cancer cells) versus anti-angiogenic agent (depriving cancer cells of their nutrients) and in combination versus stand-alone therapy. In deciding the optimal dose form and regimen, one may consider the following: whether an oral or iv or both formulation should be developed, should it be once daily or in a different dose interval, and would projected dose regimen be acceptable or convenient for the patients. The results from such an analysis form the frameworks for developing the developability criteria and become the guidelines of setting up the criterion for each desired property. For example, pharmacokinetic properties such as half-life and oral bioavailability of a drug candidate will have direct impact on developing a drug that is to be administered orally once a day.

1.2.2 The Chemistry Efforts

Medicinal chemistry is always the starting point and a driver of small-molecule drug discovery programs. In a large pharmaceutical R&D organization, early discovery of bioactive compounds (hits) can be carried out either by high throughput screening of compound libraries or by rational design, or a combination of both. Medicinal chemists will then use the structural information of the pharmacophore thus identified to optimize the structures. Chemical tractability needs to be examined carefully at the very beginning when a new chemical series is identified. Chemistry space around the core structure for modification is closely studied. Upon a thorough examination of a small number of compounds, an initial exploratory structure–activity relationship (SAR) or quantitative SAR (QSAR) should be developed. Rheault and colleagues [35] described an example of how to establish and explore SAR around a pharmacophore in the discovery of a potent and oral bioavailable BRAF inhibitor. In this example, numerous substructural changes were made leading to the most potent compounds while considering the other properties such as the pharmacokinetics and metabolism. Such efforts are normally made in parallel with several different chemical series. It is important for medicinal chemists that many different SARs are being considered, developed, and integrated into their efforts at the same time, which provide more opportunities to avoid other undesirable properties unrelated to their intended biological activities. Such factors, again, may include potential CYP450 inhibition, permeability, selectivity, stability, and solubility, etc.
Structural novelty of the compounds (in other words, can this piece of art be protected in a patent?), complexity of synthetic routes, scalability (can the syntheses be scaled up to industrial production scale?) and the cost of starting materials (cost of goods at the end of the game), potential environmental concerns, and toxic intermediate issues will all need to be closely examined at early stages of the drug discovery and development processes. It is never too early to have those thoughts and to put them into actions.

1.2.3 Biotechnology in the Discovery of Medicine

Comparing to medicinal chemistry efforts in the processes of searching a bioactive molecule, the initiation of a biotechnology-based project is more specific and target driven. The biologic activity of large molecule therapeutics is generally believed to be more specific; therefore, there are fewer unexpected off-target effects and potential toxicity issues, which can be a major advantage. Yet, many different hurdles have to be overcome.

The issues with large-molecule products during early development are similar by nature. Thus monoclonal antibodies are used as an example here. The discovery of hybridoma technology by Köhler and Milstein in 1975 was a milestone in the development of monoclonal antibodies in immunology and biomedicine [36]. The Nobel Prize in Physiology or Medicine in 1984 was awarded jointly to Niels K. Jerne, Georges J.F. Köhler, and César Milstein “for theories concerning the specificity in development and control of the immune system and the discovery of principle for production of monoclonal antibodies” [37]. It is fascinating to see how this discovery has changed the face of immunology and biomedicine nowadays [38].

Monoclonal antibodies can be made fully humanized with current technology. Several molecular and cellular biology techniques have been established to generate human monoclonal antibodies [39]. In addition to affinity maturation, engineering and selection processes for the desired specificity and binding affinity, and protein sequence and amino acid residue that may affect the stability and other physicochemical properties of the molecule are important factors in protein engineering of the molecule. The selection of a production platform and/or cell line for a stable and high-yield production of selected antibody is also a very important developability criterion that has to be considered much early on.

Immunogenicity of protein-based therapeutics has been one of the major safety concerns besides its potentially negative impact on the pharmacokinetics and pharmacodynamics. This aspect has been largely addressed by using fully human products [40]. The immunogenicity of a candidate in animal species used in pharmacology and toxicology models is also a very important factor although the occurrence and its impact are in general not predictable for humans [41]. Successful preclinical pharmacology and toxicology programs are the very first step of preclinical development. The importance of drug delivery has been exhibited even in early preclinical development for large molecule as well. Taking immunogenicity as an example, it may interfere with the investigation of pharmacokinetics and safety assessments in animal species, which may severely hinder the molecule being developed further to FIH.
Antibodies largely undergo protein catabolism leading to their eventual elimination, rather than being metabolized by the CYPs or other enzymes. FcRn (neonatal Fc receptor or Brambell [42] receptor) plays an important role in protecting antibodies from proteolysis in the lysosomes. That explains the long half-life of most therapeutic antibodies as well as endogenous ones. Transporters are rarely involved for large molecule’s absorption and excretion. It may have less of concerns for drug metabolism-based drug–drug interactions [43]. However, the potential of drug–drug interactions should still be programmatically evaluated [44], especially when a cytokine modulator is being developed since certain soluble cytokines may play a role in regulating the expressions of CYP enzymes and transporters. The effects of cytokines, such as interleukin-6 and tumor necrosis factor alpha, on CYP modulation and possible mechanisms have been studied [45].

With the introductions to medicinal chemistry- and biotechnology-based drug discovery and early development described already, it should be relatively easy to appreciate the complexities of the factors that may affect drug developability directly and indirectly for ADCs. On top of those factors that have to be considered and evaluated for a small–molecule drug and those for the development of a monoclonal antibody, the linker between the two molecules in terms of chemical type and relative stability in a biological environment is also a key factor that has to be fine-tuned before making an ADC work [46].

1.2.4 Target Validation in Animal Models

Although drug discovery efforts almost always start with in vitro testing nowadays, it is well recognized that promising results from in vitro testing do not always translate into in vivo efficacy. There are numerous reasons that could lead to this discrepancy, some of which are well understood and others are not. Therefore, target validation in animal models before clinical trials in human is a critical step. Before a drug candidate is fully assessed for its safety and brought to a clinical test, demonstration of efficacy of a biologically active compound (e.g., active in an enzyme inhibition assay) in pharmacological models (in vivo, if available) is considered as a milestone in the path of discovering a drug candidate. This is sometimes also called proof of mechanism (PoM). Many cases exemplify the challenges and importance of pharmacological models. For example, inhibitors of integrin receptor $\alpha_\beta_3$ have been shown to inhibit endothelial cell growth, which implies their potential as being clinically beneficial for an anti-angiogenic target for cancer treatment [47]. However, the proposed mechanism did not work in animal models although compounds were found very active in vitro [48, 49]. What has been recognized is that integrin receptor $\alpha_\beta_3$ may not be the exclusive pathway that tumor cell growth depends on. Inhibition of this pathway may induce or shift to a compensatory pathway(s) for angiogenesis.

Advances in mathematical modeling have been providing very useful testing environments and have generated very useful data. Anticancer drugs, for example, may be tested in animal xenograft models. Biomarkers and antitumor efficacy data with the pharmacokinetic information could be modeled for prediction of clinical drug exposure and efficacy [50]. Knowing the limitation of animal models, the information
derived from such *in vitro* and *in vivo* experiments and from mathematical modeling is invaluable for target validation and, furthermore, to provide guidance for dose selections in clinical studies. Also, it should be mentioned here that most biologic therapeutics, such as monoclonal antibodies, are very specific to human target and may not cross-react with that in animal species. This property sometimes paradoxically limits the use of preclinical animal models. Therefore, the availability of directly relevant information from preclinical species may be limited for these types of drug candidates. Nonhuman primates are often used. The development of human transgenic animals has been providing very relevant research tools. For example, hFcRn transgenic mice may predict the pharmacokinetic behavior of human monoclonal antibodies very well [51].

Ideally, an *in vivo* model should comprise all biochemical, cellular, and physiological complexities as in a real-life system, which may predict the behavior of a potential drug candidate in human much better than an *in vitro* system. In order to have a biological hypothesis tested in the system with validity, a molecule has to be evaluated in many other aspects. Knowing the pharmacokinetic parameters such as absorption, distribution, and metabolism in the animal species that is used in the pharmacological model becomes critical. Basic pharmacokinetic parameters will be briefly described in the following paragraph and discussed in detail in several chapters in the book. The importance of drug delivery is demonstrated as early as in an animal model that serves as an early milestone in preclinical drug development.

The pharmacokinetics/pharmacodynamics relationship, systemic and tissue levels of drug exposure, frequency of dosing, which allows the drug to demonstrate efficacy, and the strength of efficacy are all very important factors that may affect the future development of an NCE/NME. These are all factors that are directly or indirectly related to the topic and, therefore, have to be fully considered for drug delivery.

### 1.2.5 Drug Metabolism and Pharmacokinetics

The importance of DMPK in drug discovery and development is reflected in the statistics of attrition rates [9]. Most of the changes in the industry during early 2000s have happened in the areas of DMPK [13] and proven to be effective in reducing attrition [16]. The overall goal of DMPK in drug discovery and development is to predict the pharmacokinetic behaviors of a drug candidate in humans. Nevertheless, the focus could vary at different stages of the process. PK parameters in animal species that will be used in pharmacological (as briefed in the previous paragraphs) and safety assessment models provide very important insights (systemic and tissue exposures) for those studies. The results from pharmacokinetic studies in several animal species generate the data for physiologically-based models or interspecies allometric scaling [52, 53] to predict basic pharmacokinetic behaviors of a product in human. Assays using human tissues, cells, and genetically engineered cell lines provide a tremendous amount of information before a molecule can be tested in clinical studies. Optimizing DMPK developability factors are immensely beneficial for finding the candidate(s) with best the potential for success [54].
Desirable (or undesirable) biological effects of a drug in vivo normally are directly related to its exposure. One of the following factors, namely, total systemic exposure, maximum concentration, or duration of the concentration above a certain level, is usually used as a parameter that is correlated with the efficacy and/or adverse effects [55]. The exposure is governed at a given dose by (i) the ability for the body to remove the drug as a xenobiotic and (ii) the route via which the drug is delivered. Blood or plasma clearance (CL) is often used as a measurement of the capability to eliminate a drug molecule from the systemic circulation. Low-to-moderate clearance molecule is desirable in most situations unless a fast-action and short-duration drug is being designed [56]. Biologics such as monoclonal antibodies generally have much lower clearance when compared to small-molecule drugs. Since endosomal proteolysis of monoclonal antibody is protected by its binding to the FcRn receptors [42], the half-life of a therapeutic monoclonal antibody is normally 2–3 weeks. Monthly or even longer dosing interval thus are possible.

A drug can be directly delivered into the systemic circulation by several methods. However, for convenience and many other reasons, oral dosage forms are preferred in many situations. Therefore, oral bioavailability of the compound is one of the very important developability criteria for oral drug delivery. Many factors affect the oral bioavailability of a drug. Orally delivering a biologic therapeutic protein is still quite challenging due to the digestive system. Subcutaneous or intramuscular delivery is the commonly used route of administration in addition to intravenous infusion. The understanding of the mechanisms and factors affecting subcutaneous absorption is still primary. These factors will be discussed in detail in several of the following chapters. In addition to clearance and bioavailability, other major pharmacokinetic parameters that should be evaluated are also discussed in related chapters.

Volume of distribution is a conceptual pharmacokinetic parameter that measures the extent of a drug distributed into tissues. A well-known parameter, elimination half-life, can be derived from clearance and volume of distribution. It is a very important developability criterion, which warrants desired dose regimen. It should be noted here that a discussion of half-life has to be in the context of pharmacologically relevant concentration. A purely mathematically derived half-life is sometimes pharmacologically irrelevant. Some more definitive explanation and comprehensive discussion of the major pharmacokinetic parameters and their biological relevance have been extensively reviewed [57, 58].

These parameters should be examined across several different preclinical species to reliably predict the behavior in human. However, with therapeutic monoclonal antibodies, although available data usually are limited to only one relevant animal species, the predictability has been impressively good and reliable [59]. The pharmacokinetics and pharmacodynamics topics will be discussed in several related chapters in this book.

Inhibition and induction of drug metabolizing enzymes [60], P-glycoprotein (P-gp) substrate property [61, 62], plasma protein binding and binding kinetics [63, 64], metabolic stability in the microsomes or hepatocytes from different species including humans [65], metabolic pathway, and the metabolite(s) identified [66] are all very important developability measurements in the assessment of safety, potential drug–drug interaction,
and predictability. These factors need to be optimized and carefully examined against developability criteria. Drug metabolism-related issues are outlined and discussed in Chapter 9. The impact of transporter including efflux transporter in drug delivery and the models used to study and address these issues are discussed in Chapters 5 and 7.

**1.2.6 Preparation for Pharmaceutical Products**

Before the early 1990s, the issues of solid state, salt form, aqueous solubility, and dosing formulation for agents used in pharmacological, pharmacokinetic, and toxicological studies have not been brought to full attention. However, an inappropriate salt version or solid form may precipitate potential drug delivery and stability problems (both physicochemically and chemically) during formulation and pharmaceutical engineering. Now it has been realized that the investigation of physicochemical properties of an NCE/NME against developability criteria should start early in the R&D processes. Chapter 3 and several other chapters discuss these physicochemical properties that have major impact on drug delivery.

Aqueous solubility is one of the most important physicochemical properties. It is believed that a drug has to be in solution to be absorbed [67]. From a pharmaceutical development point of view, solid-state form is another important factor that affects solubility and dissolution rate, and eventually the developability. Solid-state form is the determinant of, to some extent, physicochemical stability, intellectual property, and formulation scalability; this factor ought to be carefully examined and optimized. Changes in crystallinity from different chemical processes, in some cases, result in a big difference in bioavailability when the drug is delivered by a solid-dosage formulation.

Many of the earlier-described properties could change when salt version and form change. The salt with the best solubility, dissolution rate (therefore, could result in best bioavailability if by solid dose), stability, and other properties such as moisture absorption should be selected before a molecule enters full development [68]. *In situ* salt screening is a new technology to select the right salt form for drug candidate [69]. For instance, the HCl salt [70, 71] used to be almost the default version for a weak base; however, it has been shown in many cases not to be the best. Application of these screening processes in early drug development is one of the major steps in integrating pharmaceutical development into drug discovery and development.

Preclinical safety assessment (toxicology) is another functional area, which in itself stands to serve as a big milestone in drug discovery and development. NCE/NMEs have to be evaluated for their genetic toxicity as well as acute, short-term, and long-term toxicity when appropriate. The results are crucial for further development of the molecule in FIH clinical study and beyond. Although the principles and importance of toxicology will not be discussed in this book, many efforts in DMPK and pharmaceutics are to assure drug delivery in the animal species used in safety assessment programs. Metabolism profiles of a drug candidate in the species used in the toxicology studies are to be compared with that from human tissues for major difference. The profiles are also examined for potential active/toxic metabolite(s).
It should be noted that process chemistry and biologics production are large functional areas that can have major impacts on a drug’s developability, but will not be covered in this book. Although developability criteria in this area will not be discussed here, it is important to point out that it is essential that collaboration with these areas is considered early on in order to define the best strategy for drug delivery.

1.3 REMARKS ON DEVELOPABILITY

The concept of ensuring developability in drug discovery and development represents an integration and synchronization of all functional areas that impact efficiency, and thus the quality and quantity as well as timelines for drug development. Coordination of these multifunctional, interlinked, parallel ongoing scientific and technological research activities is a new challenge to the management of a drug discovery and development enterprise nowadays.

The developability concept was adapted and executed much earlier and more rigorously by larger pharmaceutical companies than their smaller counterparts. However, an analysis by Munos [19] of pharmaceutical innovations in the past 60 years suggested a trend that smaller companies may have outperformed larger companies in their NME/NCE outputs. The underlying reasons for this difference are not clear, especially about whether it was due to a difference in the directions of innovation investments and/or the impact from heightened safety concerns of regulators. There were also not enough data to make the comparison on final approvals. Nonetheless, it was probably more certain that the way in which developability criteria are being adapted and applied was somewhat different. A recent publication clearly indicated varying organization-dependent criteria in different companies [34]. It is reasonable to expect a more focused and objective-driven process in smaller biotechs; whereas larger pharmaceutical companies may use more compartmentalized and criterion-driven development processes. In another word, the question of how we achieve our goals should be asked conjunctively with the questions of how likely it will be to achieve the goals, knowing that the risks, resources, and timelines have to be balanced in practice. Developability is about an in-depth understanding of the molecule regardless of the size of the company or number of molecules in the pipeline.

It is interesting to note some “exceptions” to the commonly accepted developability criteria in the recent history of drug development. In those exceptions the candidate had been successfully developed and even became a blockbuster although the molecule was inborn with some strongly undesired properties. One of the examples would be atorvastatin. The molecule had very limited bioavailability in preclinical species (e.g., ~5% in rats) due to the interplay between transporters and drug metabolizing enzymes in the intestines and liver [72]. Thus, if the preclinical bioavailability criteria used by most preclinical development organizations were applied to atorvastatin, it would not have been selected for development and, therefore, would not have made it to a top-selling drug at all. We learned that in human clinical studies, the bioavailability of atorvastatin was not very high either (14%) [73]. Another story is about a recent-approved cancer drug—dabrafenib (GSK2118436). Inhibition and induction
of major CYP enzymes are serious concerns for potential drug–drug interactions. Drug candidates usually are deselected for that reason. If the concerns of CYP3A4 induction plus the inhibition of several other CYPs (public data in gsk media) [74] were used as a litmus test, GSK2118436 would not have been selected for development and, therefore, there would not be the successful story of dabrafenib and trametinib combination therapy for melanoma [75]. The successful stories, or hypothetical arguments if one would, tell us that the developability should never be simply an artificially defined bar for a candidate to jump over. It is a complex process that requires judgment calls based on the full understanding of the properties of a molecule.

1.4 DRUG DELIVERY FACTORS THAT IMPACT DEVELOPABILITY

Delivery of a pharmaceutical agent to the systemic circulation and consequently to the site of action to produce the desired pharmacological effect is the ultimate goal of drug delivery. The developability of a drug candidate from drug delivery perspectives has become the core of developability criterion in drug development. As discussed in the previous sections, many other factors in developability criteria are closely related to drug delivery; these thoughts and practices are applicable from research laboratory all the way to clinical trials and from early discovery to post market development. In order to accomplish the task, one has to overcome numerous barriers that hinder drug delivery.

As the nature of a biological system, multiple or redundant mechanisms may exist to protect the system from exposures to almost any foreign substance while preserving the ability of nutrients uptake. The physiological arrangements and the chemical and biochemical barriers associated with the physiological structures form the first line of defense. Any drug, delivered by any route, will almost certainly encounter some of these barriers before reaching the site of action. These barriers, as well as their physiological and biochemical functions, and their role in drug delivery, will be discussed in detail in Chapter 2. In the first several chapters, general concepts that are directly related to drug delivery, principles in evaluation of drug delivery, along with some common approaches to study drug delivery from anatomical to cellular level are introduced and discussed in sequence from Chapters 3 to 8.

Earlier in this chapter we touched on some conventional routes of drug delivery, such as intravenous injection. Specific factors associated with different routes of drug delivery, such as the first-pass effects following oral administration are discussed in Chapter 9. How a drug molecule interacts with these barriers is very much determined by the intrinsic properties of the molecule. The intrinsic properties are, in another word, the physicochemical and biochemical characteristics of a molecule. In Chapter 3, the physicochemical properties and their implication in formulation and drug delivery will be extensively discussed.

Development of pharmacokinetics and pharmacodynamics relationship by mathematical modeling of the interactions of a drug molecule with the entire biological system is important to the prediction of drug concentrations in the systemic circulation, and, therefore, the pharmacological responses. Better understanding of the system will
allow a pharmaceutical scientist to utilize the system and manipulate the system for the purpose of drug delivery. Chapter 4 discusses the basic principles and topics in pharmacokinetics and pharmacodynamics. Approaches in drug delivery based on the understanding pharmacokinetic principles are essential in pharmaceutical development.

Developability in drug delivery is an overall assessment of all the important factors. For example, in oral drug delivery [76] solubility is important because a drug molecule has to be dissolved to be absorbed. Some lipophilicity is essential for the molecule to cross the cell membrane by diffusion. In order to finally reach systemic circulation, the molecule has to survive various chemical and biochemical attacks in the gastrointestinal system and the liver. A flow chart describing sequentially the factors that can impact drug delivery is illustrated in Figure 1.2. The order in which these factors are listed could also be the order of logical thinking when one plans to tackle an oral drug delivery problem, and could be a reference point for other routes of delivery too.

It is believed that permeability and metabolic stability of a drug molecule are two major factors in drug delivery or in the prediction of a drug’s absorption [77] when the molecule is in solution. Permeability can be further divided into passive diffusion and transporter-mediated processes. Metabolism of a drug molecule in the liver and intestine can be evaluated by \textit{in vitro} experimental methods. In many cases, \textit{in vitro} metabolism (intrinsic clearance) can be used to predict \textit{in vivo} metabolic clearance successfully [78]. It is obvious that when efflux transporters, such as P-gp, are

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure12.png}
\caption{The evaluation steps of various factors that impact the oral bioavailability of a drug candidate.}
\end{figure}
involved, the predictability of the in vivo clearance using metabolic intrinsic clearance becomes uncertain [79]. A more in-depth understanding of drug transporters and their function in combination with our knowledge on drug metabolism will help predict oral absorption [80, 81]. Transporter-related drug delivery issues as well as in vivo and in vitro models used to address these issues are discussed in Chapter 5.

In addition to parental delivery of a therapeutic agent, many other routes of drug delivery are developed for convenience, safety, specific targeting, and delivery of special agents. First-pass metabolism is especially applicable to oral drug delivery, and will be discussed in Chapter 9. Several other “unconventional” routes for drug delivery such as pulmonary (Chapter 10) and transdermal absorption (Chapter 11) are discussed together with strategies in development and technical challenges to be considered. Although this book does not cover most routes of delivery individually, the philosophy and logical thinking discussed should be generally applicable to the development of other route of delivery. Figure 1.2 provides, for example, thinking paths in addressing an issue for oral bioavailability. The discussions are further projected into several of later chapters on controlled target-specific drug delivery (Chapters 15–22). Targeting specific organ or tumor tissues through different technologies and potential personalized drug delivery are discussed in Chapters 17–22. Several chapters provided a number of technical approaches to improve drug delivery. Physicochemical approaches by formulation include controlled release (Chapter 15), prodrug approaches (Chapter 12), liposome vehicles (Chapter 13), and nanoparticles (Chapter 14).

It was discussed previously in this chapter that the discovery and development of biologic therapeutics have seen increasing attention and proven to be successful in recent years. Biologic therapeutics are expected to be dominant in the market in the future [29]. Unfortunately, the delivery of biologics had been mostly limited to those by parental injection. A large body of contents related to the delivery of biologic therapeutics or macromolecular drugs are newly added into this edition. Formulations for delivery of vaccines are discussed in Chapter 24. Cutting-edge researches in delivery systems for gene therapy are specifically reviewed and discussed in Chapter 25. It is known that the distribution of large molecules into intracellular space is limited. New developments in sciences and technology focused on intracellular delivery of protein and peptides are introduced in Chapter 23.

The goal of this book is to provide readers with a basic understanding of all the major issues in drug delivery. In this edition, new developments in drug delivery sciences and technology are captured in addition to updates made to those already included in the last edition. A much more detailed examination of various topics can also be found in the references cited in this chapter and the specific discussions in the relevant chapters.

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