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Early Drug Development: Progressing a Candidate Compound to the Clinics

Introductory Remarks

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Drug discovery and development is a fascinating, challenging, and multidisciplinary process where ideas for therapeutic intervention are devised, evaluated, and translated into medicines that will ultimately benefit society as a whole. As the name implies, it consists of mainly two elements: an initial discovery phase, followed by a development phase. These two phases differ significantly from each other with respect to scope, challenges, and approaches. As an example, while discovery experiments are typically executed in a laboratory setting using isolated and approximate systems (e.g. recombinant protein, cells, animals), development experiments consist of clinical trials in hospitals with human subjects and their full pathophysiological complexity. Differences notwithstanding, discovery and development must be integrated into a coherent whole for the process to be successful. Accordingly, much thought has been devoted to ensure scientific, logistical, and organizational aspects of such integration are taken into consideration and optimized [1–4].

Thankfully, the early view (and practice) of a discovery unit tasked with the delivery of a compound, typically termed a "preclinical candidate," which is then "thrown over the fence" to the development organization responsible for its clinical progression as a candidate drug, is a memory from a (not so) distant past. Alignment of research objectives and outcomes relevant to the discovery phase with clinical imperatives relevant to the development phase and commercial viability is not always straightforward, especially in new sectors of the pharmaceutical research environment where innovative therapeutic hypotheses are speculative and not clinically validated. Nevertheless, such an alignment is absolutely required for success, and a joint understanding and ownership of the practical implications of such alignment needs to be fostered within the project teams and their organizations.

Conceptual tools to support the initial definition of discovery and development alignment at a project level, and the strengthening of this alignment as the drug hunting program evolves, have been developed and provide a useful framework [5, 6]. Unsurprisingly, early drug development is where this alignment between discovery and clinical requirements is crystallized, normally by the selection of

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one or more compounds that fulfill a predefined profile, that will be progressed to clinical studies.

The definition of this so-called target product profile (TPP [7]) affects all research activities during lead optimization, including focused compound design in order to reach the set TPP standards, and planning of a screening cascade in order to maximize the number of testing cycles on key TPP parameters. Some salient TPP properties such as toxicological risks, predicted human dosing, and pharmaceutical properties can only be effectively, and practically, assessed for the first time in a project timeline during early drug development. TPP definition and compliance have therefore far-reaching effects across the drug discovery–drug development value chain: they dictate which compounds are made in the first place, which compounds will be selected for clinical development, and ultimately which compounds will be successful at the end of the development cycle.

This book is structured around the TPP to highlight its importance as an early drug development compass. Here, we set the compound(s) of interest – one of which is destined to become the new drug substance – front and center because the experimental quantities relevant to the TPP, regardless of testing paradigms and screening technologies used, are all properties inherent to the compound itself and are set when the compound is first designed. By taking this approach, we hope to stimulate readers along three main axes: (i) achieving a clear line of sight between preclinical measures and the desired clinical outcomes; (ii) the variability, uncertainty, and realm of applicability of the data generated and the methods used; and (iii) the integration of diverse data and disciplines. These three elements are constantly pondered and discussed by early drug development scientists as part of the TPP definition and fulfillment process. They provide an evidence-based approach to defining and refining the TPP and to selecting the best possible compounds to meet the TPP requirements.

The parameters comprising a TPP are more important than the specific target values of any particular TPP parameter. To highlight this concept, an example TPP is shown in Table 1.1. TPPs are, by definition, project and time specific, and they should be viewed as living documents. Project teams should strive to define the TPP as early as possible, with the attitude to refine the TPP as more data are generated, typically when pharmacological efficacy measures or early toxicity signals are established, or in response to external stimuli such as results from competitors or clinical validation studies, to name but a few examples. Similarly, even within the same overall project, the TPP for a backup compound will very likely be different from the one used for the clinical front-runner; additional insights, knowledge, and differentiation properties gleaned during lead optimization, early drug development, and clinical development will be incorporated into the revised TPP.

When considering the importance of the TPP to early drug development, it is striking that all of its parameters are, at best, surrogates of clinical readouts, each characterized by its own uncertainty and variability based on the underlying data and methods used. Although major advances have been made in predicting human pharmacokinetics from animal data, there is still ample room for surprises in Phase I pharmacokinetic studies due to the intrinsic

Table 1.1 Target product profile (TPP) example as an essential early drug development tool.

	Description	Target value	Comparator/ standard of care	Planned studies	FDA's TPP template section [8]
Project goal	A statement that the drug is indicated for the treatment, prevention, relief, or diagnosis of a particular indication of a recognized disease or condition and their associated manifestations or symptoms alone or in conjunction with a primary mode of therapy				Indication and usage
Drug substance	Physicochemical properties (e.g. crystallinity, thermal property, hygroscopicity)				
	Synthetic and purification risks				
	Estimated cost of goods				
Drug product	Route of administration				
	Recommended usual dose (maximum absorbable dose)				Dosage and administration
	Dose range shown to be safe and effective				
	Dosage intervals or titration schedule				
	Usual duration of treatment course when treatment is not chronic				
	Dosage form				Dosage forms and strengths
	Dosage strength				
	Special handling and storage conditions, chemical stability of formulation				How supplied/ storage and handling
Pharmacokinetics and pharmacodynamics	*Mechanism of action*: Summarize established mechanisms of action in humans at various levels (e.g. receptor membrane, tissue, organ, whole body)				Clinical Pharmacology
	Pharmacokinetics: Describe clinically significant pharmacokinetics of a drug or active metabolites (i.e. pertinent absorption, distribution, metabolism, and excretion parameters). Document their compatibility with intended magnitude and duration of effect (e.g. include results of pharmacokinetic studies that establish the absence of an effect, including pertinent human studies and *in vitro* data)				

(Continued)

Table 1.1 (Continued)

	Description	Target value	Comparator/ standard of care	Planned studies	FDA's TPP template section [8]
	Pharmacodynamics: Include a description of any biochemical or physiologic or pharmacologic effects of the drug or active metabolites related to the drug's clinical effect or those related to adverse effects or toxicity. Include data on exposure–response relationship and time course of pharmacodynamics response				
Toxicology	Results of long-term carcinogenicity studies – species identified				Nonclinical toxicology
	Mutagenesis results				
	Reproduction study results				
	Include a description of clinically significant adverse reactions and potential safety hazards and limitations of use because of safety considerations, as reasonable evidence of these issues is established or suspected as from, e.g. safety pharmacology and GLP toxicological studies				Warnings and precautions
	Describe overall adverse reaction profile of the drug based on available safety database (e.g. safety pharmacology, GLP toxicology studies). List adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. Within a listing, adverse reactions should be categorized by body system, severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions should be listed in decreasing order of frequency				Adverse reactions
	Describe clinically significant interactions, either observed or predicted (i.e. other prescription drugs or over-the-counter drugs, class of drugs, or foods such as grapefruit juice or dietary supplements); practical advice on how to prevent drug-drug interactions (description of results from studies conducted or observations from the integrated safety summary); drug-laboratory test interactions (known interference of drug with lab test outcome)				Drug interactions
Intellectual property	Patent status and plans				
	Freedom to operate analysis outcome				

variability of human absorption, metabolic, and excretion properties, especially with compounds characterized by low-to-moderate bioavailability [9]. When it comes to predicting pharmacological efficacy and toxicity, the current dismal clinical attrition statistics and the corresponding breakdown as to the primary reason for failure are sobering reminders of to what little extent we can predict clinical results [10], although having human-validated biomarkers and genetics evidence for a given target can help to mitigate these risks [11, 12]. Furthermore, the various TPP parameters cannot be dealt with in isolation but are intimately connected. Integration of TPP parameters so as to provide clinically useful estimates such as starting dose, dose frequency, and therapeutic windows adds an additional layer of complexity and uncertainty during early drug development. Given these premises, early drug development is where the multidisciplinary nature of drug discovery and development makes the biggest impact. Successful integration of scientific data from disciplines such as medicinal chemistry, process chemistry, pharmacology, toxicology, and pharmaceutics requires discipline experts to work seamlessly as a team, fluent in each other's vocabulary, able and willing to challenge and support each other. Their ability to proactively anticipate and address TPP-related issues, to master the interdependencies between TPP parameters, and to distill diverse inputs into actionable plans and schedules is as important to success as the quality of the scientific data generated and the validity of the therapeutic hypotheses being tested.

Part I presents practical considerations related to preparing sufficient quantities of selected compounds to enable their evaluation against the TPP. Chapters 1–3 introduce critical strategic, financial, planning, and organizational aspects of scale-up and production of sufficient drug substance so as to allow the TPP-based selection process and initial clinical development activities. Chapter 4 discusses how integration of novel chemistry methods and technologies can reduce the timelines associated with drug substance delivery, afford higher structural complexity to satisfy the constant drive for drug substance differentiation, and minimize the environmental impacts of manufacturing processes. The last two chapters describe real-life case studies of enabling chemical synthesis for early drug development purposes, with a view to manufacturing, that neatly integrate the various elements previously discussed.

Although most TPP-relevant properties of a drug substance are inherent to its chemical structure, some compound properties can nonetheless be significantly optimized or mitigated when the drug substance is engineered into a given drug product. Part II details the preparation, assessment, and selection of drug products that fulfill TPP and developability criteria. Solubility and permeability – two essential parameters of the drug substance – are categorized according to the Biopharmaceutics Classification System (BCS) framework [13]. Both parameters carry significant implications for a compound's exposure in efficacy and toxicology studies and key early drug development activities; engineering of the drug substance into a drug product involves a wide variety of techniques, most aimed at tailoring these two essential parameters. Three chapters present how the experimental characterization of solid-state properties, the selection of (co)crystal and salt forms, and traditional formulation methods enable the practical development of a wide array of drug products. The benefits of physical state manipulations such

as particle size and nanodispersions are also discussed. Examples from late lead optimization and early drug development projects are presented to showcase the flexibility provided by *ad hoc* drug substance investigation activities.

Part III introduces pharmacokinetics (PK) and pharmacodynamics (PD) as dual cornerstones of early drug development. Rather than devoting two independent chapters to each, a single chapter sets forth vital guidelines for their integration into an overarching PK/PD framework. These guidelines include not only essential scientific PK/PD principles and strategies but also the holistic mind-set and cross-disciplinary practice required for their effective implementation. A specific chapter has been dedicated to prediction of human PK/PD relationships, with an eye toward satisfying TPP and clinical parameters; particular importance is given to the applicability, uncertainty, and translational risk elements associated with the approach taken and the available data. Several case studies further anchor the usefulness of the PK/PD paradigm and expose some practical implications in PK/PD study design, compound selection and synthesis, TPP definition, and reference compound benchmarking.

Toxicology, a crucial aspect tackled during early drug development, is described in Part IV. Strategies and methods consistent with current rational and efficient industrial standards are discussed first as a key part of the project TPP. In keeping with the previous PK/PD section, a quantitative and integrated approach to assess toxicological risk throughout early drug development is presented. Advantages and limitations of the various methods are discussed, especially from a translatability and risk management point of view. Safety pharmacology activities are addressed as complementary and dependent upon efficacy-based studies so as to allow the derivation of safety margins via toxicokinetic–toxicodynamic (TK/TD) approaches. Available computational approaches to predict toxicological outcomes are surveyed and described based on their applicability domain and predictive power. Given the difficulty in precisely predicting toxicological endpoints, several real-world project examples in risk assessment and mitigation are presented to highlight the diversity of the chosen approaches.

Part V completes the TPP-centered motif of this book by describing intellectual property (IP) matters and requirements. After a review of patent law relevant to early drug development, a number of patent protection strategies are discussed in terms of their impact and implications for adequately safeguarding a specific invention. Two additional perspectives, in line with recent changes in the drug discovery and development environment, are then presented. The first details IP challenges and opportunities associated with the development of generic drugs and the attendant consequences for companies developing first-in-class or best-in-class products. Here, an elaboration on generic companies' drivers and IP approaches is offered to support innovators in evaluation of their own IP strategy. The second describes special considerations that need to be assessed when developing drugs – as is increasingly commonplace – as part of a collaborative venture, which brings additional IP complexity and consequences for ownership and IP rights.

Another important aspect to be considered during an early drug development program is the regulatory environment in which the project operates. While

a detailed discussion of regulatory agencies and associated practices is beyond the scope of this book, each section and chapter describes, whenever possible, the fundamental regulatory principles that need to be considered as part of the process. This is of particular relevance during toxicology-based assessments, as the safety risk each new drug product will impose upon the patient is an area of intense regulatory scrutiny. Accordingly, the chapters in Part IV list relevant International Congress on Harmonization (ICH) guidelines, with direct links to the original sources to support the reader in addressing these regulatory elements. Here, special emphasis has been placed on framing a regulatory discussion rather than providing a checklist of data to be generated. Each development program will have to develop a fit-for-purpose data package (as opposed to a standardized one) for discussion, negotiation, and agreement with the regulatory agencies. Early discussions with regulatory agencies are of the utmost importance, as they provide mutual buy-in into acceptable and not acceptable risks, help the agencies to familiarize themselves with novel scientific and therapeutic approaches, and help the project team to focus its resources and efforts on the most critical (from a regulatory viewpoint) issues.

Integration and alignment of the many disciplines and activities presented in this book is a prerequisite to successful early drug development. Each project is challenged with defining and achieving competitive requirements for progression to clinical studies while factoring in associated data variability, risks, and uncertainties. Accordingly, early drug development scientists need to devise the best possible set of studies that are feasible and relevant with respect to risk reduction and decision making. A common understanding of the advantages and limitations specific to a proposed early drug development plan allows its effective execution and builds in the necessary flexibility to respond and adapt to the data generated. Against a backdrop of mounting clinical attrition, unmet medical need, and patient safety concerns, early drug development is the most critical gate to success.

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