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Review article

An integrated early formulation strategy – From hit evaluation to preclinical candidate profiling

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Abstract

The selection of a suitable vehicle for preclinical compound profiling is a very important task during the early developmental phases to ensure the quality of candidates and the speed of compound progression. Apart from biopharmaceutical and pharmaceutical technical considerations, i.e. solubility/dissolution improvement or route of application, other aspects have to be taken into account, as well: (i) availability and quality of the compound, (ii) tolerability of the vehicle in the selected animal model, (iii) developmental possibilities, i.e. whether the formulation can be transformed into a clinical one.

The approach described in this paper is based on results of team collaboration between functions involved in the conduct of animal experiments (Pharmacology, Pharmacokinetics, Toxicology, and Pharmaceutical Sciences). Very early *in vivo* studies should be performed with dissolved API as available information on solid-state characteristics is usually limited at this time. Later studies should be performed with developable formulations, taking into consideration pharmacological, toxicological, and pharmaceutical requirements. At this stage, delivery strategies (i.e. advanced formulations and/or alternative routes of administration) should be considered, as well. In addition, a minimum level analytical characterization of compounds and formulations used in animal studies is required to explain unexpected results.

Keywords: Early formulation strategy; Poor solubility compounds; Physical-chemical properties; Standard formulations; Enabling formulations; Harmonization; Customized vehicles

1. Introduction

The duration of drug developmental cycles are continuously challenged by an increasingly competitive environment. Due to modern high-throughput technologies, such as combinatorial chemistry and pharmacological screening, the number of new chemical targets intended for preclinical and clinical development has increased tremendously over the last few years [1]. To accelerate the selection process, more and more *in vivo* studies are conducted in parallel including those that (i) determine absorption, distribution, metabolism, and excretion (ADME)-parameters of a candidate per se, (ii) evaluate the compound's pharmacological effects, (iii) correlate its pharmacokinetic (PK) properties with its pharmacological effects (PK/PD studies), and last but not least, (iv) early safety studies that detect potential toxicological problems [2] (Fig. 1).

Despite the differences in objectives, sufficient and reliable exposure of the selected organism to the early-stage candidate is mandatory to obtain tangible results from these studies. Moreover, as target profiling is a multi-factorial optimization approach, comparable exposures derived from these studies are required for a successful candidate optimization and profiling.

Unlike late-stage development projects, early candidates are neither available in substantial quantities, nor do they have their manufacturing processes and physical quality

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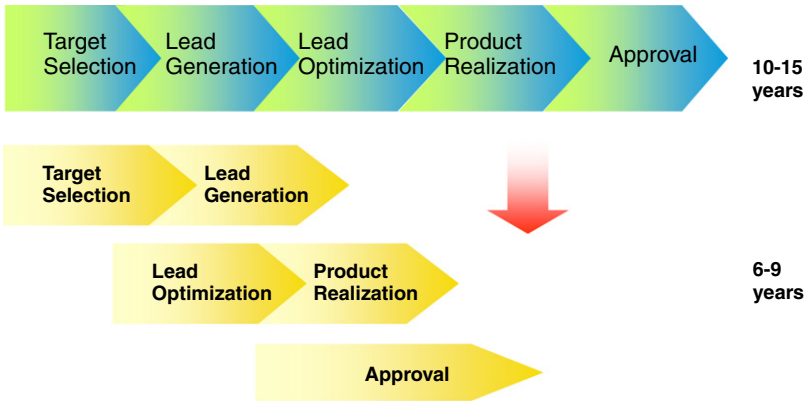

Fig. 1. Parallel working: change from sequential to overlapping value chain to reduce cycle time.

parameters optimized [3,4,9]. The latter facts lead to considerable variability in particle size and often also in crystalline state, hence the formulation system selected may also affect exposure.

In contrast to the past, when the majority of research compounds had a relatively small molecular weight and acceptable solubility, the number of larger and less soluble molecules displaying permeability- and/or solubility-limited absorption has increased tremendously during the last few years [5–7]. Therefore, it is not surprising that traditional formulation approaches, such as "disperse and dose", are no longer adequate in pharmacology laboratories as either the solvents required to dissolve hardly water-soluble compounds, or physical quality parameters of the early-stage candidates are likely to confound the biological results. Furthermore, the use of different formulation systems for the various *in vivo* studies in early development may lead to completely different exposures and hence inconclusive results.

Although the awareness of the relevance of physico-chemical drug parameters in compound development (e.g. "Rule of 5" and BCS [7,8]) has increased, preclinical formulation development needs to deal with poor compound properties, e.g. low solubility, more than ever. Consequently, scientists planning early *in vivo* studies need to address several challenges to allow fast and successful candidate profiling:

- Define strategies to select and provide well-characterized formulations yielding sufficient exposure and tolerability
- Define strategies to overcome drug delivery challenges due to unfavorable biopharmaceutical or physico-chemical properties of early candidates
- Define strategies to achieve optimum data comparability for different studies ("Harmonization/Standardization")

This paper describes a new approach to ensure optimum exposure in preclinical animal studies, while considering study-specific requirements, such as tolerability and limited compound availability, hence increasing the quality and speed of compound progression.

2. Preclinical formulations

While numerous publications have documented the significant efforts that have been invested into improving the throughput of screening technologies in chemistry, pharmacology, and in early stages of pharmacokinetic assessments [10], only a few addressed the many challenges associated with preclinical formulations [11,12].

Incomplete physico-chemical characterization, limited compound availability, and short timelines impair the development efforts already for "simple" formulations, such as solutions and suspensions. Another set of obstacles with potential effect on exposure is variations in physical quality parameters that need to be accounted for or better yet, compensated by preclinical formulations. Unfavorable compound properties, namely, poor solubility and poor permeability, further complicate the above difficulties and make the systematic development of enabling formulations even more necessary. In addition, conflicting requirements regarding formulation properties may force scientists to develop several different formulations for the various preclinical studies required to select an appropriate candidate for further development. A structured approach to efficient selection and development of preclinical formulations that targets all of the above-described challenges has been elaborated.

2.1. Efficient formulation development

Good intestinal permeability, as well as sufficient gastrointestinal dissolution are regarded as key factors in successful compound delivery following oral administration [8]. The permeability of a compound is a function of inherent determinants, such as molecular weight, ionized state (pKa), log D, H-bonding, and polar surface area [5,7,13–17]. It is a constant parameter under given pH conditions.

Efficient formulation development starts with assessing a compound's physico-chemical properties. These are typically available from high-throughput assays performed in chemistry departments or can be predicted using specialized software, such as ACD labs [18,13]. Classical decision