Chapter 1
Organic Synthesis in Drug Discovery and Development

Abstract The discovery and development of a new drug entity (NDE) to become a marketable drug is a complex, costly and time-consuming process. It is subject to increasingly stringent regulations and high attrition, which squeeze the time available both for the development and sale of the final product within the remaining window of patent coverage.

Organic synthesis of NDEs is challenged by the creation of novel, biologically active, safe and suitably targeted molecules and the improvement of lead compounds, as well as by the need to scale up compound quantities for safety and clinical studies. Even though natural and biologically derived drug molecules are *en vogue*, small synthetic molecules are preferable for oral drug administration and organic synthesis is required to modify natural compounds.

Biologically orientated synthesis can generate compounds with multiple activities. The industrial use of genomics research to identify potential target proteins and of high throughput screening to test compounds, including synthesized libraries of DNA sequence-programmed small molecules, all increase the chance of identifying totally new NDEs.

Chirality of NDEs is crucial because of the three-dimensional nature of biological target molecules and 68% of the top 200 marketed drugs are optically pure. Consequently, the stereoselective approach to drug molecules will remain important for many years to come.

1.1 Introduction

The complexity of the process leading to the marketing of a new drug entity (NDE) and its introduction to therapy is well recognized. As a matter of fact, complexity has become synonymous with high risk and frequent failure, or attrition, in searching for an NDE. Currently, innovative pharmaceutical companies that are focused on the development of NDEs are facing huge financial and organizational problems. This is related to the decreasing likelihood of being able to introduce successfully a "blockbuster", or "$1 billion drug" to the world market. This situation is, in part, the consequence of the ever more stringent requirements of regulatory authorities in

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developed countries, primarily of the Food and Drug Administration (FDA) in the USA, concerning the required documentation for all phases of preclinical and clinical investigations of an NDE. In addition, the diseases for which new therapies are still needed are now generally complex chronic diseases, which are difficult to categorize and require long-term, safe drug treatment.

These factors also enhance the risk of investment in long-term NDE-orientated research and development (R&D) due to the prolonged period between the first patent application and the appearance of the drug on the market. Consequently, the number of new first-in-class drugs that have reached the market in the last decade has been steadily declining. As a result of new technological developments, interest and investment in biological (protein-based) drugs is increasing, partially because of their relative specificity and the expected higher price, which companies can set following their introduction to the market (see also Sect. 1.2). However, this approach too has its limitation as biologicals cannot usually be given orally and the pressure of reimbursement agencies is likely to reduce pricing in the future.

An NDE is expected to meet an unmet medical need or to improve therapy where existing drugs have proved ineffective due to lack of efficacy, development of resistance or tolerance, to unexpected toxic side-effects, or have shown incompatibility with other drugs. New pathological states or diseases are also being continuously revealed and require effective therapy.

In spite of all these incentives to the development and marketing of new drugs, the success rate is decreasing. Rapid progress in the sophistication of the technical and analytical methods used to monitor all NDE development steps has resulted in clearly safer drugs. But, at the same time, this has further contributed to the delay in the introduction of drugs to the world market. The span between the first patent claiming biological activity of the new chemical entity and its introduction to the market has been prolonged from less than 6–8 years in 1970–1990 to over 15 years today. Two economic drawbacks for innovative pharmaceutical companies have been the inevitable consequences: much higher investment is needed for the whole R&D process, and the periods available for exploration of the original drug under patent protection and for recovering this investment with drug sales are now much shorter.

In the next three sections, we briefly present some characteristics of the R&D process in the pharmaceutical industry and the specific approaches that are being taken to confront the scientific and organizational problems.

1.2 Synthetic Organic Chemistry in Pharmaceutical R&D

The discovery of a drug has always depended on creative thinking, good science and serendipity. Due to the ever more stringent criteria that need to be satisfied for the introduction of an NDE to the market, drug discovery has always had a high attrition rate. A key goal is therefore to reduce this attrition rate by transforming drug discovery into a high-throughput, rational process. This is possible at some

specific early stages during drug discovery, particularly with biological assays that identify numerous hit compounds and when the data accumulated support progress towards synthesis of a limited number of lead compounds.

To provide background information for the role of synthetic chemistry, some aspects of the R&D process in innovative pharmaceutical companies deserve comment. The complexity of the usual multidisciplinary research process in developing an NDE is presented schematically in Fig. 1.1.

The *organizational and value chain in pharmaceutical R&D* requires that a wide range of activities are interconnected, some of them loosely, the others strongly integrated. Individuals prepared to champion this progression are crucial, and they are recruited from among the scientists and physicians involved.

The importance of synthetic chemistry in the research shuttle arises from the need to access promptly the progressively increasing amounts of active substance or active pharmaceutical ingredient (API) that are required. This becomes most essential when approaching crucial activities such as safety studies (toxicology in animal species), and the development of suitable dosage forms and testing in human beings (clinical phases I–III). Lack of well-planned, timely delivery of reproducibly standardized API can result in long delays in the progression of the new product to the market, mainly by failing to arrive on time at the milestones of nomination for selection of a clinical candidate (CC) or a candidate drug (CD) [1]. The requirements for active substance at various points along the R&D shuttle process are presented in Fig. 1.2.

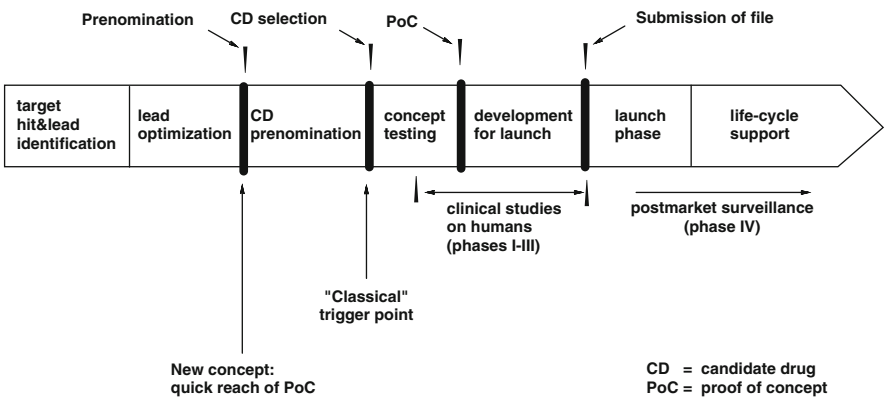

Fig. 1.1 R&D "shuttle" for delivering an NDE

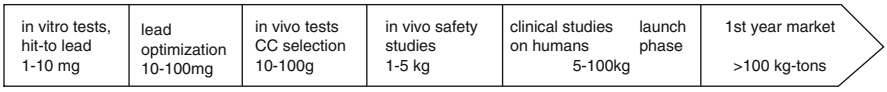

Fig. 1.2 Requirements for active compound along the R&D process

This scheme outlines the exponential requirements for the active substance over a period of approximately 10 years. The critical period for the research chemists on the project, however, lies between the selection of the lead and the clinical candidate. In this period, scale-up to kg production is undertaken for the process that was previously used for mg preparation. Besides the usual modification of the separate synthetic steps, often the complete synthetic scheme needs substantial modification to enhance efficiency, expressed as the average yield of the process, and to reach a reproducibly high level of purity of the final product. At this stage, initial consideration of the requirements for the future multi-kg production process is made. This includes planning the technological, ecological and economic aspects of the future process. The subsequent large-scale synthesis of API for clinical trials, these days, is usually contracted out to a specialized manufacturing company, for whom the research chemist will provide technical details.

Lead generation and, to a greater extent, *lead optimization* are the processes that make the most creative demands on the synthetic organic chemist. Lead generation is the process by which a series of compounds is identified that has the potential to be developed into a drug. Creativity is not only demanded in synthesizing a compound with the desired biological activity. The molecule must also have suitable physical properties for the route of administration planned, exert little or no toxicity and on administration, must be taken up efficiently into the body and distributed at adequate concentration to the desired site of action (pharmacokinetic properties).

The shuttle model in Fig. 1.2 is particularly challenged by the high attrition of the potential drug entities in the course of R&D process. Attrition of potential NDEs (termination of research projects due to their failure to satisfy the criteria set up for the different phases of the shuttle process) has various causes. Among them are toxicity in non-human tests (35%), lack of clinical efficacy (18%), unacceptable clinical safety (15%), together with unsatisfactory pharmacokinetic (PK) and bioavailability properties (9%). These data indicate that proof of concept (PoC) and clinical studies in humans are the stages at which most potential drugs fail to satisfy the criteria. Although synthetic chemistry is not directly involved in these activities, it is the basis for the unsuitable biological properties of the chemical entity. The only way to overcome the deficiencies is to design and synthesize new lead molecules.

Together with the identification of biological targets and lead optimization, the chemical synthesis of novel compounds forms one of the key steps in drug discovery (Fig. 1.1). According to Gillespie [2], the *attributes of a high-quality lead compound* are:

- Its synthetic tractability
- The patentability of the series around the lead
- Availability of chemistry space for optimization
- Acceptable solubility, permeability and protein binding
- Lack of inhibition of *cytochrome P450* (CYP; family of enzymes responsible for oxidative drug metabolism)

– Lack of inhibition of *human ether-à-go-go related gene* (hERG; a gene that codes for a potassium ion channel in the heart, inhibition of which can cause cardiac arrest)
– Acceptable *absorption–distribution–metabolism–excretion* (ADME)
– Its confirmed interaction with the biological target (e.g. by X-ray or NMR)
– Defined apparent *structure–activity relationship* (SAR)
– Its confirmed biological activity in vivo

However, natural compounds, which represent a rich source of new NDEs as discussed in Sect. 1.3.1, do not usually conform to these criteria.

Selection of the CD is shown as the "classical" trigger point in Fig. 1.1. According to the most recent concept, the CD should be moved forward as soon as possible to "prenomination" which commits the R&D organization to rapid attainment of the PoC in humans. Prenomination at such an early stage sets a new challenge to synthetic chemistry to provide the active substance in sufficient quantity and purity.

Without underestimating any step in the process of the R&D shuttle, demands on the first stages, prior to prenomination, make it increasingly important to get the concept right from the beginning and avoid costly late attrition. This depends largely on the skill and creativity of medicinal and synthetic chemists.

1.3 New Concepts in the Drug Discovery Process

Traditionally, synthetic chemistry in drug discovery has been the main source of new structural classes for biological testing of any kind. *Analogue-based drug design*, presented in a systematic manner in a recent monograph [3], was the leading concept. Since analogy plays an important role in applied research, it is not surprising that it became a crucial strategy in medicinal chemistry. According to the authors of the recent book, a specific aspect of this approach involves a search for a *structural and pharmacological analogue* (also called a *full analogue*) of an existing drug as a lead compound. It is also a pragmatic approach, since the therapeutic target has already been validated, although the project will race against unknown competitors who may start from the same scaffold at about the same time. On the other hand, it is not a simple research method, but a way of thinking that uses a combination of modern in silico and in-solution experimental methods. A number of stand-alone drugs taken as starting points for this approach are discussed in the monograph [3].

As biological targets for drugs are complex three-dimensional molecules, it is almost axiomatic that *chiral compounds may be potential drugs*, and synthetic methods leading to optically pure compounds represent the most important synthetic armamentarium. *Chiral drugs in an optically pure* form are present in 68% of the top 200 brand-name drugs, and in 62.5% of the top 200 generic drugs [4]. The importance of stereochemistry in drug development and medical application

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