START SMALL, THINK BIG — THE ART OF PROCESS R&D

Process R&D is becoming increasingly crucial to the overall efficiency of drug development.

Around 25 years ago, process research and development (PR&D) had a low scientific profile. Its main task was to provide scale-up quantities of compounds, notably active pharmaceutical ingredients, to be used in the further development of marketable drugs. Many thought of PR&D as being an appendage to full-scale commercial production, and the fact that successful scale-up requires a process that can meet demands was largely ignored. Supply of material was what counted.

Today, the situation has changed greatly, and PR&D is regarded as a discipline in its own right, in which chemical and technical challenges are addressed, often of a complex nature. This change has put more stringent requirements on PR&D, increasing the need for cross-functional collaborations, in particular in earlier stages of drug discovery.

Integrating drug discovery and PR&D

Much effort has been made in recent years to improve the efficiency of drug development at each stage of the process. Indeed, there have been cases, such as sildenafil and orlistat, in which a New Drug Application (NDA) has been filed just 5 years after the nomination of a candidate drug, compared with the typical time of 7–8 years. Under these 'high speed' circumstances, PR&D is becoming increasingly crucial to the efficiency of the overall process. Many more programmes (clinical and toxicological studies) and activities (development of formulations), demanding larger quantities (from tens and hundreds of kilograms up to tonnes throughout the whole of a development project), have to be supported in shorter and shorter times. Moreover, molecular complexity, and hence often the difficulty of the chemical synthesis, is increasing in general.

To address the challenges of this now widely adopted way of operating requires the back-integration of activities, starting as early as possible. As shown in FIG. 1, from a PR&D perspective, this means that involvement begins in the lead-optimization phase, 1–2 years ahead of candidate-drug nomination. For PR&D, this offers the advantage of a longer period for knowledge build-up and planning, whereas medicinal chemists benefit from a feedback mechanism that provides quality advice and guidance on issues such as synthetic feasibility, potential threats to successful scale-up, cost of goods, safety, health and environmental concerns, and raw-material availability. As the work proceeds into pre-nomination (FIG. 1), mutual contacts and collaborations are considerably intensified. A synergy is thus established that is beneficial not only to the parties involved, but also to the entire business, with a higher degree of confidence that the time lines will be met.

Skill sets and tools

The field of PR&D is best described by its combination of scientific and engineering components. To deliver the requested output in the form of a viable and robust chemical production process that has been thoroughly qualified and validated with commercial equipment, these two areas need to work intimately together, preferably in a project-driven way. To be successful in this respect and to find innovative and preferably patent-worthy solutions requires expertise from numerous disciplines, such as synthetic organic chemistry, a broad range of analytical chemistry techniques, chemical-unit operations, safety studies and hazard analysis, handling of process equipment and operating a pilot-plant facility. As the design of the method of manufacture has to take into account the logistics in a future factory setting, software simulations are extremely useful in identifying bottlenecks and shortcomings. Furthermore, to ensure that a process operates under optimized conditions, powerful data tools are applied. However, it is important to acknowledge that although each part of the process has to make its respective contribution in the best possible way, it is the combined efforts that will ultimately decide the quality of the final result.

Where to acquire knowledge

An educational background in chemical sciences and engineering is a prerequisite, and this is often the starting point for a career in this field. What has to be acquired during on-the-job training, in addition to developing skills in a particular area of expertise, is the ability to see the bigger picture. Experience with R&D lateral thinking and working in cross-functional teams (which more and more frequently operate globally) are essential assets that will be required before reaching a leading position in the highly challenging and stimulating field of PR&D.

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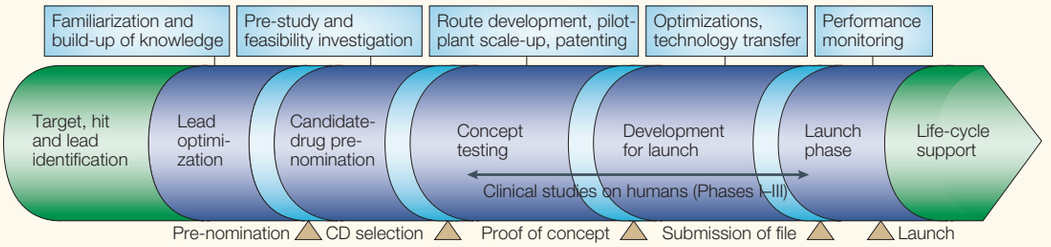

Figure 1 | **Role of process R&D in drug development.** Activities at each stage are indicated in blue boxes. CD, candidate drug.