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## What is the most important approach in current drug discovery: doing the right things or doing things right?

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**Doing the right things or doing things right: what is the most important focus for current drug discovery to secure delivery of new drugs of sustainable value to patients, healthcare professionals and healthcare providers? Some of the challenges faced today in drug discovery are addressed here: the relationship between R&D speed, cost and quality; how selection of performance metrics can affect the quality of the R&D output; the importance of leadership and management; how process orientation can affect, for example, creativity and innovation; the importance of selecting the right pharmacologic target and the right chemical lead; and why the use of drug–target kinetic and thermodynamic data to drive lead selection and lead optimization could increase success rates.**

### Introduction

The main objective for pharma companies is to discover and develop medicines that are valued by regulatory authorities, patients, healthcare professionals and healthcare providers (i.e. payors) alike. All of these stakeholders want efficacious and safe drugs that improve patient quality of life. However, they also expect new drugs to be more cost efficient (i.e. 'health economical') than alternatives. In addition, pharma also needs to produce sustainable revenues and return on investment for shareholders. Therefore, speed, quality and cost have become a mantra for all drug discovery and development activities. Most pharma companies have tried to address all three aspects, but these efforts have not translated into increased productivity or efficiency in generating new drugs. The number of new drugs per year that have been approved by the FDA has remained

constant for the past ten years (<http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM247465.pdf>), despite our efforts to understand the causes of drug attrition better and to learn from previous drug discovery efforts (see, e.g. Refs [1–10]).

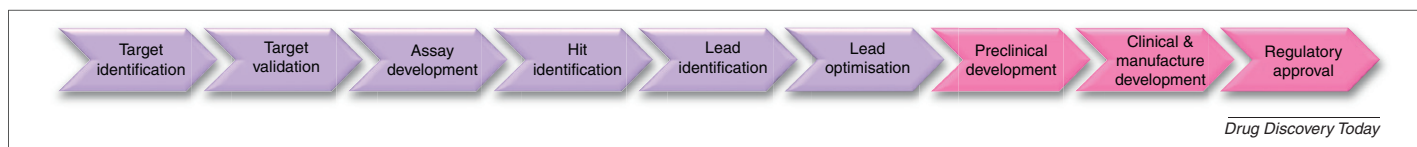
There is a clear need for pharma to become more effective (i.e. do the right things) and efficient (i.e. do things right), for definitions and explanations of the terms effective and efficient as used in this article, see <http://www.dailyblogtips.com/effective-vs-efficient-difference>. However, which one is the most important theme to focus on for current drug discovery: being effective or being efficient?

### Some effectiveness and efficiency challenges in drug discovery

*Trying to cut R&D timelines and costs can be detrimental to quality, whereas*

*improving the quality of R&D and drugs can reduce timelines and costs*

Pharma intends to have robust pipelines of new innovative medicines. However, in recent decades, many pharma companies have experienced the fact that their drug pipelines have started to run dry. In addition to mergers and acquisitions, increasing speed and reducing costs in the R&D process (Fig. 1) have become familiar themes in delivering drug pipelines that can sustain profitability. Strategies to achieve this include running more drug projects in parallel [6], quicker and with less people, and by applying high-throughput methodologies. However, using these strategies can potentially find promising drug candidates quicker and at lower cost, but might also unintentionally increase failure rate through application of simplified (i.e. superficial) science or insufficient documentation of claimed drug effects. Thus, in

**FIGURE 1**

Overview of the drug discovery (purple) and development (pink) process. Each box denotes a phase of the drug discovery and development process. Each phase can consist of several parallel or sequential sub-processes. Generally, a process consists of several steps that are either decision points or actions (work or tasks), which can be repeated. For an example of a repetitive drug discovery sub-process, see Ref. [16]. This article focuses mainly on the drug discovery process and underlying science.

the extreme case, measures to increase speed and lower costs might actually lead to reduced quality of new medicines in the pipeline and ultimately reduce profitability. Conversely, efforts to improve quality of science and candidate drugs, for example by using more-advanced science such as translational biology and biomarkers in building confidence in targets (e.g. human relevance) and linkage to human disease, should in the long-term result in reduced timelines and costs (although short-term costs and timelines might increase owing to investment in more-sophisticated science). Ultimately, this can lead to increased success rates and profitability (Fig. 2).

#### *Choosing too many and/or the wrong performance metrics could adversely affect the quality of pharma output*

It is widely recognized in performance management that 'you get what you measure' (see, for example, Ref. [11]). Thus, certain performance metrics can induce inappropriate behaviors, for example counting and rewarding the number of drug projects that pass each milestone in the drug discovery process could result in running many drug projects in parallel and/or keeping them alive as long as possible to meet the goal for the number of drug projects that pass each milestone [6]. However, people and organizations would be less prone to accept this behavior

if it was known that performance-based remuneration for passing milestones will only be granted if the drug reaches the market. An individual's objectives should always be aligned to the objectives of the team and the team's objectives should be clearly aligned to the drug project's objectives – with the project's objectives of course being aligned to the company objectives. Clearly, fostering an environment focused on delivering a robust and sustainable longer-term pipeline through high-quality innovative science is paramount and, as such, we must be mindful not to compromise scientists' motivation by too detailed, short-term focused performance metrics (for a discussion of how productivity metrics can affect motivation and creativity, see Ref. [12]).

#### *Leadership is more important than management in drug discovery*

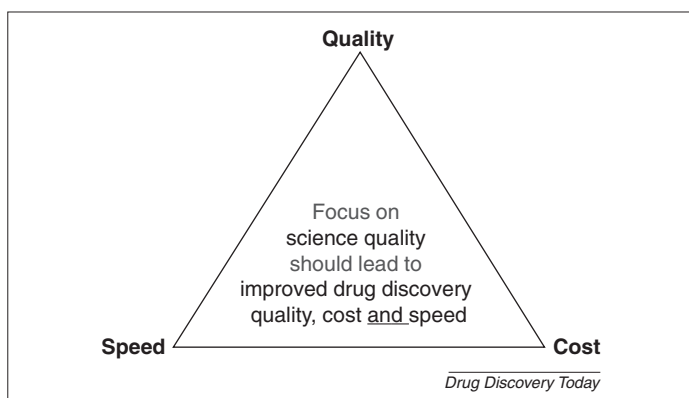
Leadership and management are both very important. The management consultant Peter F. Drucker ([http://www.en.wikipedia.org/wiki/Peter\\_Drucker](http://www.en.wikipedia.org/wiki/Peter_Drucker)) claimed that, 'Management is doing things right; leadership is doing the right things'. Management by objectives can be efficient and powerful, but it should not replace leadership (i.e. articulating a clear and compelling vision, frequent coaching interactions with co-workers, etc.). In big pharma, as described by Knutsen [13], a risk is that managers are

frequently occupied by management tasks and meetings, whereas managers in smaller companies such as biotechs appear to be more available for co-workers because it seems to be more possible to 'manage by walking around' in smaller companies. Pharma co-workers could clearly benefit from more leadership and coaching (mostly forward-looking) than management by metrics (mostly backward-looking) to inspire future generations of drug hunters.

#### *Too much process thinking in drug discovery can block enthusiasm, creativity, intuition, innovation and serendipity*

A process contains steps that are either decision points or actions (work or tasks). Implementation of common, well-defined processes in a drug discovery unit can increase effectiveness and efficiency, as evident from comparing the following two situations: (i) each and every drug project has to negotiate which drug metabolism/pharmacokinetic (DMPK) investigations can be undertaken for each new compound made during lead optimization (i.e. a process is agreed for each new compound); (ii) DMPK capacity (how many compounds that can undergo each test every fortnight) has been agreed for each drug project, as well as how and when the compounds shall be delivered for each test and when the results can be expected. Obviously, situation (ii), a common, well-defined process, is more effective and efficient than (i), and most probably to be appreciated by everyone if resource allocation is fair and transparent. For examples of efforts employed to improve various parts of the drug discovery process, see Refs [14–16]. However, whether defining and using processes in drug discovery is good or bad, it remains controversial [17,18].

Before embarking on defining and implementing common, well-defined processes, it is advisable to judge whether or not the majority of co-workers eventually will buy into and support the changes, although they might initially be skeptical and resistant to the potential constraints. Moreover, it is crucial that the process is

**FIGURE 2**

Speed, quality and cost are inter-related core aspects of R&D.

defined and implemented by co-workers that have performed the tasks before and will continue to work in the area while also gaining input from customers. In addition, to get co-workers to embrace and appreciate a well-defined process is very important to avoid blocking enthusiasm, creativity, intuition, serendipity and, of course, innovation. Thus, although there are activities in drug discovery where process orientation makes sense, creativity-driven activities can be less suitable for process orientation [19].

### Selecting the right pharmacologic target and the right chemical lead are key decisions in drug discovery

When trying to invent a small-molecule drug that can be used to treat human disease, selection of the pharmacologic target and the molecular lead are key decisions [20]. Thus, it is imperative that modulation of the pharmacologic target by a small molecule translates into a desired effect in the treatment of the disease in humans (see, for example, Refs [2,21]). First, to assess whether this is the case, it is advantageous to have access to a disease model with robust biomarkers and pharmacodynamic markers relevant to the human disease. Focusing on high-quality target selection can take more time before starting the project but the increase in quality and confidence can reduce time and cost in the longer term. Second, it is very important to find and select a molecular lead (starting point) that can be optimized into a drug that not only is a potent modulator of the chosen pharmacologic target but also is efficacious and safe (no debilitating side effects) in the disease model(s)

and in patients. Judging from published case histories, pharma often does not have all these prerequisites in place but relies on *in vitro* or *ex vivo* models that are too simple. Not surprisingly, most candidate drugs fail in preclinical or clinical evaluations owing to insufficient efficacy or safety issues [22].

### Today's practice in lead optimization could still lead to failure in the clinic

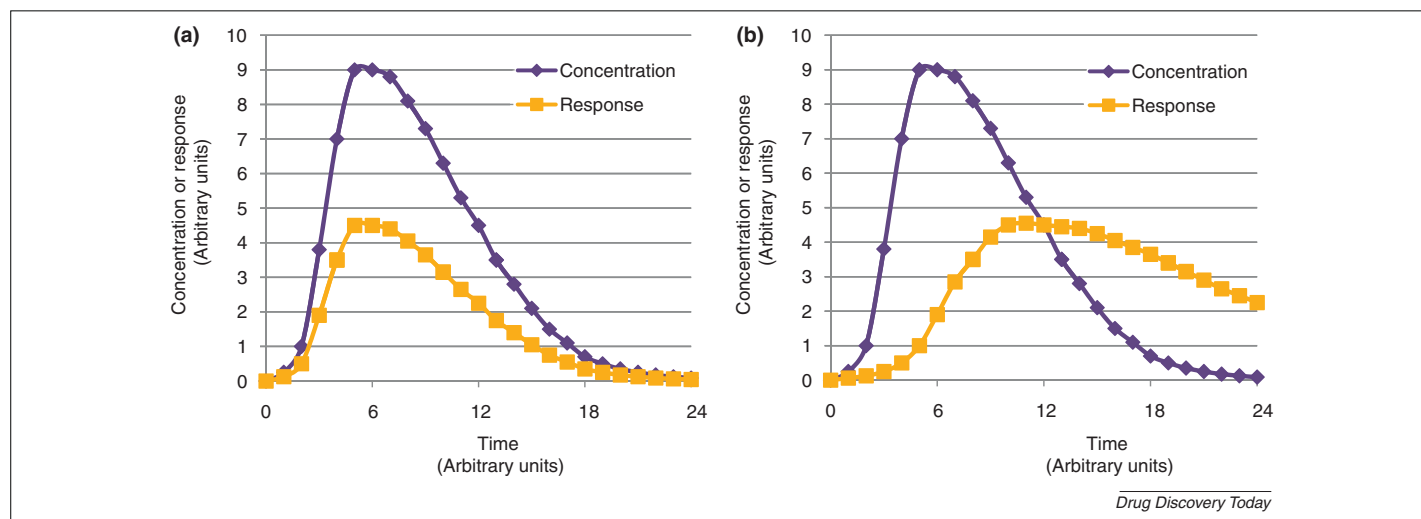
The predominant lead optimization strategy today is to optimize potency and ADME of compounds by designing and testing compounds that are confined to what has been defined as 'drug space', which in essence is the physicochemical property space that should give ADME characteristics that are acceptable for oral drugs [23]. It is our view that trying to achieve an acceptable ADME profile through modulation of physicochemical properties could also lower potency and increase daily dose, but high-dose drugs have been shown to cause toxicity more frequently than low-dose drugs [24].

Another common lead optimization objective is to increase the free concentration of the drug at the pharmacologic target by focusing largely on the pharmacokinetic profile of a compound [25]. However, increase of the free concentration at the target will generally also lead to an increase of the free concentration at anti-targets (i.e. pharmacologic targets that can convey side-effects and cause adverse safety findings). Although current lead optimization practice is efficient, a more effective strategy could be to optimize drug–target interaction kinetics as well (i.e. the drug–target residence time) and, hence,

deliver drugs with appropriate pharmacokinetic/pharmacodynamic (PKPD) relationships for their pharmacologic targets (see below; also see Fig. 3 and, for examples, Refs [26–30]).

### Using drug–target kinetic and thermodynamic data to drive lead selection and lead optimization could significantly increase the success rate in drug discovery

There is a growing body of evidence in the literature that drug–target interaction kinetic and thermodynamic data can help us understand why certain candidate drugs worked in clinical trials and reached the market and why others were less successful (see, for example, Ref. [28]). Thus, in many cases successful drugs display non-equilibrium kinetics, often with long drug–target residence time (slow off-rate) but shorter plasma exposure time. However, there are of course exceptions where prolonged target engagement would be detrimental and, in the case of mechanism-based side-effects, drug–target residence time should preferably be optimized rather than maximized [31]. Moreover, analyses suggest that best-in-class drugs have a different thermodynamic profile (more enthalpy driven) than first-in-class drugs [32] (i.e. more specific interactions as indicated by a typical change in the balance between enthalpic and entropic contributions to the overall binding). It has also recently been suggested that drug–target interaction kinetic and/or thermodynamic data should be used to drive lead selection and optimization (see, for example, Refs [26–29,31–34]).



**FIGURE 3**

Schematic pharmacokinetic–pharmacodynamic relationships for rapidly (a) and slowly (b) equilibrating drug–target interactions. Rapidly and slowly equilibrating drug–target interactions might or might not be accompanied by side-effects, the magnitude of which might or might not be proportional to the plasma concentration of the drug at any one time. However, in general, a better therapeutic index could be expected for slowly equilibrating drugs (b) because lower exposure levels are needed to achieve the desired response.

## Concluding remarks

### *Pharma needs to improve the quality of its drug discovery science and output*

Defining and selecting the right pharmacologic target, drug product profile, chemical lead and candidate drug are key decisions that seal the destiny of a candidate drug. The subsequent activities in the R&D process are about exploring and documenting whether the target and candidate drug can actually deliver what is required. Pharma consistently craves new disease targets, which is readily evidenced from the wealth of patent applications and scientific publications. But, is exploiting a 'new' target more effective and successful than exploiting the 'right' target that might be 'old'? Is there more that can be done? Perhaps by pharma adopting a more holistic, drug hunting approach to reach new innovative medicines it should prove more productive in meeting the needs of healthcare professionals, patients and payors, for example: what is the current disease treatment?; are there significant problems with the current standard of care?; and what if the significant problems could be overcome by using a novel drug?.

### *Effectiveness in drug discovery is far more important than efficiency*

Peter F. Drucker allegedly said, 'There is nothing more wasteful than becoming highly efficient at doing the wrong thing'. Translating to the drug discovery setting this could mean: there is nothing more wasteful than efficiently producing failing candidate drugs. Therefore, we suggest that being effective (i.e. doing the right things) in drug discovery (e.g. improving quality of science and candidate drugs) is far more important than being efficient (i.e. doing things right, e.g. designing and implementing well-defined drug discovery processes). So far, improvement efforts in pharma have mainly resulted in improvements of effectiveness and efficiency from speed and cost perspectives. Cost and speed of R&D (e.g. 'first to market') will of course continue to be very important because they, in addition to success rate, are important factors in delivering revenue and return on investment to shareholders. However, in the future, improvements of drug discovery effectiveness need to focus more on the quality of the science (i.e. relevance, accuracy and sophistication) and on the quality of candidate drugs (i.e. efficacy and safety). Thus, in the long run,

pharma should become more effective and successful by focusing far more on the quality of science and drug candidates, ultimately delivering sustainable value to healthcare professionals, patients and payors.

## Conflicts of interest

The authors declare that no conflicts of interest exist.

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