

# Drug Delivery<sup>®</sup>

Technology

March 2008 Vol 8 No 3

www.drugdeliverytech.com

## Breakthrough Cancer Pain Challenges

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# Drug Development

## The Challenges of Medical Diversity

**By:** Udo Kiessling, MD, PhD, Corporate Vice President & Worldwide Head of Medical Affairs, Clinical Research Services, PAREXEL International

### Introduction

The development of new medicinal products is guided by internationally accepted principles and practices in the conduct of both individual clinical trials and overall development strategies starting from drug discovery, lead identification, and preclinical testing all the way through the clinical phases of development and drug approval. The major aim of this highly regulated process is to prove efficacy of new medicines and ensure patient safety throughout development and commercialization.

Drug development continues to be inherently challenging, with recent figures indicating that less than 11% of new pharmaceutical agents entering clinical development reach the marketplace, no matter whether those are new chemical/molecular entities or biologics. Although a number of approaches to increase the probability of success in drug development have been investigated, the cost and duration of getting new medicines to market remain high, and the success rates are unchanged. The Tufts Center for the Study of Drug Development has estimated that the cost of developing a new drug is in the range of \$800 million to \$1 billion and takes an average of 8.5 years.

Drug developers and other

stakeholders in the biopharmaceutical industry, including regulators, owners of health expenditures, policy makers, and patients are increasingly concerned about growing healthcare spending in aging societies. Changes in the demographic structure are heralding increased incidences of neurological disorders, cancer, and cardiovascular diseases, which put additional pressures on the development of affordable medicines. In recent years, we have also seen an unprecedented interest in patient safety and the quality of healthcare. The call for new, safer, and more efficacious medical products is steadily increasing, particularly for the elderly and pediatric patient groups.

Most medicines are currently prescribed empirically, based on practical medical experience. However, recent advances in understanding the mechanism of underlying diseases and drug responses, as well as adverse drug reactions, are increasingly creating opportunities to match patients or groups of patients with therapies they are more likely to respond to in a safe and effective manner.

The complex nature of drug development is now well recognized and is mainly due to the heterogeneity and nature of the underlying disease in a patient population. This poses the question whether

different therapeutic areas and various diseases require a specific approach in drug development. Interestingly, there are key differences among major therapeutic areas with regard to success rates in clinical development. Oncology and central nervous system (CNS) drug discovery have poor records for investigational drugs in clinical development as compared to cardiovascular drugs. The drug development success rate in oncology (5%) and CNS (7%) is more than three times lower than in cardiovascular development (20%). The therapeutic areas of oncology, cardiovascular, and CNS share a number of factors. All three are characterized by high incidence rates and affect large parts of the population, particularly in Europe and North America, with clear signs of increase in the Asia-Pacific region. These areas of specialized medicine are putting increasing burdens on the global healthcare expenditure, and despite decades of research and development, still contribute significantly to morbidity and mortality rates.

The drug development process follows an international consensus framework, as outlined primarily by the International Conference of Harmonization (ICH) guidelines and the Council for International Organizations of Medical Sciences

(CIOMS), consequently adapted into regulations by health authorities. With the common scheme of the development process in mind, all steps of the process bear a potential for differences among these major therapeutic areas, resulting in different success or alternatively various attrition rates. Differences can be assumed at the level of 1) discovery (lead identification/optimization); 2) preclinical testing (disease models for efficacy and animal toxicology/pharmacology); and 3) throughout the entire clinical phase of development (choice of trial design, patient population/control groups and definition of primary outcome measures). Throughout all stages of drug development, differences in the knowledge about pathophysiology and the natural course of the disease will have a potential impact on strategic decisions and thus final outcomes.

Comparing cardiovascular (CV), CNS (including neurology and psychiatry), and oncological diseases, there seems to be obvious differences with regard to the availability of appropriate animal models and their predictive value, validated biomarkers, and surrogate markers to guide clinical development. There are also differences concerning the definition of primary outcome in clinical trials. Ideally, the outcome of a clinical trial is defined as the clinical benefit of the investigational drug in comparison to a control group. The demonstration of clinical benefit as a variable to measure how patients feel, function, or survive largely depends on the method used to establish this benefit. This assessment could be based on objective tests or subjective descriptions, such as performance scales or even patient reported outcomes. In CV drug development, the primary outcome is mostly related to a clinical benefit expressed by improvements of mortality rates or surrogate markers, such as blood pressure control, electrocardiogram (ECG) normalization, or reduction of lipid concentration. Most surrogate markers in

cardiology were proven to be predictive for a clinical benefit (eg, improved survival, in large clinical trials).

A clinical benefit is more difficult to establish in some types of cancer trials, in particular, in tumor entities with long progression-free intervals, and is regarded as almost impossible. In some CNS diseases, where the demonstration of a clinical benefit might require patient follow-up in clinical trials for 10 or more years, this is not feasible under both economic and ethical considerations.

## Cardiovascular Diseases

Incidence and prevalence data indicate that cardiovascular diseases globally remain a significant challenge contributing to overall morbidity and mortality rates observed in most of the developed countries. Nevertheless, incredible advances have been made in diagnosis, treatment, and prevention of cardiovascular diseases during the past half century. Evidence-based medicine to a large extent has contributed to the development of efficient therapies and procedures in the treatment of myocardial infarction, hypertension, and congestive heart failure. As a significant difference to CNS and cancer, in cardiovascular medicine, considerable knowledge about pathophysiological mechanisms and environmental- and life style-related risk factors has been accumulated, providing good guidance in drug development. As a result, the success rates are among the highest in drug development. The understanding of the underlying mechanisms and the complex nature of the disease support the choice of the right drug target, addressing a relevant physiological pathway and the best possible timing of the intervention. The profound knowledge of disease and the potential mechanism of intervention also translates into the choice of the right subjects or subgroups of subjects in CV clinical trials. Better knowledge of the mechanism of action enables the drug

developer and the investigator to identify a well-defined group of patients likely to respond to an intervention, and therefore most likely resulting in an improved clinical outcome. The development of treatments for acute myocardial infarction, such as thrombolysis and PCI together with the administration of  $\beta$ -blockers, ACE inhibitors, and platelet aggregation inhibitors, resulted in a major improvement of clinical outcome. However, subtle difference between available standards of care and new treatments in CV drug development require clinical trials larger (often 10,000+ patients) than in any other therapeutic areas to reach results with statistical significance.

The existence of proven surrogate markers as mentioned earlier is providing a clear advantage in CV drug development compared to CNS and cancer. However, this is true only for well-understood disease modalities. The difference is smaller in areas of cardiovascular development in which underlying pathogenetic mechanisms are not known in detail. In recent years, attempts were made to reduce post-MI reperfusion injury, a major risk factor of unfavorable outcomes. Most of the trials so far failed to show a significant benefit of treatment versus placebo. Therefore, the complexity of the pathophysiology of the myocardium post-MI and the (limited) understanding of the pathogenesis appear to be important drivers toward therapeutic success or failure. Available biomarkers, suitable animal models, and a better understanding of pathogenesis in CV diseases do seem to increase predictability of clinical outcome and overall success in drug development. Nevertheless, even three-fold higher success rates when compared to CNS and oncology drug development, an 80% failure rate remains challenging and encourages further improvements.

## Central Nervous System Diseases

In CNS drug development, only about 7% of drug candidates reach the market. CNS treatments take an average of 12.6 years to develop, compared to 6.5 years for cardiovascular indications. Despite many decades of effort, the progress in developing new therapies for neurological and psychiatric disorders has been somewhat disappointing and unsatisfactory. Disorders of the CNS are among the most prevalent, devastating, and yet poorly treated diseases. Most existing treatments are symptomatic and do not affect the underlying cause of the disease. There are a number of reasons making CNS drug development so challenging, beginning with the complexity of the brain itself. The blood-brain barrier (BBB) adds a degree of uncertainty in predicting CNS drug pharmacokinetics and pharmacodynamics, particularly due to changes in permeability and function recognized in a number of neurological conditions. A further complication is the lack of validated biomarkers to understand whether a given neuro-therapeutic agent is reaching the brain in concentrations sufficient to modulate the desired target. The limited understanding of disease mechanisms and pharmacological action has impeded discovery of more effective therapies. In addition to the previously discussed reasons to explain the challenges in CNS drug development, and the difficulties to translate experimental findings into clinical benefits, one of the more important is the lack of suitable *in vitro* and *in vivo* animal models, particularly models that address functional aspects of brain tissue, such as neuronal connectivity. The development of appropriate animal models with some predictive value is an obvious challenge in development of drugs for the treatment of psychiatric conditions. Adding to the complexity are the heterogeneous and, hence, poorly understood nature of psychiatric diseases, such as schizophrenia

or depression, in addition to subjective rating scales to diagnose patients and measure primary outcomes in clinical trials. This poses the question of whether animal models addressing specific behaviors or symptoms of schizophrenia, dementia, or depression can be predictive at all. Current models rely on the assumption that the neuronal circuitry in animals somewhat mirrors that of human conditions, an assumption that is difficult to prove.

However, there seems to be some light at the end of the tunnel. The “omics” era has had considerable impact on target definition and selection, with more targets becoming available. This also opens up new avenues of drug development and allows for a new paradigm in CNS drug discovery and development based on defined molecular mechanisms and understanding of diseases. Because this approach had a positive impact on drug development for cardiovascular diseases, it seems likely that the same can be observed for disorders of the CNS. Conversely, the task of unraveling the pathophysiology of very complex, heterogeneous, and progressive disorders of the brain should not be underestimated.

There are other reasons for optimism – considerable progress is being made in the field of neuroimaging. Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) are playing an increasingly important role in drug development. Neuroimaging and related research are aiming to support the development of biomarkers that could allow the identification of sub-groups of patients more likely to benefit from treatment. In addition, it offers the potential for using biomarkers as surrogate endpoints for more timely and quantitative data collection than the traditional trial endpoints of morbidity and mortality. Neuroimaging applied to neurological and psychiatric drug development could help expedite and strengthen go/no-go decisions and thus positively impact cost and time to market.

## Cancer Drug Development

Oncology, similar to neurology and psychiatry, also has a poor track record in clinical development and the lowest success rate overall when compared to the three therapeutic areas discussed here. Most factors differentiating drug development in oncology from cardiovascular development are reflecting the complexity of cancer biology. As, at the molecular level, two cancers are hardly identical, the resulting variety of diseases is perhaps wider than for any other area in medicine. The phenotypic manifestation of tumor heterogeneity is reflected in extremely different drug responses observed in clinical praxis. In patients diagnosed with histologically identical tumors, age, stage of disease, individual performance status, ethnicity, and many other factors have an impact on response and relapse rates as well as overall survival. It is well known that clinical toxicity and efficacy are difficult to predict from preclinical experiments or basic science. Cancer models similar to animal models in CNS diseases are notoriously unreliable, and it remains risky to advance compounds into clinical development on the basis of suppression of tumor growth in mouse xenografts. Subtle differences in cancer biology between patients may translate into significantly different anticancer activities of new compounds, considering the challenging complexity of cancer immunology, the role of dozens of cellular efflux pumps, various cell cycle checkpoints, and proliferation control mechanisms. Molecular research in oncology, however, has led to the identification of multiple new anticancer drug targets. Anticancer drug targets are commonly differentiated into those addressing essential versus non-essential functions. The inhibition of essential functions to kill tumor cells was historically the principle mode of action of cytotoxic drugs. It leads to on-target toxicity in normal cells and is reflected in

narrow therapeutic windows. The principle concern is on-mechanism toxicity, which clinicians and drug developers are trying to resolve by careful dose-response titrations, an approach well known from the development of drugs like taxol or methothrexate. In addition, for many of the newer small-molecule drugs, attacking single or multiple targets of protein kinase networks off-target toxicity is likely to occur. The increased efficacy, however, might offset the burden of toxicity to some extent.

The high complexity of cancer as a disease and the issues related to the design of clinical trials in oncology contribute to the low success rate in this therapeutic area. In the design phase of clinical trials, the definition of study endpoints (primary outcome measures) and the selection of patient eligibility criteria are amongst the most difficult steps. The classical endpoints for drug approval have been survival, time to progression (TTP), or progression-free survival (PFS). There are, however, problems with each of them. Even the endpoint of survival, seen as the “gold standard” in oncology trials, has been potentially confounded by the administration of efficient second or further lines of therapy. TTP and PFS have the advantage of not being confounded by various lines of therapy; however, progression is sometimes difficult to measure, assessments (CT scans or MRI) tend to occur as scheduled observations, and results are more related to protocol design than clinical reality. Tumor response rates as surrogates for a clinical benefit, although assessing the objective shrinkage of the tumor, are equally dependent upon the frequency of evaluations and can potentially be misleading in cases of asymptomatic progression. The definition of the primary outcome and related monitoring schedule will have a significant impact on overall outcome of the clinical development effort. There are many trials of new compounds that have failed to demonstrate a clinical benefit when compared to standards of

care. The exceptional heterogeneity and variability in tumor response has resulted in the attempt to categorize patient populations by applying selection criteria based on biomarkers characteristic to the target and mechanism of action. Several novel designs have been tested, such as “enrichment designs” in two-stage Phase II studies, and “randomized discontinuation” design, all aiming to increase the predictive value of early clinical development. So far, major improvements in success rates of anticancer drug development have not been reported. High attrition rates as well as low response rates to new treatments remain rather common.

## Summary

Comparing the number of approvals of new chemical entities and biologics by the FDA and the European regulatory authorities throughout the past couple of years to the growing cost of development, there continues to be a gap in productivity, despite advances in the improvement of clinical trial design and effectiveness. And the industry continues to generally believe that this productivity gap can be overcome by investing further in both traditional research and development.

The major differences among the three major therapeutic areas discussed need to be better understood, including the inherent complexity of the disease under investigation, the underlying pathophysiological and pharmacogenetic mechanisms, and the mechanisms of drug activity. Major roadblocks still need to be overcome, including the identification and validation of biomarkers to assess safety and efficacy both in animal models and in humans in order to improve the success rate of drug development, bringing new safe and efficacious drugs to the market more quickly. ♦



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