

JOHN KELLY

# PRINCIPLES OF CNS DRUG DEVELOPMENT

FROM TEST TUBE TO PATIENT



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# Principles of CNS drug development: from test tube to patient

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# **Principles of CNS drug development**

***To***

***Angela, Laura, Seán and Ciarán***

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# Preface

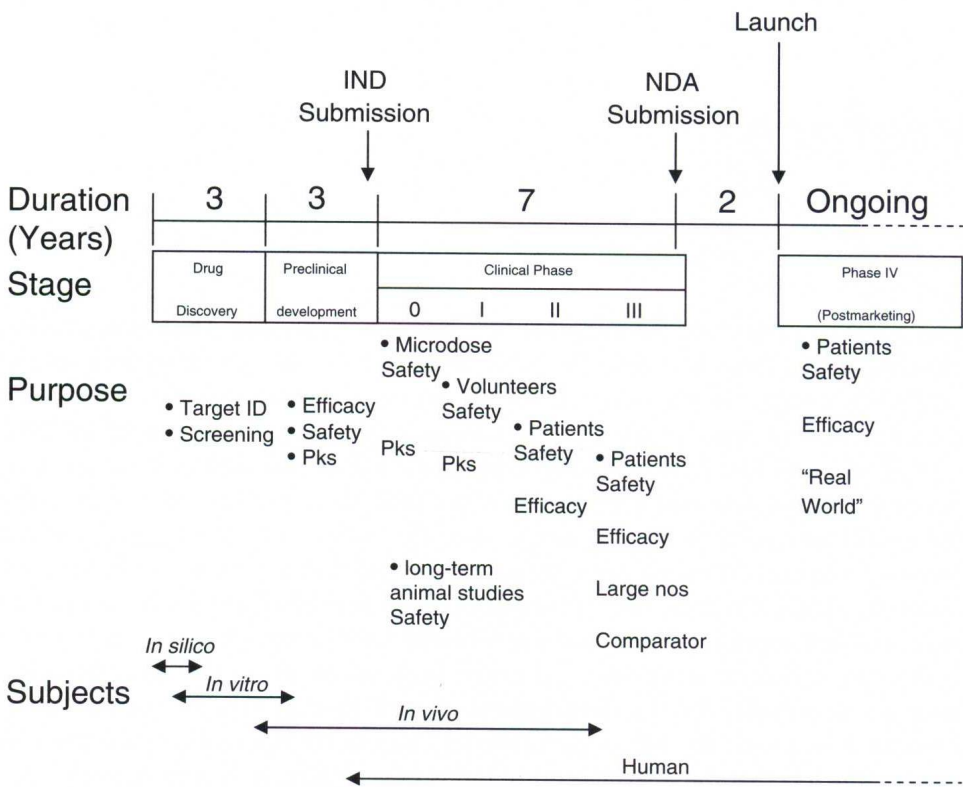
As a society, our faith in the potential of drugs is considerable. There is a growing expectation that there is a drug that will, if not cure, at the very least alleviate the symptoms of each and every disease. This expectation has been brought about by the great advances in drug treatments that have occurred in the latter half of the 20th century and early 21st century in several therapeutic domains, such as in cancer, viral and other infections, and in disturbances of the endocrine, cardiovascular, respiratory and gastrointestinal systems. In contrast, when we consider the CNS (central nervous system) therapeutic domain, there have been limited drug-development milestones. However, such endeavours have sometimes yielded true blockbuster CNS drugs that have provided encouragement that pharmacological approaches can yield effective treatments. Moreover, they have generated huge revenues to the pharmaceutical company responsible for the development of such blockbusters for the remaining duration of its patent life, following marketing. This has led to another perception in society, which is that the pharmaceutical industry is making an inappropriately large profit, on the back of human suffering. Industry counters this argument by outlining the high-risk nature of drug development, and the need to be able to invest profits in further research and development that will generate improved pharmacological treatments on those currently available.

The discovery and development of a new drug can be divided into several consecutive stages, which can vary in sequence. Regardless, the process always begins with attempts at identifying biochemical or physiological elements that are not functioning properly in the disease. From such investigations, a series of ‘druggable’ targets are identified, and of these, one is selected for experimental evaluations with drug candidates. These evaluations address three broad questions:

- Does the drug candidate produce the expected therapeutic effect?
- Is the drug candidate safe?
- Does the drug candidate get to its desired target?

These questions are addressed through a long process that consists of a drug-discovery stage and a drug-development stage that is outlined in Figure P.1. At the





**Figure P.1** The stages of drug discovery and development. IND = investigational new drug; NDA = new drug application.

end of the drug discovery and preclinical development stages, a lead compound ought to have been identified which has the desirable properties, at least as far as can be judged from *in vitro* (i.e. test-tube) and *in vivo* (i.e. laboratory animals) models. The development stage serves to evaluate whether this early promise is realised in a series of evaluations in humans. If they do, the drug will be registered and marketed. The drug evaluation process doesn't stop here, as an ongoing postmarketing surveillance is conducted with a particular emphasis on verifying the safety of the drug in the real-world situation.

Drug discovery and development involves the utilisation of a series of experiments that requires the deployment of a vast array of resources. These experiments each have a specific aim and utilise relevant and appropriate models that are aimed at providing an answer to the three questions raised above, at different stages in the development process. Thus, it can be viewed as an evidence-based decision-making process, which, at crucial points, will determine whether a particular compound will proceed to the next stage, with the ultimate stage being the conduction of a Phase III



trial, i.e. an experiment investigating the benefit of the test drug against no treatment (placebo) and a comparator compound (if such exists).

The purpose of this book is to explore the process by which drugs are developed to treat CNS disorders and it is divided into three sections. The first section consists of four chapters and aims to set the scene, by using six CNS disease areas, drawn from psychiatric diseases (bipolar and unipolar depression, anxiety disorders and schizophrenia) and neurological/neurodegenerative diseases (epilepsy, Alzheimer's disease and Parkinson's disease). The first chapter describes the global burden that CNS disorders represent, whilst the second chapter provides a brief description of these major CNS disorders, from the perspective of the criteria that need to be fulfilled, and the different rating tools that have been developed to identify those patients suffering from such CNS disorders. Chapter 3 describes the theories that have been proposed for the aetiology of CNS disorders, which have to date largely centred upon changes in central chemical neurotransmission. The section is concluded by describing the current pharmacological approaches for the treatment of a selection of CNS disorders.

The second section describes the CNS drug development process in detail, and also consists of four chapters. The first of these concentrates on the methods that are used to identify the therapeutic benefit of a candidate drug, beginning at the earliest preclinical models, progressing through more elaborate animal models, and ultimately to clinical evaluation involving Phases I, II and III, which will determine whether the promise of preclinical examination is realised in patients. Chapter 6 covers the area of pharmacokinetics (i.e. the processes by which the drug is absorbed, distributed, metabolised and eliminated), which tends to accompany the efficacy evaluation of a candidate drug, and similarly involves a range of preclinical and clinical investigations. These investigations help to answer the question as to whether the candidate drug has the desired pharmacokinetic profile, most particularly whether it penetrates the brain in appropriate concentrations. The final two chapters cover the safety aspects of CNS drugs. The first of these chapters investigates the safety concerns that currently are to the forefront of CNS drug development, whilst the second chapter examines the methodologies that have been developed to address these concerns in preclinical evaluation.

The final section consists of a single chapter that examines the challenges faced in developing CNS drugs of the future. This chapter examines some of the important emerging strategies that are having or will have a considerable impact on CNS drug development. In addition a selection of the novel therapeutic targets that are currently being evaluated are presented, either preclinically or clinically in four CNS disorders, namely depression, schizophrenia, Alzheimer's disease and Parkinson's disease. These diseases have been selected, as they probably represent those in the CNS arena into which the greatest amount of research and development is currently being carried out. This book is intended to provide the reader with an overview of a multifaceted, challenging and constantly evolving process.

# Abbreviations

5-HT	Serotonin (5-hydroxytryptamine)
A $\beta$	Amyloid $\beta$ protein
ACC	Anterior Cingulate Cortex
ACh	Acetylcholine
AChE	Acetylcholinesterase
ACTH	Adrenocorticotrophin
AD	Alzheimer's disease
ADLs	Activities of Daily Living
ADME	Absorption, Distribution, Metabolism and Elimination
ADR	Adverse Drug Reaction
AED	Antiepileptic Drug
AMPA	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AMPT	$\alpha$ -methyl-p-tyrosine
ANS	Autonomic Nervous System
APP	Amyloid Precursor Protein
AUC	Area Under the Curve
BACE 1	$\beta$ -site amyloid-cleaving enzyme 1
BBB	Blood-brain barrier
BDNF	Brain-Derived Neurotrophic Factor
BDZ	Benzodiazepine
BHK	Baby Hamster Kidney
BPD	Bipolar Disorder
BPRS	Brief Psychiatric Rating Scale
cAMP	Cyclic Adenosine Monophosphate
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBP	CREB Binding Protein
CGI	Clinical Global Impression Scale
CHO	Chinese Hamster Ovary
CLOGD	Calculated octanol/water partition coefficient
CNS	Central Nervous System
CNV	Copy-Number Variation
COMT	Catechol-O-methyl transferase
COX	Cyclo-oxygenase

CRF	Corticotrophin Releasing Factor
CSF	Cerebrospinal fluid
Css	Steady-state concentration
CT	Computerized Tomography
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia
CVS	Cardiovascular
CYP	Cytochrome p450
DA	Dopamine
DAD	Disability for Dementia Rating Scale
DALYs	Disability-Adjusted Life Years
DAT	Dopamine Transporter
DLB	Dementia with Lewy bodies
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
DZP	Diazepam
EEG	Electroencephalography
Eh	Hepatic extraction
EMA	European Medicines Agency
EPM	Elevated Plus Maze
EPS	Extrapyramidal Symptoms
FDA	Food and Drug Administration
FDG	[18F]fluoro-2-deoxy-D-glucose
FGA	First Generation Antipsychotic
FIH	First-In-Human
fMRI	Functional Magnetic Resonance Imaging
FTD	Frontotemporal Dementia
FTI	Fatal Toxicity Index
GABA	$\gamma$ -aminobutyric acid
GBD	Global Burden of Disease
GIT	Gastrointestinal
GLP	Good Laboratory Practice
GPCR	G-protein-coupled receptor
GRPD	General Practice Research Database
GSK-3	Glycogen Synthase Kinase-3
H&Y	Hoehn and Yahr Rating Scale
HAD	Hospital Anxiety and Depression Scale
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HEK	Human Embryonic Kidney
hERG	human ether a-go-go
HR-QoL	Health-Related Quality of Life
ICD	International Classification of Diseases



ICH	International Conference on Harmonization
ILAE	International League Against Epilepsy
IND	Investigational New Drug
ITT	Intention To Treat
Ki	Inhibitory constant
KO	Knockout
LI	Latent Inhibition
LOCF	Last Observation Carried Forward
mAChR	Muscarinic receptor
MADRS	Montgomery-Asberg Depression Rating Scale
MAO	Monoamine Oxidase
MAOI	Monoamine Oxidase Inhibitor
MAS	Bech-Rafaelsen Mania Scale
MDD	Major Depressive Disorder
mGluR	Metabotropic glutamate receptor
MIST	Metabolites in Safety Testing
MMSE	Mini Mental State Exam
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MTC	Mesiotemporal Cortex
NA	Noradrenaline
nAChR	Nicotinic receptor
NARI	Selective Noradrenaline Reuptake Inhibitor
NBRA	Nonbenzodiazepine Receptor Agonist
NDA	New Drug Application
NICE	National Institute for Health and Clinical Excellence
NMDA	<i>N</i> -methyl- <i>D</i> -aspartate
NOEL	No Observed Effect Level
NPI	Neuropsychiatry Inventory Rating Scale
PANSS	Positive and Negative Syndrome Scale
PCP	Phencyclidine
PD	Parkinson's disease
PDUFA	Prescription Drug User Fee Act
PET	Positron Emission Tomography
P-GP	P-glycoprotein
pKa	Ionization constant
PoC	Proof of Concept
PPI	Prepulse Inhibition
PTSD	Post-Traumatic Stress Disorder
QSAR	Quantitative Structure-Activity Relationship
RCB	Rodent Cancer Bioassay
rCBF	Regional Cerebral Blood Flow



rCBV	Regional Cerebral Blood Volume
RIMA	Reversible Inhibitor of MAO-A
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
S&E	Schwab and England Rating Scale
SERT	Serotonin Transporter
SGA	Second Generation Antipsychotic
SNP	Single-Nucleotide Polymorphism
SNpc	Substantia Nigra pars compacta
SNRI	Serotonin/Noradrenaline Reuptake Inhibitor
SPECT	Single-Photon Emission Computerized Tomography
SSRI	Selective Serotonin Reuptake Inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
TCA	Tricyclic Antidepressant
TDM	Therapeutic Drug Monitoring
TdP	Torsades de Pointes
UPDRS	Unified Parkinson's Disease Rating Scale
Vd	Volume of distribution
WHO	World Health Organization
YLD	Years Lost to Disability
YLL	Years lost to premature mortality
YMRS	Young Mania Rating Scale

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# 1

## Introduction

Diseases of the central nervous system (CNS) are of an enormous diversity. They can range from diseases that are present from an early stage of life to those that are primarily of a later-age onset. For a long time, CNS disease was labelled and stigmatised by society, with it being believed that the sufferers were possessed by demons or evil spirits, or that it was the consequence of some personality deficit or weakness in the afflicted individual. In the nineteenth and early twentieth century, the prevailing attitudes resulted in the committing of many mentally ill individuals to asylums. Such attitudes were hard to shift, and residues of them are still apparent. The alterations in attitudes to mental health and its treatment can most vividly be seen with the remarkable reduction in the population suffering from mental illness in long-term residential care (Figure 1.1), and consequential growth in the treatment of patients within their communities (Manderscheid *et al.*, 2009). The process of deinstitutionalization and psychiatric reform gathered momentum after World War II, originally in the United States and UK, but gradually spread across the world (Novella, 2008). The consequences were that, in the United States, there was a peak in the number of residents in the mid 1950s. This peak coincides with the introduction of the first pharmacological treatments for psychosis and depression. Since then, after nearly 50 years of decline, the resident population in psychiatric institutions is beginning to stabilise at around 50,000, with a modest rise even being seen in 2005, which may be due to a number of factors, including demographic age-related and ethnic changes, as well as pressures on the provision of community services (Manderscheid *et al.*, 2009).

The major challenge in the pharmacological treatment of disorders of the brain is that they have a greater complexity than most other diseases or conditions. For example, most other diseases have a well-defined biological origin, from which drug