THE TEXTBOOK OF Pharmaceutical Medicine

7TH EDITION

EDITED BY
John P. Griffin, John Posner
and Geoffrey R. Barker

WILEY-BLACKWELL

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The editors

Professor John P. Griffin, BSc, PhD, MBBS, FRCP, FRCPath, FFPM graduated in medicine at the Royal London Hospital, where he was also in clinical practice. He was a lecturer in Physiology at King's College, London and held the post of Head of Clinical Research at Riker Laboratories from 1967 to 1971. Professor Griffin joined the then Medicines Division of the Department of Health, now Medicines Healthcare Agency (MHRA) London, as a Senior Medical Officer, in 1971, and was subsequently appointed Medical Assessor to the Committee on Safety of Medicines. From 1977 to 1984, Professor Griffin was Senior Principal Medical Officer and Professional Head of Medicines Division in addition to being Medical Assessor to the Medicines Commission. As the Professional Head of Medicines Division he also attended the Scientific Sub-Committee of the Veterinary Products Committee of the Ministry of Agriculture, Food and Fisheries. During this time he was a member of the EC committee on Proprietary Medicinal Products and Chairman of the CPMP's Working Party on Safety Requirements.

From 1976 to 1984 John P. Griffin served on the Joint Formulary Committee of the British National Formulary, during which period the first eight issues of the current format were produced.

John P. Griffin was the director of the Association of the British Pharmaceutical Industry from 1984 to 1994. During this time he was a member of the Executive Board of the European Federation of the Pharmaceutical Industries' Associations and IFPMA. He chaired the ICH Safety Working Group from 1988 to 1994 and presented papers at ICH1 and ICH2 in the plenary sessions.

In 1992 he was invited to deliver the Thomas Young Lecture and was awarded the Thomas Young Gold Medal at St George's Hospital Medical School, University of London.

Since June 1994, John P. Griffin has run his own independent consultancy company, which has provided independent and impartial advice to governments on the development of a pharmaceutical policy, and to national trade associations and individual companies. John P. Griffin was Visiting Professor in Pharmaceutical Medicine at the University of Surrey for 6 years and was also Honorary Consultant Clinical Pharmacologist at the Lister Hospital in Hertfordshire, UK.

Professor Griffin was on the Board of the Faculty of Pharmaceutical Medicine for 12 years, was Chairman of the Board of Examiners of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians for 7 years, and was Academic Registrar and served on the Task Force on Specialist Medical Training in Pharmaceutical Medicine. He has served on a number of Royal College of Physicians, London Working Parties including that on the 'Development of Clinical Pharmacology and Therapeutics in a Changing World'.

Professor Griffin is the author and co-author of over 250 publications on adverse drug reactions and iatrogenic disease, aspects of neurophysiology and clinical pharmacology and toxicology and drug regulation. Notable among his publications are the following four standard texts:

- *Iatrogenic Diseases*. Oxford University Press, 1st edn 1972, 3rd edn 1986; jointly with Professor P.F. D'Arcy.
- *A Manual of Adverse Drug Interactions*. John Wright, Bristol, 1st edn 1975; Elsevier Press, Amsterdam, 5th edn. 1997; jointly with Professor P.F. D'Arcy.
- *The Textbook of Pharmaceutical Medicine*. The Queen's University of Belfast Press, 1st edn 1993, 2nd edn 1994, 3rd edn 1998, 4th edn 2002 published by the BMJ Publishing Group in 2002, 5th edn 2006 and 6th edn 2009, Blackwell.
- *Medicines, Research, Regulation and Risk*. The Queen's University of Belfast Press, 1st edn 1989, 2nd edn 1992.

From 1991 to 2003 he served as Editor in Chief of *Adverse Drug Reactions and Toxicological Reviews*, a peer-reviewed journal produced quarterly by Oxford University Press.

In 2005 he was awarded the Faculty of Pharmaceutical Medicines Commemorative Medal for outstanding services to the Faculty.

Professor John Posner, BSc PhD MBBS FRCP FFPM gained a BSc and PhD in pharmacology at King's College London and qualified in medicine at King's College Hospital in 1974. After holding various medical posts in London, he completed a residency in Internal Medicine at the Soroka Medical Centre in Beer Sheva, Israel. He subsequently worked as an Attending Physician at Soroka and Lecturer at Ben Gurion University of the Negev.

With the desire to spend more time in clinical drug research, John returned to the UK in 1982, joining the Wellcome Research Laboratories. He developed and validated models of analgesia in healthy volunteers and applied these to the evaluation of novel, peripherally acting opioids. He also used a variety of pharmacodynamic tests in the evaluation of drugs for epilepsy, stroke and migraine. Other areas of investigation included drugs for allergy, asthma depression and anti-infectives. Studies in patients included investigation of a novel agent for sickle cell disease and one of the first biologics for lymphoma.

In 1986, John was appointed Head of Clinical Pharmacology at Wellcome, becoming responsible for the evaluation of all new molecular entities emanating from Wellcome's discovery research in the UK. He negotiated the design and build of a new clinical research facility at King's College Hospital Medical School, where his department subsequently conducted their phase I studies. He continued to practise medicine and teach students on a part-time basis as Honorary Senior Lecturer in Medicine at King's. With the acquisition of Wellcome by Glaxo in 1995, John was appointed an International Director of Clinical Pharmacology at GlaxoWellcome.

After a period with a consultancy and contract research organisation, John started working as an independent consultant in 1999. He continues to work in a wide range of therapeutic areas, assisting companies with their strategic planning, design, conduct and reporting of exploratory studies of novel compounds from 'first-in-human' to 'proof of concept'. His work also includes preparation of clinical overviews, summaries and briefing documents for regulatory submissions worldwide, serving on data monitoring and governance committees and advising on licensing opportunities.

John has extensive postgraduate teaching commitments, organising and participating in courses for physicians and scientists in pharmaceutical companies and academia. He has been a long-standing, active member of the Board of Examiners of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians and served as its Chair for a period of 3 years. John established a Diploma and Certificate in Human Pharmacology for the Faculty; the Diploma is now a recognised qualification for Principal Investigators. He continues to serve as Director of these programmes and has responsibility for a number of MSc modules at King's College, London, where he is a Visiting Professor in the School of Biomedical Sciences. John has published extensively and is an Executive Editor of the *British Journal of Clinical Pharmacology*.

Professor Geoffrey R. Barker, TD, BSc, MSc, FDSRCS, FRCS, FFPM graduated from Guy's Hospital Dental and Medical Schools with a 1st class honours degree in physiology, a distinction and honours in dental surgery and MBBS medicine in 1973. He held assistant lecturer posts in Dental anatomy, Physiology and Restorative Dentistry at Guy's Hospital Medical and Dental Schools and subsequently completed his training to become a Principal in Medical Practice. Over the next several years Professor Barker continued to pursue his interests in clinical research, medical and surgical practice and gained a Masters in Medicine from Manchester University and Fellowships in London (FDSRCS) and Edinburgh (FRCS).

In 1987 he was awarded the Chair in Oral Surgery Medicine and Pathology for the University of Wales. In this role Professor Barker specialised in major reconstructive surgery, cleft lip and palate surgery, and the clinical development of osseo-integration for the replacement of lost bone with titanium implants. By application of oral pathology he also advanced the understanding of oral manifestations of underlying systemic diseases and their management.

In 1990, his continued interest in the translation of new treatment concepts from the laboratory bench into clinical practice resulted in the opportunity to join the pharmaceutical industry while continuing to hold a position as a consultant surgeon. As Medical Director for Astra Pharmaceuticals UK, Professor Barker played a key part in the development of acid proton pump inhibitors to treat and prevent gastro-esophageal reflux disease and peptic ulceration and was able to advance the use of once-daily inhaled steroids for respiratory disease and new management regimens for cardiovascular disease.

In 1997 Professor Barker joined the Medicines Control Agency working with product licensing. In 1999 he was appointed Global Head of Medical Affairs at Actelion Pharmaceuticals and, as a member of the senior management team, successfully steered the company through its IPO and the launch and marketing of its new treatment for pulmonary hypertension.

In 2001 Professor Barker moved to North Carolina to serve as Chief Medical and Scientific Officer for Quintiles Translational Corp, overseeing worldwide clinical trials and the continued development of new medicines. In 2004 he was appointed Adjunct Professor in Immunology at Duke University Medical Center, North Carolina. On retiring from Quintiles, Professor Barker joined Pappas Ventures, a leading health care venture capital fund investing in the development of new medicines and he continues to consult for several venture capital and pharmaceutical companies

Professor Barker became a Member of the Faculty of Pharmaceutical Medicine in 1995 and Fellow in 1998 and was elected Registrar and a Member and Trustee of the Board of the Faculty in 2009.

Acknowledgements

This is the 7th edition of *The Textbook of Pharmaceutical Medicine* in the 20 years since its first publication. The size of the book has progressively increased and, with it, the breadth of expertise of its contributors. For example, there were 22 contributors to the 1st edition; 44 to the 6th edition and 54 to the current edition. The increase in expertise that this represents has changed the *Textbook* from being a good book targeted at pharmaceutical physicians to a one-stop shop and the outstanding information source in this field of medicine.

The success of a book depends on the quality of contributors and the editors would like to thank all of them for their delivery of high quality manuscripts. In particular we wish to acknowledge the diligence of those contributors who have contributed to all seven editions.

We would also like to thank those who have generously given permission to reproduce figures and documents; this is acknowledged in the appropriate places in the *Textbook*.

It is fitting to pay tribute to Professor John O'Grady, co-editor of the first five editions of the *Textbook*, who died in 2011. His expertise will be missed greatly.

It is fitting to thank our publishers, Wiley-Blackwell, for their exceptional continuing support over many years, particularly Adam Gilbert, Elisabeth Dodds and Rebecca Huxley, whose patience, courtesy and expertise have been outstanding. We are grateful to Aileen Castell for the invaluable help she provided during the production stage of this edition. We would like to thank Jan East for her exemplary copyediting skills on this and the 6th edition. We also wish to thank Mary Banks, who retired in September 2011 but was a pillar of strength in preparing previous editions and in the early stages of the current edition.

Finally, thanks are due to the World Medical Association (WMA) and the European Medicines Agency (EMA) for permission to publish key documents as Appendices. Others have allowed us to quote or use their material and this generosity is acknowledged in the text; however, a general thanks is appropriate at this point.

List of abbreviations

ABPI	Association of the British Pharmaceutical Industry
ACE	angiotensin converting enzyme
AChE	acetylcholinesterase
ACPM	Advisory Committee on Prescription Medicines
AD	Alzheimer's disease
ADA	antidrug antibody
ADEC	Australian Drug Evaluation Committee
ADME	absorption, distribution, metabolism and elimination
ADMET	absorption, distribution, metabolism, excretion and toxicological properties
ADR	adverse drug reaction
AEFI	adverse event following immunisation
AF	atrial fibrillation
AFR	annual financial return
AHEC	Australian Health Ethics Committee
AHMAC	Australian Health Ministers' Advisory Council
AIMD	active implantable medical device
AMWG	Access to Medicines Working Group
ANCOVA	analysis of covariance
ANDA	abbreviated New Drug Application
ANVISA	Brazil's National Health Surveillance Agency
ANZTPA	Australia New Zealand Therapeutic Products Agency
API	active pharmaceutical ingredient
ARB	angiotensin II receptor blockers
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARR	absolute rate reduction
ARSAC	Administration of Radioactive Substances Advisory Committee
ARTG	Australian Register of Therapeutic Goods
ARU	attack rate in the unvaccinated population
ARV	attack rate in the vaccinated population
ASA	Advertising Standards Authority
ATMP	advanced therapy medicinal product
AUC	area under the curve
AUSFTA	Australia–US Free Trade Agreement
AusPAR	Australian Public Assessment Report
AWMSG	All Wales Medicines Strategy Group
BACE	beta-secretase
BCS	Biopharmaceutics Classification System
BER	base excision repair
BLA	Biological Licence Application
BMA	British Medical Association
BNF	British National Formulary
BP	British Pharmacopoeia
BPCIA	Biologics Price Competition and Innovation Act
BPR	Business Process Reform
cAMP	cyclic adenosine monophosphate
CAT	Committee for Advanced Therapies
CBA	cost–benefit analysis
CBER	Center for Biologics Evaluation and Research
CCA	cost–consequence analysis
CCDS	Company Core Data Sheet
CCG	clinical commissioning group
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDR	Common Drug Review
CDSM	Committee on Dental and Surgical Materials
CEA	cost-effectiveness analysis
cGMP	cyclic guanosine monophosphate
CHM	Commission on Human Medicines
CHMP	Committee on Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organization of Medical Science
CJEU	Court of Justice of the European Union
C_{max}	maximum concentration

CMD(h)	Coordination Group for Mutual Recognition and Decentralised Procedures for Human Medicinal Products
CMD(v)	Coordination Group for Mutual Recognition and Decentralised Procedures for Veterinary Medicines
CMI	Consumer Medicine information
CML	chronic myeloid leukaemia
CMS	Concerned Member State
COFEPRIS	Mexico's Federal Commission for the Protection against Sanitary Risks
COMP	Committee for Orphan Medicinal Products
COPD	chronic obstructive pulmonary disease
CPAB	Code of Practice Appeal Board
CPMP	Committee on Proprietary Medicinal Products
CPP	Certificate of Pharmaceutical Product
CPP	Code of Practice Panel
CRD	clinically relevant difference
CRF	case report form
CRO	contract research organisation
CRS	cytokine release syndrome
CSD	Committee on Safety of Drugs
CSI	Core Safety Information
CSM	Committee on Safety of Medicines
CT	computed tomography
CTA	clinical trial agreement
CTA	clinical trial authorisation
CTC	Clinical Trial Certificate
CTD	Common Technical Document
CTFG	Clinical Trials Facilitation Group
CTM	Community Trade Mark
CTN	clinical trial notification
CTS	common technical specification
CTX	clinical trial exemption
CUA	cost–utility analysis
CVMP	Committee for Medicinal Products for Veterinary Use
DALY	disability adjusted life year
DESI	Drug Efficacy Study Implementation
DH	Department of Health
DHSS	Department of Health and Social Security
DISK	dry powder inhaler
DLT	dose limiting toxicity
DPP	dipeptidyl peptidase
DRF	dose-range-finding
DSMC	Data Safety Monitoring Committee
DSUR	Development Safety Update Report
DTC	direct-to-consumer
EAG	expert advisory group
EC	ethics committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
ECSC	European Coal and Steel Community
ED	exploratory development
EDC	electronic data capture
EDTA	ethylene diamine tetra acetic acid
EEA	European Economic Area
EEG	electroencephalography
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Association
EGFR	epidermal growth factor receptor
ELA	Establishment Licence Application
ELD	Evaluation and Licensing Division
EMA	European Medicines Agency
EMC	electromagnetic compatibility
EMEA	European Medicines Evaluation Agency
EPC	European Patent Convention
ESG	Expert Scientific Group
EU	European Union
EUFEPS	European Federation for Pharmaceutical Sciences
EURATOM	European Atomic Energy Community
FBDD	fragment-based drug discovery
FD	full development
FDA	Food and Drug Administration
FDC	fixed drug combination
FD&C Act	Food, Drug, and Cosmetic Act
FHSA	Family Health Service Authority
FIH	first-in-human study
FOIA	Freedom of Information Act
FPC	Family Practitioner Committee
FPS	Family Practitioner Service
FTC	Federal Trade Commission
GAVI	Global Alliance for Vaccines and Immunization
GCG	Global Cooperation Group
GCP	Good Clinical Practice
GDP	gross domestic product
GFR	glomerular filtration rate
GLP	glucagon-like peptide
GLP	Good Laboratory Practice
GM	genetically modified
GMC	General Medical Council
GMP	Good Manufacturing Practice
GP	general practitioner

GPS	general product safety
GPSP	Good Post-Marketing Study Practice
GQP	good quality practice
GRAS	generally recognised as safe (drug)
GSK	glycogen synthase kinase
GSL	general sales list
GVP	Good Vigilance Practice
HCV	hepatitis C virus
HED	human equivalent dose
hERG	human ether-a-go-go related gene
HESC	human embryonic stem cells
HHS	Department of Health and Human Services
HLA	human leucocyte antigen
HMAC	Herbal Medicines Advisory Committee
HMPC	Herbal Medicinal Products Committee
HPB	Health Policy Bureau
HREC	human research ethics committee
HTA	Health Technology Assessment
HTS	high-throughput screening
IATA	International Air Transport Association
IB	investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	independent data-monitoring committee
IEC	independent ethics committee
IES	Integrated Efficacy Summary
IFN-α	interferon α
Ig	immunoglobulin
IMP	investigational medicinal product
IMPACT	International Medical Products Anti-Counterfeiting Taskforce
IMPD	Investigational Medicinal Product Dossier
IMS	international medical statistics
IND	investigational new drug
INR	international normalised ratio
INTERPOL	International Criminal Police Organization
IP	intellectual property
IPS	indicative prescribing scheme
IRB	institutional review board
ISS	Integrated Safety Summary
ITP	immune thrombocytopenic purpura
ITT	intention to treat
IVD	*in vitro* diagnostic device
IVRS	interactive voice randomisation system
IVRT	interactive voice response technology
JFC	Joint Formulary Committee
KFDA	Korea Food and Drug Administration
LA	Licensing Authority
LCM	life cycle management
LDC	least developing country
MAA	Marketing Authorisation Application
mAB	monoclonal antibodies
MABEL	minimal anticipated biological effect level
MAH	marketing authorisation holder
MALDI	matrix-assisted laser desorption/ ionisation
MAOI	monoamine oxidase inhibitor
MAP	minimum acceptable profile
MC	Medicines Commission
MCA	Medicines Control Agency
MCCT	multinational cooperative clinical trial
MCDA	multicriteria decision analysis
MDD	medical devices Directive
MDI	metered-dose inhaler
MDU	Medical Defence Union
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MHRA	Medicines and Healthcare products Regulatory Agency
MID	minimum intolerated dose
MOT	margin of tolerance
MPD	medicinal products Directive
MPS	Medical Protection Society
MRA	Mutual Recognition Agreement
MRC	Medical Research Council
MRD	maximum repeatable dose
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSD	maximum recommended starting dose
MRUS	maximum rate of urea synthesis
MS	multiple sclerosis
MTD	maximum tolerated dose
MW	molecular weight
MWTD	maximum well-tolerated dose
NAS	National Academy of Sciences
NBE	new biological entity
NCA	national competent authorities
NCE	new chemical entity
NDA	New Drug Application
NEAF	National Ethics Application Form
NHI	National Health Insurance
NHMRC	National Health and Medical Research Council

NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NK	natural killer
NMDA	*N*-methyl-D-aspartic acid
NME	new molecular entity
NMR	nuclear magnetic resonance
NNT	number needed to treat
NOAEL	no observed adverse effect level
NOEL	no observed (non-toxic) effect dose level
NRES	National Research Ethics Service
NRG	Name Review Group
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NTD	neglected tropical disease
OCSC	oversulfated chondroitin sulfate
OECD	Organisation for Economic Cooperation and Development
OFT	Office of Fair Trading
OMA	Office of Medicines Authorisation
OPG	osteoprotegerin
OR	odds ratio
OTC	over-the-counter
PAC	Pharmaceutical Affairs Committee
PAD	pharmacologically active dose
PADER	periodic adverse drug experience report
PAFSB	Pharmaceutical Affairs and Food Safety Bureau
PAFSC	Pharmaceutical and Food Sanitation Council
PAGB	Proprietary Association of Great Britain
PAGE	poly-acrylamide gel electrophoresis
PAL	Pharmaceutical Affairs Law
PARP	poly-ADP-ribose polymerase
PBAC	Pharmaceutical Benefits Advisory Committee
PBPA	Pharmaceutical Benefits Pricing Authority
PBRER	Periodic Benefit Risk Evaluation Report
PBS	Pharmaceutical Benefits Scheme
PCG	primary care group
PDCO	Paediatric Committee
PDE	phosphodiesterase
PDG	pharmacopoeial discussion group
PDUFA	Prescription Drug User Fee Act
PEG	polyethylene glycol
peg-IFN-α	peg-interferon α
PET	positron emission tomography
PFS	progression-free survival
PFSB	Pharmaceutical and Food Safety Bureau
PGx	pharmacogenomic
PhVWP	Pharmacovigilance Working Party
PI	product information
PIL	patient information leaflet
PIP	paediatric investigation plan
PK	pharmacokinetic
PK-PD	pharmacokinetic–pharmacodynamic
PL	Product Licence
PLA	Product Licence Application
PLM	pre-launch marketing
PLR	Product Licences of Right
PMCPA	Prescriptions Medicines Code of Practice Authority
PMDA	Pharmaceuticals and Medical Devices Agency
PMSB	Pharmaceutical and Medicine Safety Bureau
PoC	proof of concept
POM	prescription only medicine
PPA	Prescription Pricing Authority
PPC	prescription prepayment certificate
PPE	personal protective equipment
PPP	public–private partnership
PPRS	Pharmaceutical Price Regulation Scheme
PRAC	Pharmacovigilance Risk Assessment Committee
PSD	Public Summary Document
PSUR	Periodic Safety Update Report
PTL	Product Team Leader
PTSC	Predictive Safety Testing Consortium
PUMA	Paediatric Use Marketing Authorisation
PV	pharmacovigilance
QA	quality assurance
QALY	quality-adjusted life-year
QbD	Quality by Design
QC	quality control
QoL	quality of life
QPPV	Qualified Person for Pharmacovigilance
R&D	research and development
RANKL	receptor activator of nuclear factor-kB ligand
RBC	red blood corpuscle
RECIST	response evaluation criteria in solid tumours
REMS	Risk Evaluation and Mitigation Strategies
RHA	Regional Health Authority
RMP	risk management plan

RMS	Reference Member State
ROC	return on capital
RP2D	recommended phase II dose
RPW	randomised-play-the-winner
RR	relative risk
RR	response rate
RTK	receptor tyrosine kinase
SAD	single ascending dose
SAE	serious adverse event
SAG	scientific advisory group
SAL	sterility assurance level
SAR	structure–activity relationship
SAS	special access scheme
SAWP	Scientific Advice Working Party
siRNA	small interfering RNA
SMC	Scottish Medicines Consortium
SME	small and medium-sized enterprises
SMO	site management organisation
SmPC	Summary of Product Characteristics
SMT	Safety Matrix Team
SMW	small molecular weight
SOP	standard operating procedure
SPA	special protocol assessment
SPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
SSAR	suspected serious adverse reaction
ssRNA	single-stranded RNA
STB	Scientific and Technical Branch (of the DHSS)
SUSAR	suspected unexpected serious adverse reaction
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVR	sustained virological response
TdP	torsade de pointes
TFT	trifluorothymidine
TGA	Therapeutic Goods Administration
TGP	therapeutic group premium
Th1	T-helper 1
Th2	T-helper 2
TK	thymidine kinase
TKI	tyrosine kinase inhibitor
TLR	toll-like receptor
TMA	tissue microarrays
t_{max}	time to maximum concentration
TMDD	target mediated drug disposition
TNF	tumour necrosis factor
TPN	total parenteral nutrition
TPPA	Trans Pacific Partnership Agreement
TRIP	trade-related aspect of intellectual property rights
TTC	Threshold of Toxicological Concern
UDS	unscheduled DNA synthesis
USDA	US Department of Agriculture
VAS	visual analogue scale
VDR	virtual data room
VE	vaccine efficacy
VEGF	vascular endothelial growth factor
WFI	water for injection
WHA	World Health Assembly
WHO	World Health Organization
WMA	World Medical Association
WOCBP	women of child-bearing potential

Preface

The 7th edition of the 'Textbook' reflects the enormous changes in the environment in which the pharmaceutical industry and the pharmaceutical physician operate, many of which have occurred since 2009 when the 6th edition was published.

The arrangement of the material is now in three parts:

Part I: Research and Development;

Part II: Regulation;

Part III: Healthcare Marketplace.

There are fundamental changes in all three areas with new chapters on topics that have not featured in previous editions. These include biological therapeutics, vaccines, drugs for cancer, drug development in paediatrics and neonates, pharmacovigilance, the European clinical trials directive, lifecycle management of medicines, availability of medicines on-line and counterfeits and the supply of unlicensed medicines. Several pre-existing chapters have undergone major revision, often by new authors. New chapters on the ethics of human experimentation in Part I and legal and ethical issues in Part III reflect a greater emphasis on ethical issues, which are of such critical importance to the pharmaceutical industry as a whole.

The 'Textbook' started 20 years ago as essential reading for the pharmaceutical physician preparing for the professional qualification of the Diploma in Pharmaceutical Medicine and for Membership of the Faculty of Pharmaceutical Medicine of The Royal Colleges of Physicians of the UK. Over subsequent editions, the scope of the book has broadened and much of its content should now be pertinent to the wide range of personnel involved in the development, regulation and marketing of medicines. This includes clinical trial investigators and their research teams as well as those in the industry. We have attempted to make this book a 'first stop shop' for all these readers, with sufficiently generous referencing to guide further detailed study included in each chapter.

It is to be hoped that the broad international scope will make the book of interest to those in the developed markets of Europe, North America, Japan and Australasia and also to those in the developing markets.

Whilst recognising that it is impossible for all its content to remain up to date, we thank the publisher Wiley-Blackwell for permitting late changes to some text where regulations have been updated very recently so that information is as up to date as it can be.

John P. Griffin
John Posner
Geoffrey R. Barker

Part I Research and development

1 Discovery of new medicines

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Introduction

Patients rely on discovery researchers to embrace innovation, make advances and deliver new therapies that will improve their lives. The discovery of drugs is a complex, costly and lengthy process involving several distinct stages on the path towards delivery of a marketable drug (Figure 1.1). It is becoming increasingly important in the ever competitive enterprise of drug discovery for researchers to develop innovative drug discovery strategies in order to fill their pipelines. This chapter is designed to highlight these modern approaches to drug discovery and the changing therapeutic landscape for the currently available drugs.

Progress in drug discovery relies on fundamental biological research in pharmaceutical and biotechnology companies as well as academia to identify new biological targets, to implement target validation strategies and to confirm target relevance in a disease state. Initially, drug discovery researchers select a target that can interact with a modulator, such as a protein or small molecule. After a target has been chosen, researchers must demonstrate that the target is relevant to a disease in both living cells and animal models. The promise of determining the whole genome sequence, new insights into molecular sources of disease, technological advances in both target and lead validation, and high-throughput screening (HTS) strategies all provide potentially novel opportunities for target validation in drug discovery. After such validation, the search begins for a 'hit' molecule that interacts with the desired target. These 'hits' may originate from nature, *de novo* design or HTS but, in most cases, require optimisation to 'leads' via cycles of altering the structure and properties of the molecules followed by iterative screening. During this process, lead compounds are further optimised for the desired *a*bsorption, *d*istribution, *m*etabolism, *e*xcretion and *t*oxicological (ADMET) properties. ADMET optimisation supplies the 'lead compound', which advances to later stages of drug development.

A case study around the investigation of phosphodiesterase (PDE) inhibitors illustrates the successful applications of the principles of contemporary drug discovery and development. Based on the discovery of an endothelium-derived relaxing factor and the interplay of nitric oxide, cyclic guanosine monophosphate (cGMP) and PDEs in vasodilation, researchers at Pfizer reasoned that a PDE inhibitor might be advanced for the treatment of angina [1]. Their comparison of the structure of cGMP, with consideration of how it may bind to PDEs, with that of the weak vasodilator Zaprinast, also a PDE inhibitor, further supported their hypothesis. The screening of existing compound collections as well as the rational design of analogues produced active molecules that targeted PDE-5, a cGMP-specific PDE located in coronary smooth muscle. Further optimisation of these compounds for the desired potency and ADMET properties led to a clinical candidate for angina; the compound was found to be ineffective, and its development as a cardiovascular drug was halted. During the clinical trials, however, some patients reported experiencing enhanced penile erections. Subsequently, PDE-5 was identified as the main cGMP-degrading enzyme in the corpus cavernosum. Thus, efforts were redirected toward proving the effectiveness of the lead compound as a treatment for

The Textbook of Pharmaceutical Medicine, Seventh Edition. John P. Griffin, John Posner, and Geoffrey R. Barker.

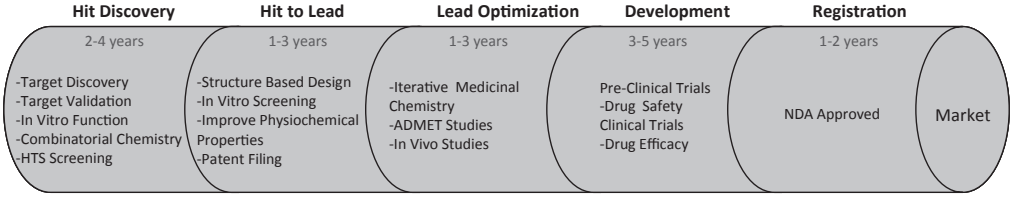

Figure 1.1 Drug discovery pipeline.

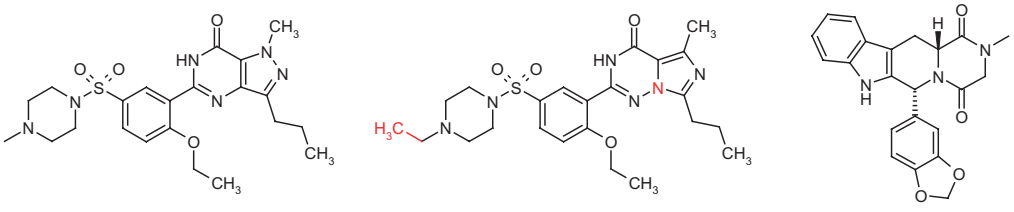

Figure 1.2 Structures of PDE-5 inhibitors for erectile dysfunction.

erectile dysfunction and the eventual approval of sildenafil (Viagra) in 1998 as a prescription medicine for erectile dysfunction [2,3].

Important parts of drug discovery and development are intellectual property protection and the ability to navigate around prior art. Pfizer filed patent applications proactively around the lead compound/series, as well as its therapeutic use, to deter competitors from achieving success in the PDE arena in similar chemical space. Others interested in advancing compounds in this therapeutic area became faced with searching for gaps in the patent coverage or pursuing alternative structural classes. Implementation of a 'patent busting' strategy enabled the discovery of vardenafil (Levitra). Analogues outside of the Pfizer patents were identified, optimised and evaluated in clinical trials ahead of product launch in 2003. Conversely, Icos and Lilly investigated an unrelated molecule as a longer-acting PDE-5 inhibitor that led to the approval of tadalafil (Cialis), also in 2003. Figure 1.2 highlights the structural similarities, and differences, of these three medicines.

Medicines marketed in the years 2008–2011

The pharmaceutical and biotechnology industries spend billions on cutting-edge research and development (R&D), clinical trials and marketing to introduce drugs to market. However, fewer than one in 50 drug discovery projects results in the delivery of a drug to market [4], and the average time from concept to market is 15 years, at a cost of nearly a billion dollars per drug [5]. Further, since 2008, new drug approvals have declined sharply despite an increase in R&D spending [6]. The observed high attrition rate is unsustainable and researchers must constantly reassess their tactics in order to translate discovery research into clinical success.

Despite the steady decline in overall new drug approvals there has been a steady increase of new products in the therapeutic areas of anti-infective, metabolic and orphan diseases, as well as a shift into specialty-care therapies (Tables 1.1, Table 1.2, Table 1.3 and Table 1.4) [7–9]. The majority of new molecular entities (NMEs) continue to be small molecules; however, vaccines and non-biological oligonucleotides employed as macromolecular therapeutics are directed at enzymes and receptors that have been classically modulated by small molecule drugs.

In response to the decline in new drug approvals, new approaches have been put in place:

1. drug combinations that target multiple pathways continue to increase in drug discovery to modulate the interplay of complex chemical pathways involved in diseases;

Table 1.1 New molecular entities (NME) approved 2008. Reproduced from Hegde S, Schmidt M. To Market, To Market Annual Reports in Medicinal Chemistry 2009; 44: 577 with permission from Elsevier [8]

Proprietary	Established	Applicant	Treatment/indication
Entereg	Alvimopan	GlaxoSmithKline/Adolor	Oral treatment of postoperative ileus following bowel resection surgery
Biomatrix	Biolimus drug-eluting stent	Biosensors	Antiresenotic
Lonasen	Blonanserin	Dainippon-sumitomo	Dual antagonist of dopamine D2 and serotonin 5-HT2 for schizophrenia
Zeftera	Ceftobiprole medocaril	Basilea/Johnson&Johnson	New injectable cephalosporin antibiotic
Cimzia	Certolizumab pegol	UCB	TNF-α blocker for Crohn's disease
Trilipix	Choline fenofibrate	Abbott/Solvay	PPARα dyslipidaemia
Cleviprex	Clevidipine	The Medicines Co.	IV treatement for hypertension
Pradaxa	Dabigatran	Boehringer Ingelheim	Oral administered anticoagulant
Pristiq	Desvenlafaxine	Wyeth	SNRI for antidepression
Intelence	Etravirine	Tibotec	NNRT antiviral for HIV
Toviaz	Fesoterodine	Pfizer	Orally active pro-drug from treatment of overactive bladder
Ivemend	Fosapreptiant dimeglumine	Merck	Anti-emetic
Firazyr	Icatibant	Jerini	Hereditary angiodema (HAE)
Vimpat	Lacosamide	Schwarz Pharma	Anticonvulsant
Relistor	Methylnaltrexone bromide	Wyeth/Progenics	Opiod-induced constipation
Pirespa	Pirfenidone	Shinogi	Idiopathic pulmonary fibrosis (IPF)
Arcalyst	Rilonacept	Regeneron	Recombinant fusion protein for symptoms of inherited auto-inflammatory syndrome
Xarelto	Rivaroxaban	Bayer/Ortho-McNeil	Anticoagulant
Nplate	Romiplostim	Amgen	Recombinant fusion protein for treatment of thrombocytopenia
Gracevit	Sitafloxacin hydrate	Daiichi Sankyo	Antibacterial
Bridion	Sugammadex	Schering-Plough	Reversal of neuromuscular blockade
Taflotan	Tafluprost	Santen/Asahi Glass	Antiglaucoma
Recothrom	Thrombin alfa	Zymogenetics	Recombinant human protein for haemostat
Recomodulin	Thombomodulin	Asahi Kasei Pharma	Recombinant human protein as an anticoagulant

NNRT, non-nucleoside reverse transcriptase; PPAR, peroxisome proliferator-activated receptor; SNRI, serotonin–norepinephrine reuptake inhibitor; TNF, tumour necrosis factor.

2. drug repurposing has accounted for two-thirds of new drug applications. Increased focus on re-purposing existing drugs for orphan indications emanates from disease-focused philanthropic groups; and

3. collaboration strategies between pharmaceutical companies and academic research institutions have contributed to the drug discovery process [10,11]. While academic research is focused principally on the underlying mechanistic components of a disease and

Table 1.2 NME approved 2009. Reproduced from Hegde S, Schmidt M. To Market, To Market Annual Reports in Medicinal Chemistry 2010; 45: 467 with permission from Elsevier [9]

Proprietary name	Established name	Applicant	Treatment/indication
Nuvigil	Aromodafinil	Cephalon	Sleep disorder, α1-adrenoceptor agonist
Saphris	Asenapine	Merck/Schering-Plough	Schizophrenia and bipolar 1, dual antagonist dopamine D2 and serotonin 5-HT2
Besivance	Besifloxacin	Baush & lomb	Antibacterial, ophthalmic use
Ilaris	Canakinumab	Novartis	Recombinant monoclonal antibody, anti-inflammatory
Removab	Catumaxomab	Trion	Trifunctional monoclonal antibody, anticancer
Priligy	Dapoxetine	Janssen-Cilag	Premature ejaculation
Firmagon	Degarelix acetate	Ferring Pharmaceutical	Antagonist of GNRH, anticancer
Kapidex	Dexlansoprazole	Takeda	Gastroesophogeal reflux disease
Multaq	Dronedarone	Sanofi-Aventis	Anti-arrhythmic
Promacta	Eltrombopag	GlaxoSmithKline	Antithrombocytopenic
Zebinx	Eslicarbazepine	Eisai	Anti-epileptic
Adenuric	Febuxostat	Takeda/Teijin/Ipsen	Antihyperuricaemic, selective xanthine oxidase inhibitor
Simponi	Golimumab	Centocor Ortho	Recombinant monoclonal antibody, anti-inflammatory
Onbrez breezhaler	Indacaterol	Novartis/Skye Pharma	Chronic obstructive pulmonary disease, inhaled β2 adrenoceptor agonist
Victoza	Liraglutide	Novo Nordisk	Antidiabetic
Recalbon, bonoteo	Minodronic acid	Ono/Astella Pharma	Osteoporisis
Remitch	Nalfurafine hydrochloride	Toray/Japan Tobacco	Pruritus (chronic itching)
Arzerra	Ofatumumab	Genmab/GlaxoSmithKline	Recombinant monoclonal antibody, anticancer
Votrient	Pasopanib	GlaxoSmithKline	VEGF, anticancer
Mozobil	Plerixafor	Genzyme	Haematological malignancies, autologous haemtopoietic stem cell transplantation
Folotyn	Pralatrexate	Allos	Injectable DHFR inhbitior, anticancer
Effient	Prasugrel	Daiichi Sankkyo/Eli Lilly	Antiplatelet therapy
Onglyza	Saxagliptin	Bristol-Myers-Squibb/ Astrazeneca	Antidiabetic
Nucynta	Tapentadol	Ortho-McNeil-Janssen	Analgesic, pain intervention
Arbelic, vibativ	Telavancin	Theravance/Astellas Pharma	Antibiotic
Samsca	Taolvaptan	Otsuka America	Hyponatraemia
Ellaone	Ulipristal acetate	HRA Pharma	Contraceptive, progesterone receptor antagonist
Stelara	Ustekinumab	Janssen-Ortho	Humanized IGG1K monoclonal antibody, antipsoriatic

DHFR, dihydrofolate reductase; GNRH, gonadotrophin-releasing hormone; VEGF, vascular endothelial growth factor.

Table 1.3 NME approved 2010. Reproduced from Bronson J, Dhar M, Ewing W, Lonberg N. To Market, To Market Annual Reports in Medicinal Chemistry 2011; 46: 433 with permission from Elsevier [7]

Proprietary name	Established name	Applicant	Treatment/indication
Lastacaft	Alcaftadine	Vistakon Pharmaceuticals	Ophthalmologic, histamine antagonist
Nesina	Alogliptin	Takeda/Furiex Pharmaceuticals	Antidiabetic, DPP-4
Bilaxten	Bilastine	Faes Farma, Menarini, Pierre Fabre, Merck-Serono	Antiallergy, histamine antagonist
Jevtana	Cabazitaxel	Sanofi-Aventis	Anticancer, tubulin inhibitor
Teflaro	Ceftaroline fosamil	Forest Laboratories	Antibacterial, bacterial cell wall synthesis inhibitor
Elonva	Corifollitropin	Merck	Infertility, FSH agonist
Ampyra	Dalfampridine	Acorda Therapeutics	Multiple sclerosis, potassium channel blocker
Prolia / xgeva	Denosumab	Amgen	Osteoporosis, recombinant monoclonal antibody
Diquas	Diquafosol	Santen	Ophthalmologic dry eye, P2Y2 purinergic receptor agonist
Kalbitor	Ecallantide	Dyax Corp	Angiodema, plasma kallikrein inhibitor
Halaven	Eribuline	Eisai	Anticancer, tubulin inhibitor
Gilenya	Fingolimod	Novartis	Multiple sclerosis, S1P receptor agonist
Inavir	Laninamivir	Daiichi-Sankyo	Antiviral, neuraminidase
Lurasidone	Lurasidone	Dainippon Sumitomo Pharma	Schizophrenia, dopamine 5-HT receptor antagonist
Junovan	Mifamurtide	Takeda	Anticancer
Rapiacta	Peramivir	Biocryst Pharmaceuticals	Antiviral, neuraminidase inhibitor
Daxas	Roflumilas	Nycomed	Chronic obstructive pulmonary disorder, PDE4 inhibitor
Istodax	Romidepsin	Celgene	Anticancer, histone deacetylase inhibitor
Provenge	Sipuleucel-t	Dendreon	Anticancer, therapeutic cancer vaccine
Egrifta	Tesamorelin	Theratechnologies	HIV lipodystrophy, growth hormone-releasing factor
Brilique	Ticagrelor	Astra-Zeneca	Antithrombotic, P2Y12 antagonist
Brinavess	Vernakalant	Merck/Cardiome Pharma	Anti-arrhythmic, atrial potassium channel blocker
Javlor	Vinflunine	Pierre Fabre	Anticancer, tubulin inhibitor
Civanex	Zucapsaicin	Winston	Analgesic, TRPV1 channel activator

FSH, follicle stimulating hormone; PDE4, phosphodiesterease 4; TRPV1, transient receptor potential cation channel subfamily V member 1.

Table 1.4 NME approved 2011. Reproduced with permission from U.S. Food and Drug Adminstration, 'How Drugs are Developed and Approved?', http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm121136.htm. Last accessed 13 Aug 2012

Proprietary name	Established name	Applicant	Treatment / indication
Zytiga	Abiraterone	J&J	Advanced prostate cancer
Eylea	Aflibercept	Regeneron/Bayer	Wet AMD
Edarbi	Azilsartan	Takeda	Hypertension angiotensin II receptor blocker
Nulojix	Belatacept	Bms	Renal transplant
Benlysta	Belimumab	HGSI, GSK	Lupus
Victrelis	Boceprevir	Merck	Hepatitis C
Adcetris	Brentuximab vedotin	Seattle Genetics	Hodgkin lymphoma, anaplastic large cell lymphoma
Teflaro	Caftaroline	Cerexa	Acute bacterial skin infections and pneumonia
Erwinaze	Crisantaspase	Eusa	ALL
Xalkori	Crizotinib	Pfizer	NSCLC
Promacta	Eltrombopag	GSK	Chronic immune (idiopathic) thrombocytopenic purpura
Potiga	Ezogabine	GSK, Valeant	Epilepsy
Corifact	Factor xiii	Behring	Prevention of bleeding with genetic defects in factor XIII
Horizant	Gabapentin enacarbil	GSK, Xenoport	Restless legs syndrome
Firazyr	Icatibant	Shire	Hereditary angioedema
Arcapta neohaler	Indacaterol	Novartis	COPD
Yervoy	Ipilimumab	Bms	Metastatic melanoma
Tradjenta	Linagliptin	Lilly, Boehringer Ingelheim	Type 2 diabetes
Edurant	Rilpivirine	J&J	HIV
Xarelto	Rivaroxaban	Bayer, J&J	Blood clot prevention
Daliresp	Roflumilast	Forest	COPD
Jakafi	Ruxolitinib	Incyte, Novartis	Myelofibrosis
Natroba	Sphinosad	Parapro	Head lice
Incivek	Telaprevir	Vertex, J&J, Mitsubishi Tanabe	Hepatitis c
Brilinta	Ticagrelor	Astra Zeneca	Blood clot prevention
Caprelsa	Vandetanib	Astra Zeneca	Medullary thyroid cancer
Zelboraf	Vemurafenib	Roche, Daiichi Sankyo	Melanoma
Zictifa	Vendetanib	Astra Zeneca	Thyroid cancer
Viibryd	Vilazodone	Forest, Merck KGAA	Major depressive disorder

ALL, acute lymphocytic leukaemia; AMD, acute macular degeneration; COPD, chronic abstructive pulmonary disease; NSCLC, non-small cell lung cancer.