APPENDIX 2 Glossary of Medicinal Chemistry Terminology

ACE inhibitor	An antihypertensive drug that works by inhibiting the angiotensin converting enzyme, preventing the synthesis of a powerful vasoconstrictor.
acetylcholine (ACh)	A messenger molecule in the nervous system. In the central nervous system, acetylcholine and the associated neurons form the cholinergic system, which tends to cause anti-excitatory actions (see also cholinergic).
ADMET	Referring to the absorption, distribution, metabolism, excretion and toxicology of drug candidates.
agonist	A drug that produces the same response at a receptor as the natural messenger.
allosteric	Referring to a protein binding site other than the one used by the normal ligand, which affects the activity of the protein. An allosteric inhibitor binding to an allosteric binding site induces a change of shape in the protein which disguises the normal binding site from its normal ligand.
antagonist	A drug that binds to a receptor without activating it, thereby inhibiting the binding of the natural messenger or an agonist.
antibacterial	A natural or synthetic molecule that can kill or inhibit the growth of bacterial cells.
antibody	A Y-shaped glycoprotein that is generated by a body's immune system to interact with an antigen present on a foreign molecule. Marks the foreign molecule for destruction.
antibody-drug conjugate	An antibody with a drug covalently bonded to its structure.
antigen	A region of a molecule that is 'recognised' by the immune system and interacts with antibodies that target it.
antimetabolite	The inhibitor of an enzyme that is crucial to the normal metabolism of a cell. Used in antibacterial and anticancer contexts.
beta-blocker	A drug that blocks or antagonises beta-adrenergic receptors. Used in cardiovascular contexts.
bioassay	An assay conducted to measure the effects of a substance on a living organism.
bioavailability	The fraction or percentage of an administered drug or other substance that becomes available in plasma or to the target tissue after administration.
biomarker	An indicator of a biological state that can reliably measured and evaluated as an indicator of a biological process or a response to a therapeutic intervention.
black box warning	The most serious safety warning required on a pharmaceutical label, indicative of a significant risk of a serious or even life-threatening adverse drug reaction.
blood-brain barrier	Blood vessels in the brain are less porous than those in the periphery, and have a fatty coating. Drugs targeted at the brain must be lipophilic in order to cross this barrier.
chemically mediated toxicity	A toxicity that is due to the physical and chemical properties of a particular chemical or an entire chemical class.
cholinergic receptors	Receptors that are activated by acetylcholine.
chronic myelogenous leukaemia	A haematological cancer characterised by excessive proliferation of cells of the myeloid lineage.
clinical trials phase 1	A drug is first tested in 50–200 healthy volunteers to establish suitable dose levels, evaluate its pharmacokinetics and identify side-effects.
clinical trials phase 2	In this phase a drug is tested in groups of patients (100–500) with the target disease in order to verify its therapeutic effects. Different groups receive different doses, usually under double-blind conditions.
clinical trials phase 3	Similar to phase II, but with larger numbers of patients (1000–5000). It is in this phase that the beneficial effects, or otherwise, of a drug are proven and fully evaluated.
clinical trials phase 4	Monitoring the performance of a drug after it has been approved and marketed is an unending process and is now referred to as phase IV studies. New side-effects may be observed, or effects on particular groups (e.g. children or pregnant women) may be revealed by long-term statistics. A drug can be withdrawn if necessary.
CNS	central nervous system

combinatorial chemistry	The generation of large collections, or 'libraries,' of compounds by synthesising combinations of a set of smaller chemical structures.
combinatorial technology	Synthetic technologies to generate compound libraries rather than single compounds.
cytochrome P450	Members of the cytochrome P450 superfamily of haem proteins have a key role in the metabolism of drugs, and so understanding the roles of these enzymes is important for issues such as drug bioavailability and drug–drug interactions.
development-limiting toxicity	A toxicity that is either irreversible or unmonitorable, has an unacceptable safety margin or therapeutic index, or would negatively affect sales, patient compliance, competitive advantage or marketability.
discovery	Refers to various drug research activities from target identification to preclinical development.
DNA	Deoxyribonucleic acid
dose-limiting toxicity	Any toxicity that limits the ability to continue escalating the dose.
double-blind	Neither the individuals nor the researchers know who belongs to the control group and who belongs to the drug group. Only after all the data have been recorded do the researchers learn which individuals are which.
drug-like	Sharing certain characteristics with other molecules that act as drugs. The set of characteristics – size, shape and solubility in water and organic solvents – varies depending on who is evaluating the molecules.
EC_{50}	The half-maximal effective concentration of a drug, *i.e.* the concentration of a compound at which 50% of its maximal effect is observed.
electrophilic metabolite	A reactive metabolite characterized by an affinity to form covalent modifications with endogenous nucleophiles.
EMEA	European agency for the evaluation of medicinal projects.
enzyme	A protein that acts as a catalyst for a reaction.
exaggerated pharmacology	Toxicity that is due to excessive modulation of the activity of the primary pharmacological target beyond the point necessary for efficacy.
expression	see protein expression
freedom to operate	The ability to synthesise new molecular entities in a chemical space that has not been previously described in relevant existing patents.
gating	Mechanism by which ion channels are opened or closed.
GMP	see good manufacturing practice.
Good manufacturing practice	Scientific codes of practice that pharmaceutical companies must apply to their production plants. Compliance is monitored by regulatory authorities.
G-protein	A membrane-bound protein with three sub-units that are key to the signal transduction process from activated G-protein coupled receptors.
G-protein coupled receptor	A membrane-bound receptor that interacts with a G-protein when it is activated by the binding of a ligand.
half-life	The time taken for the plasma (circulating) concentration of a drug to fall by half.
hERG	Human ether-a-go-go-related gene, the gene that encodes the -subunit of the IKr channel, a major determinant of human cardiac repolarisation.
hit	A biologically active compound that exceeds a certain activity threshold in a given assay.
hit-to-lead	The hit-to-lead phase is usually the follow-up of high-throughput screening in which the structure of an active compound ('hit') is confirmed and then modified to optimise its desirable properties.
hormone	Endogenous chemicals that act as chemical messengers. They may be released from glands and travel to their targets in the blood, or may be released and act locally.
HTS	High-throughput screening
hydrophilic	Refers to compounds that are polar and water-soluble ('water loving').
hydrophobic	Refers to compounds that are non-polar and insoluble in water ('water hating').
IC_{50}	The concentration of an inhibitor required to inhibit an enzyme by 50%.
idiosyncratic toxicity	A toxicity that occurs rarely (with a frequency that is typically less than 1 in 1000) and unpredictably among the population.
in vitro	Refers to experiments or assays carried out on isolated cells, macromolecules or tissue samples in laboratory vessels, e.g. dishes or test-tubes.
in vivo	Refers to experiments or assays carried out on animals or humans.

ion channel	Protein complexes in a cell membrane that allow the passage of specific ions across the membrane.
kinase	Enzyme that catalyses the phosphorylation of alcoholic or phenolic OH groups present in a substrate (normally a protein).
lead compound	A chemical structure or series of structures that show activity and selectivity in a pharmacological or biochemically relevant screen.
ligand	A term used for any molecule capable of binding to a binding site.
Lineweaver-Burk plot	A plot which can be used to determine whether an enzyme inhibitor is competitive or non-competitive.
Lipinski's rule of five	Lipinski's analysis of the World Drug Index led to the 'rule-of-five,' which identifies several key properties that should be considered for small molecules that are intended to be orally administered. These properties are: molecular mass <500 Da; number of hydrogen-bond donors <5; number of hydrogen-bond acceptors <10; calculated octanol–water partition coefficient (log P, an indication of the ability of a molecules to cross biological membranes) <5.
lipophilic	Refers to compounds that are fatty and non-polar in character ('fat loving').
log P	The octanol/water partition coefficient is the ratio of the solubility of a compound in octanol to its solubility in water (also known as K_{ow}). The logarithm of this partition coefficient is called log P. It provides an estimate of the ability of the compound to pass through a cell membrane.
MAA	Marketing authorisation application. A document provided to the EMEA in order to receive marketing approval for a new drug.
messenger RNA (mRNA)	Carries the genetic code required for the synthesis of a specific protein.
micronucleus assay	An assay that identifies chromosomal aberrations, visible as an extra staining material in metaphase/anaphase cells. Both an in vitro and in vivo chromosomal aberration assay are required before first-in-human studies.
multidrug resistance	The situation where a cancer cell acquires resistance to a range of drugs other than the one to which it was exposed. Related to the overexpression of P-glycoprotein which expels drugs from the cell.
mutagenicity	This is DNA damage that is considered to be predictive of carcinogenicity.
NCE	New chemical entity, i.e drug candidate molecule
neurotransmitter	A chemical released by a neuron ending that acts as a chemical messenger by interacting with a receptor on a target cell.
new molecular entity	A medication containing an active ingredient that has not been previously approved for marketing in any form.
NME	see new molecular entity
NOAEL	No observable adverse effect level is the highest exposure at which no adverse effects are observed.
nucleoside	A building block for RNA or DNA consisting of a nucleic acid base linked to a sugar molecule.
nucleotide	A nucleoside linked to one, two or three phosphate groups.
oxazolidinones	A group of synthetic antibiotics that target bacterial protein synthesis.
patch-clamp assay	An assay that uses a microelectrode to study the activity of ion channels in single cells.
PET	see positron emission tomography
pharmacodynamics	The study of how ligands interact with their target binding site.
pharmacokinetics	The study of the absorption, distribution, metabolism, excretion and interactions of a drug (see ADME).
pharmacophore	The ensemble of steric and electronic features – atoms and functuional groups – that is necessary to ensure optimal interactions with a specific biological target structure and to trigger (or to block) its biological response.
phase 1, 2, 3, 4	see clinical trials
phosphatase	An enzyme that catalyses the hydrolysis of phosphate bonds.
placebo	A compound or preparation that contains no active drug, although it looks and tastes as though it might. Can cause the placebo effect, in which a patient improves because they believe they have received a drug even though they have not.
plasma proteins	Proteins in the plasma of the blood. If a drug binds to plasma proteins it will be unable to reach its target.
PNS	peripheral nervous system

positron emission tomography	Positron emission tomography, a 3-D imaging technique based on the detection of a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule.
primary pharmacology	Also referred to as target-based toxicity, this is toxicity that is caused by a modulation of the primary pharmacological target.
process chemistry	Application of the principles of organic synthesis and physicochemical analysis to the issues surrounding the scaling up of drug manufacture.
prodrug	A molecule that is itself inactive, but which is converted into an active drug in the body, e.g. by an enzymic or hydrolytic reaction. Used to manipulate the pharmacokinetics and targeting of a drug entity.
protein expression	The synthesis of protein in an organism according to the blueprint provided by RNA. Occurs in the ribosomes, and can be controlled so as to produce particular proteins for use in drug research and assay.
QT prolongation	The QT interval is a measure of the total time of ventricular depolarisation and repolarisation. In recent years, several drugs have been withdrawn from the market because of unexpected reports of sudden cardiac death associated with prolongation of the QT interval. Blockade of the hERG channel has been linked to this effect.
reactive metabolite	A chemically reactive metabolite that binds covalently to cellular proteins.
receptor	A protein with which a chemical messenger or drug can interact to produce a biological response.
ribosome	Structure composed of ribosomal RNA and protein, whose function is to bind a molecule of messenger RNA and catalyse the synthesis of the protein for which it is encoded.
RNA	Ribonucleic acid
safety margin	A preclinical indication of the safety of a compound that represents the ratio of a maximum safe exposure divided by an efficacious exposure.
SAR	see structure-activity relationship
Scatchard plot	A plot used to measure the affinity of a drug for its binding site.
screening	A procedure by which compounds can be tested for biological activity.
secondary pharmacology	Toxicity caused by a lack of specificity for the primary target resulting in a molecule crossing over onto and modulating the activity of a secondary, often structurally and/or evolutionarily related target.
semi-synthetic	Synthesised from a naturally-occurring compound (as opposed to synthesised from scratch).
signal generation	A study intended to identify the dose-limiting safety liability of a compound or drug target.
solid-phase synthesis	Synthesis of compounds on the solid surface of an insoluble resin support, which allows them to be readily separated (by filtration or centrifugation) from excess reagents, soluble reaction by-products or solvents.
statin	A class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase.
STR	see structure-toxicity relationship
structure-activity relationship	The correlation of structural features with the activity of compounds in a given assay.
structure-toxicity relationship	An assessment of the structural features that determine the occurence and/or severity of a particular toxicity.
substrate	A chemical which undergoes a reaction that is catalysed by an enzyme.
therapeutic index	A clinical indication of the safety of a compound determined by dividing the exposure at which dose-limiting clinical adverse effects are first observed by the exposure at which efficacy is achieved.
topoisomerases	Enzymes that catalyse the temporary breaking of one or both strands of DNA to allow coiling or uncoiling of the molecule. These enzymes are targets for several antibacterial and anticancer drugs.
toxicology	A branch of biology, chemistry, and medicine concerned with the study of the adverse effects of chemicals on living organisms.
tyrosine kinases	Enzymes that catalyse the phosphorylation of tyrosine residues in protein substrates.
vasoconstriction	The narrowing of the blood vessels resulting from contraction of the muscular wall of the vessels. The process is the opposite of vasodilation, the widening of blood vessels.