Index

A
Absorption
- drugs, intestinal tract, 310
- food and defecation reflexes, 300
- and GI, 309–310
- and intestinal permeability, 301
- mucosa, 298
- ototoxicity studies, 276
- vascular system, 226
- water and electrolytes, 298
ABST system. See Automated blood sampling and telemetry (ABST) system
Abuse liability
- assessments, 119, 121
- CCALC, 117
- CNS, 84
- CSS, 122
- design of, 123
- drugs, 37
- guidelines, 35
- history, 116
- preclinical, 116, 129
- scientific database, 122
Action potential
- cardiac, 165
- electrophysiological changes, 59
- guinea pig (see Guinea pig papillary muscle action potential)
- IA antiarrhythmic drugs, 55
- L-type calcium current, 57
- QT PRODAPT initiative, 218
Activation
- ECG intervals, myocardial cells, 191
- gate particle, 167
- K⁺ channels, 178, 182, 189
- Na⁺ channels, 168, 169, 171, 175
- sequential cell, 159
ADCs. See Antibody-drug/toxin conjugates (ADCs)
Aminoglycoside antibiotics, ototoxicity studies, 284
Amyloid precursor protein (APP), 74
Anthracyclines, 415
Antibody-drug/toxin conjugates (ADCs), 418
Anticancer agents
- cardiovascular toxicities, 424
- "core battery" tests, 406
- EGFR signaling, 426
- ICH S9 guidance, 407, 427
- infusion reactions, 426
- large-molecule anticancer agents, 418–424
- PDGF receptor signaling, 426
- proteinuria, 425
- QT prolongation, 425
- repeated-dose toxicity testing, 406
- small molecule anticancer agents, 409–417
- systolic dysfunction and heart failure, 425
- VEGF signaling, 425
Antihistamines
- blood-brain barrier, 78
- candidate selection, 79
- cytochrome CYP450 3A4, 78–79
- and hERG, 78–79
- histamine-H1 receptor antagonists, 78
- peripheral H1 receptors, 78
- QT interval prolongation, 78
- terfenadine, 78
APP. See Amyloid precursor protein (APP)
Association of the British Pharmaceutical Industry (ABPI), 23, 27, 38
Atrial preparation, 49–50, 153
Auditory brainstem response (ABR)
- cytocochleogram, 275, 280
- data collection, 276
Auditory brainstem response (ABR) (cont.)
DPOAEs, 282
hearing deficits, 281
ototoxicity studies, 273–274

Auditory function
ototoxicity studies (see Ototoxicity studies)
physiology
auditory neurotransmission, 271
cochlea, 269
cochlear anatomy, 270
cytocochleogram, 275
guinea pig ear, anatomy, 269
hearing, 268
organ of Corti, 271
pressure waveform, perilymph, 270

Automated blood sampling and telemetry (ABST) system, 96

B
Bazett’s QT correction, 450

Behavior
assessments
data analysis and interpretation, 90–91
drug-induced cognitive impairment, 104–105
EPA, 86
FOB arose, 86
ICH S7A guidelines, 86
Irwin experimental protocol, 86–90
pharmaceutical/chemical industries, 85
strengths, 91–92
CNS, 84
drug-induced, 85
organism’s, 68
preconvulsive and convulsive behaviors, 94
sleep disruption, 100
traditional behavioral assays, 85
Bevacizumab (Avastin), 423

Biomarkers
blood-borne, 365
channel modulation, 152–156
genomic and proteonomic, 35–36
GI injury of
blood, stool and breath, 312
calprotectin and lactoferrin, 313
CRP, 312
13C sucrose breath test (SBT), 314
diamine oxidase (DAO), 313
fecal miRNA assays, 313
gastrins, 313
HPLC, 312
in preclinical drug development, 314
risk assessment and management, 311
toxicity identification, 311
kidney injury of
albumin, 342–343
β2-microglobulin, 342
chromatin environment/microRNAs, 344
CysC, 342
DIKI biomarkers, 344
exploratory approaches, 344
KIM-1, type I cell membrane glycoprotein, 341–342
TFF1, TFF2 and TFF3, 342
total urinary protein, 343
pharmacodynamic toxicity, 35–36
Biopharmaceuticals (BPs)
abuse and dependency potential, 399
advantages, 387
bispecific antibodies, 388
cardiovascular system, 392–396
characteristics, 386, 387
CNS, 396–397
factors, 389
features, 386
ICH S7A guideline, 398
in vitro safety pharmacology, 392
innovative variations, 386
noninvasive methods, 389, 400
regulatory guidelines, 390–391
respiratory system, 397–398
test species, 391–392
US-FDA, 389

Blood gases
alveolus-pulmonary capillary, 134
and oxygen saturation, 144
PaO2, 144
SaO2, 144

Blood pressure (BP)
anacetrapib, 223
CETP, 222

CVD
estimation, AHA, 225
NCE effects, 225, 226
pathologies, 225
prevalence, 225
risk, 225
secondary hypertension, 225–226
systolic and diastolic BP, 225
dose-dependent changes, 71
drug safety
animal model, clinical trial, 224
arterial, 222
CETP inhibitor, 222–223
increment, 223
mid-1990s, 222
PDGF, 224
therapeutic and NCEs, 223–224
VEGF signalling agents, 224
HDL-C and apolipoprotein A-1, 222–223
off-target evaluation, receptors and enzymes, 72–74
C
Calcium (Ca^{2+}) channels
molecular and pharmacological properties
α-subunits, 173–174
biophysical properties, 174, 175
blocking drugs, 176
genesis of APs, 173
hetero-oligomeric protein complexes, 173
L- and T-type, 174, 175
mammalian isoforms, 174
pacemaker activity, 176
polypeptides, 174
myocyte level, 173
voltage-gated, 173
Calcium-dependent inactivation (CDI), 58
Calcium-induced calcium release (CICR), 58
Cardiac action potential
biophysical and physiological properties, 166
Ca^{2+} channels, 166
coupled myocardial cells, 167
genesis, 166
inward rectifier, 166
K^+ current, repolarisation, 166
Na^+ channels, inactivation, 166
pacemaker cells, 166
shape, 167
ventricular myocyte, phases, 164–166
Cardiac arrhythmia suppression trial (CAST), 54
Cardiac conduction and repolarisation
cardiac channels, 53–54
cardiac delayed-rectifying potassium current (I_{Kr}), 8
dihydropyridines, 60
preclinical safety pharmacology assays, 22
“TQT” study, 28
Cardiac ion channels
blockade assays, 150
calcium (see Calcium (Ca^{2+}) channels)
electrocardiogram (see Electrocardiogram (ECG))
in vitro proarrhythmia assay
in silico methods, 157–159
stem cells and CIPA, 156–157
TQT study, 156
myocardium
bioelectrical properties, 160–163
cell types, 159
myocyte coupling, 159
potassium (see Potassium (K^+) channels)
QT as surrogate biomarker
atrial preparation, 153
coronary-perfused wedge preparation, 155–156
ion channel modulation, 152–153
Langendorff heart, 154–155
Purkinje fibre, 153–154
sodium (see Sodium (Na^+) channels)
voltage-gated (see Voltage-gated ion channels)
Cardiac Safety Research Consortium (CSRC), 27, 28, 34, 38
Cardiovascular system
advantages, 393–394
anaesthetics, 245
BPs, 395
cardiac function, 393
CNS, 132
drug-induced effects, 101
heart rate and ECG, 393
hemodynamic parameters, 393
and lung, 135
QTc prolongation, 394, 396
risk assessment, 392
SM therapeutics, 394, 395
therapeutic target, 394
TQT study/QT warning, 394, 395
Case studies
hERG channel, 33
QT prolongation, 33
CAST. See Cardiac arrhythmia suppression trial (CAST)
Cats
conscious, 247
DSI, 246
HDO tail cuff measurements, 256, 257, 259
CATS (CONT.)

Cats (cont.)
large-scale GLP studies, 244

CBER. See Center for biologics evaluation and research (CBER)

CCALC. See Cross-Company Abuse Liability Consortium (CCALC)

CDER. See Center for drug evaluation and research (CDER)

CDI. See Calcium-dependent inactivation (CDI)

Center for biologics evaluation and research (CBER), 85, 86, 88, 93
Center for drug evaluation and research (CDER), 10, 19, 85, 93

Central nervous system (CNS)
activity, 118
adverse effects, 84 (see also CNS adverse effects)

APP, 74
assessment, 396
BPs, 396
brain tumors, 396
dopamine D2 receptors, 71
“hierarchy of organ systems”, 15
H1 receptors, 51
ICH S7A guidance, 121
molecular agents, 35
non-CNS drugs, 120
off-target evaluation, 72–73
spontaneous locomotor activity, 397

Cetuximab, 423–424
Channel kinetics, 151
Cholesteryl ester transport protein (CETP), 222

CICR. See Calcium-induced calcium release (CICR)

Clinical ECG assessment
drug-induced effects, 453
ER analysis (see Exposure-response (ER) analysis)
oncology drugs, 454–456
potent QT-prolonging drugs, 437, 438
QTc interval, 437
SAD/MAD, 437
TQT study (see Thorough QT/QTc (TQT) study)

Clinical risk profile, torsades de pointes arrhythmia, 59

CNS. See Central nervous system (CNS)

CNS adverse effects
behavioral assays, 84, 85 (see also Behavior)
CDER and CBER, 85
cognitive impairment (see Drug-induced cognitive impairment)
S7A safety pharmacology studies, 85
seizure risk assessment (see Seizure risk assessment)
sleep disruption (see Drug-induced sleep disruption)
torsades de pointes, 84

Cognition
chronic effects, 103
CNS adverse events, 92
in vitro electrophysiology, 106–107
Common marmosets, 245–247, 251, 254

Compliance
and Cgas, 139
GLP, 11, 15–16
and resistance, 141–143
Comprehensive in vitro proarhythmia assay (CiPA), 28, 38–39, 156
Conditioned place preference, 129

Controlled Substance Staff (CSS)
CCALC, 117
and FDA flowchart, 127
pharmaceutical industry, 129
Cross-Company Abuse Liability Consortium (CCALC), 117–118, 129

CSRC. See Cardiac Safety Research Consortium (CSRC)

CSS. See Controlled Substance Staff (CSS)

Cynomolgus, 245–247, 250, 253, 254
Cytocochleogram
albino and pigmented guinea pigs, 278
chinchillas, 278
drug distribution and metabolism, 281
ototoxicity studies, 275–276

D

Delayed afterdepolarisations (DADs), 195–196
Diabetes, 244, 262, 445

DIKI. See Drug-induced kidney injury (DIKI)

Discriminative stimulus, 125

Distortion product otoacoustic emissions (DPOAEs), 281–282

Dogs
anesthetised, 247
beagle, 245
cardiac lesions, 357
cardiovascular parameters, 244
conscious non-restrained, 140
convulsions, 94
echocardiography, 364
EEG, 101
gastric and intestinal function, humans, 368
HDO curve, 249, 255
HSE, 246
lung structures, 135
neurobehavioural systems, 367
Penh, 143
PR and QRS measures, 56
primates, 138, 139
respiratory assessment, 141
respiratory parameters, 368
safety pharmacology assessments, 362–363
tail-cuff blood pressure method, 365
ventilatory changes, 136
Drug dependence, 35, 117, 123

Drug development
clinical development and post-approval, 4
effects drugs, 244
eventual approval of lorcaserin, 51
pharmaceutical industry, 116
safety pharmacology
BPS, 71
ethics committees, 78
“high-impact targets”, 70–71
IND-enabling stage, 76–78
IUPHAR, 71
low-impact targets, 71
neurotransmitter systems, 71
“off-target” interactions, 70
strategy, 75

Drug discovery. See also Drug development
anatomy and physiology
GI organs, 296–298
physiology, 298–301
antihistamines (see Antihistamines)
characterization, 68
“design-make-test-analyze” cycle, 32
DNA transcription, 68
drug-induced gastrointestinal injury, 293–295
drug toxicity, 67
efficient drug development, 66
“frontloading” studies, 67–68
GLP requirement, 67
guideline recommendations, 302
pharmacological responses, 68
principles of safety pharmacology, 5
putative ligand screens, 68–69
safety studies, 49
SP single-dose and repeat dose tests, 301
target-directed effect assessment, 69–70
toxicology, 66

TPP, 68
Drug-induced cognitive impairment
acute effects category, 103
behavioral assessment, 104–105
chemotherapy patients, 103
comprehensive approach, 107
evoked and event-related potentials, 105–106
GABAergic system, 103
in vitro electrophysiology and cognition, 106–107
mechanisms, 103
practice, 103

Drug-induced kidney injury (DIKI)
ADRs, 325
biomarker, 326
drug classes, renal side effects, 326
preclinical development, 325
validation strategy, 344–345

Drug-induced sleep disruption
behavioral approaches, 100
in humans, 100
in vitro sleep and sedation assessment, 102–103
phase I clinical trial, 99
REM sleep, 99
rodent/non-rodent species, 99–100
sleep EEG, 101–102
slow-wave stage, 99

Drug safety
dehydration and non-specific toxicological effects, 239
drug-induced CNS effects, 85
haemodynamic safety profile, oncology agents, 224
non-clinical assay, 154
preclinical screening models, 224
rabbit and guinea pig hearts, 155
Tdp arrhythmias, 181

E
Early after depolarization (EAD), 58, 195
ECVAM. See European Centre for the Validation of Alternative Methods (ECVAM)
EEG. See Electroencephalogram (EEG)
EFPIA. See European Federation of the Pharmaceutical Industry Association (EFPIA)
Electrocardiogram (ECG)  
activation and inactivation properties, 191  
AV node (AVN), 191  
changes, myocardium, 193–195  
components, 191  
composition, 192  
DADs, 195–196  
depolarisation, 191–192  
diseasediagnoses, 191  
diversity, ion channels, 193  
EADs, 195  
electrical activity, 191  
generation, electrical impulses, 191  
observation, variations, 193  
PR interval, 192  
P-wave, 191  
re-entrant arrhythmia pathways, 196  
segments, 192  
sino-atrial node (SAN), 191  

Electroencephalogram (EEG)  
abnormalities, 95  
ABST system, 96  
drug-induced changes, 95  
event-related potential (ERP) techniques, 104  
in vitro brain slices, 102  
rhythm activity, 102  
seizure detection, 95–96  
sleep studies, 101–102  
spectral changes, 96  

EMEA. See European Medicines Agency (EMEA)  

Emesis  
in vivo models, 307–308  
PDE4 inhibition, 74  
in silico approaches, 308  

ER analysis. See Exposure-response (ER) analysis  

European Centre for the Validation of Alternative Methods (ECVAM), 27  
European Federation of the Pharmaceutical Industry Association (EFPIA), 10, 18, 19, 22–23  
European Medicines Agency (EMEA), 9, 20, 25, 127  

Exposure-response (ER) analysis  
early SAD/MAD studies, 456, 457  
vs. E14 time-matched analyses, 459–460  
pharmacological positive control, 460–461  
QT data, 456  
role of, 457–459  
TQT study, 457  

FDA. See United States Food and Drug Administration (FDA)  
Field potential, 107  
Functional observational battery (FOB), 84, 86, 92, 94, 104  
behavioral assays, 85  
behavioural tests, 358  
CNS function, 396  
Irwin experimental protocol, 86, 94  
neurobehavioural assessment, 366  
rodent toxicology study, 372  

Gastric secretion  
acute model, 307  
fistula models, 307  
GI function, 301  
in vitro models, 306–307  
in vivo models, 307  
pharmacological studies on acid secretion, 306  
Gastrointestinal stromal tumor (GIST), 224, 455  
Gastrointestinal (GI) system  
asorption  

cell culture-based permeability screening models, 309  
in vitro techniques, 309  
in vivo techniques, 310  
gastric emptying and intestinal motility  
in vitro models, 303–304  
in vivo models, 305–306  
in silico organ modeling, 304–305  
gastric secretion  
in vitro models, 306–307  
in vivo models, 307  
gut–brain axis, 297–298  
gastrointestinal stromal tumor (GIST)  
gerded food and xenobiotics, 298  
intestinal permeability and absorption, 301  
motility and transit, 298–300  
nausea and emesis, 307–308  
neural and hormonal reflexes, 300  
translational, humans, 311  
GIST. See Gastrointestinal stromal tumor (GIST)  
Good laboratory practice (GLP)  
compliance, 15–16  
and FDA requirement, 252  
ICH S7A, 13  
pharmaceutical industry, 32  
preclinical testing centers, 36
regulatory studies, 11
Guinea pig papillary muscle action potential assay
contractile tissue and movements, 208
IKr assay, 208
IKr IC50/EC10 values, 218
non-clinical models, 218
preparation, 208
QT PRODACT (see QT interval prolongation: project for database construction (QT PRODACT))
risk assessment, 219
sensitivity, 218–219
size, 208

H
Haemodynamics assessment
BP (see Blood pressure (BP))
conduct of
  behavioural interactions, 236
  Circadian cycles, cardiovascular animal models, 234–235
data quality and review, 234, 237
dosing systems, 236
  heart rate data, cynomolgus monkeys, 235, 236
  interferences, environmental factors, 235–236
  intravenous injectable drug products, 236
  volumes, dose rate and physicochemical characteristics, 236–237
features, vascular system (see Vascular system)
  study design and statistics (see Study design and statistics, safety pharmacology)
Hazard identification vs. risk assessment in exploratory safety studies, 49–50
hERG channel. See Human ether-a-go-go related gene (hERG) channel
High-definition oscillometry (HDO)
  accuracy and reliability, 247–251
  conventional non-invasive systems, 245–246
dogs and rabbits, 246
FDA requirements, 244, 252
and GLP, 252
limitations, 262
pulse rates, 246–247
SP and Tox studies (see Safety pharmacology (SP))
vascular resistance, 262
High-precision QT measurement (HPQT), 453, 458, 459
Hippocampus, 97, 105, 106
Hodgkin–Huxley equations, 163–164
Human ether-a-go-go related gene (hERG) channel
  blocking drugs, 59
  chemical-hERG channel interactions, 33
cytochrome P450 (CYP) screening, 78–79
drug-hERG channel interactions, 33
  potassium channel, 71
QT prolongation, 33

I
ICH. See International conference on harmonization (ICH)
ICH E14
  EWG meeting, 23
  implementation, 24
  IWG, 27
  nonclinical data, 24
  positive control agent, 26–27
ICH S9, 224, 391, 407, 408, 427
ICH S7A
  adoption, 11–13
  bioassays, 32–33
  chronology, 14
  description, 85
  EWG, 8, 14–15
  Expert Working Group members, 10
guideline, 13
guidelines, 93
and ICH S7B, 25
  in vivo assays, 135–136
  lung anatomy and physiology, 133–135
  mechanisms, 33–34
  physiological homeostatic systems, 145
  plethysmography (see Plethysmography)
  preclinical GLP testing centers and scientists, 36
  regulations, 34–35
  respiratory safety pharmacology studies, 132–133
  scientists, 34
  in silico model, 34
  translation, 35–36
  ventilatory function, 137
ICH S7B
  clinical guidance document, 21
  CPMP, 20
ICH S7B (cont.)
draft S7B guidance, 21
ey early events, 20–22
events associated, 22–25
events leading, 25–26
Expert Working Group members, 19
and ICH S7A, 11, 13, 18
ICH Steering Committee, 21
TDP, 20
the US FDA parties, 21
Imatinib, 416–417
Inactivation
ECG, 191
gate particle, sodium channel, 167–169,
171, 172, 174, 175
HERG block, 189
K+ channels, 178, 182, 184
L-type calcium current, 158
Na+ channel, 164, 166
In silico models, 159, 194
International conference on harmonization
(ICH)
repeat-dose toxicity studies, 396
safety pharmacology assessment, 390
S7A guideline, 398
S6(R1) guideline, 386, 391
International Life Sciences Institute, Health
and Environmental Sciences
Institute (ILSI-HESI), 22, 23
International Union of Basic and Clinical
Pharmacology (IUPHAR), 71
In vitro safety pharmacology profile, 392
Inward rectifier (K\text{ir}/I_{K1})
functional and pharmacological properties
A-H and H-V cardiac ECG, 190
APD reduction, 190
cellular repolarisation, 189
G-proteins, 190
ligand-gated currents, I_{KATP} and I_{KACk},
189
QT interval, rabbit heart, 189
regulation, 190
resting membrane potential, 188–189
sulfonylurea drugs, 189–190
terikalant, 189
T-wave morphology, 189
molecular genetics, 188
resting membrane potential, 187
\alpha-subunits, 188
Irwin
experimental protocol, 86–90
FOB, 94

J
Japan Association of Contract Laboratories for
Safety Evaluation (JACL), 23
Japanese Safety Pharmacology Society (JSPS),
23, 31

K
Kidney
blood pressure regulation, 333
collecting ducts: excretion unit, 330
description, 327
diuretic role, 333
fluid and electrolyte balance, 347
glomerular and hemodynamic function, 347
glomerular filtration, 330–331
gross structure, 327
juxtaglomerular apparatus, 330
nephron
and qualified DIKI biomarker, 327, 329
renal corpuscle, filtering unit, 327
renal tubule, reabsorption unit, 329–330
tubular reabsorption and secretion,
331–332
unipyramidal, multilobar kidney section,
327, 328
vascularization, 330

L
Langendorff isolated heart, 154–156
Large-molecule anticancer agents
ADCs, 418
anticancer therapeutics, monoclonal
antibody, 418–421
Brentuximab vedotin (Adcetris), 418
ipilimumab (Yervoy), 418
monoclonal antibodies, 422–424
vs. small molecule pharmaceuticals,
407–409
Loop diuretics, ototoxicity studies, 283–284

M
Metabolic
blood pressure parameters, 251
diabetes, 262
and hematological changes, 76
Minipig, 133
left ventricular function, 364
repeatdose toxicology studies, 362–363
Monkey, 136, 141, 143, 207, 211
cardiac lesions, 357
cynomolgus, 230, 232, 235, 247, 251
echocardiography, 364
HDO, 365
safety pharmacology assessments, 362–363
Monoclonal antibodies
bevacizumab (Avastin), 423
cetuximab and panitumumab, 423–424
trastuzumab (Herceptin), 422–423
Motility
and GI (see Gastrointestinal (GI) system)
nearal and hormonal reflexes, 300
outer hair cell, 281
Mouse
EEG sleep studies, 101
Jervell and Lange-Nielsen syndrome, 185
ototoxicity studies, 276
safety pharmacology assessments, 362–363
seizure detection, 95
Myocardial cell types and myocyte coupling, 159
Myocardium
bioelectrical properties
capacitance, 160
cardiac AP, 160
circuit elements, 160
conductor, 160
drug–ion channel interactions, 160
electric current, 160
ionic solutions, 160
voltage, 160
cell types, 159
Myocyte coupling in heart, 159
N
Nausea
drug effects, GI function, 302
in vivo models, 307–308
phase I clinical trials, 308
in silico approaches, 308
Nernst equation
assumption, electric field, 161
calculation, 161
equivalent circuit model, 162–163
GHK voltage equation, 161–162
intracellular K⁺ ions, 161
resting membrane potential, 160, 161
transmembrane potential, 161
NIBP monitors, 246
Nonclinical testing
animal species, 134
clinical chemistry endpoints, 76
delayed ventricular repolarization, 19–20
ICH safety guidances, 15
M3(R2) nonclinical safety studies, 85
Noninvasive telemetry
ambulatory tail-cuff methods, 365
safety pharmacology assessments, 361–363
toxicology studies, 361
O
Off-target
cardiovascular safety assays, 49
common receptors and enzymes, 72–73
hERG channel, 79
5HT-2B receptors, 51
pharmacologic activity, 50
safety pharmacology studies, 66–67
On-target
adverse effects, 48
pharmacology, 50
safety pharmacology studies, 66–67
tissue-organ distribution, 70
Oscillometry, airway, 143
Otic microscopy, 274–275, 281
Ootoxicity studies
ABR, 273–274
aminoglycoside antibiotics, 284
cytocochleogram, 275–276
design, 279–281
DPOAEs, 281–282
FDA, 272
loop diuretics, 283–284
middle ear exposure, 272–273
otic microscopy, 274–275
platinum-based chemotherapeutics, 284–285
salicylates, 283
semiquantitative hair cell assessments, 282–283
spiral ganglion evaluations, 282
Oxygen saturation, 132, 144
P
Panitumumab, 423–424
Papillary muscle action potential assay
gastrointestinal prokinetic agent cisapride, 206
guinea pig (see Guinea pig papillary muscle action)
ICHST7B guidance, 206–207
IKr channel, 207
Papillary muscle action potential assay (cont.)
  TdP liability, 206
Pentylenetetrazol (PTZ), 94–95
Peripheral nervous system, 86
Platinum-based chemotherapeutics, ototoxicity studies, 284–285
Plethysmography
  airway oscillometry, 143
  blood gases and oxygen saturation, 144
  plethysmograph (restrained), 137–139
  plethysmograph (unrestrained), 139–140
  pneumotachograph, 137
  resistance/compliance, 141–143
  RIP, 140–141
Pneumotachograph, 137, 140
Potassium (K+) channels
  diversity, voltage-gated
    amiodarone, 176
    blockade, 181
    cardiac tissue, 180
    CAST trials, 176
    functional properties, 178
    genomes, 177
    heterogeneous, 176
    inward rectifier, 180
    ion channel conductance, 179
    mammalian, 176–177
    molecular correlation, 177, 179
    molecular structures, 177, 178
    myocardial cell resting potential, 181
    NCEs, 181
    nucleotide polymorphisms, 180–181
    primary amino acid sequence, 177, 178
    regulate cell function, 176
    repolarisation, 178–179, 181
    sensitivity, 181
    α-subunits function, 177–178
  TdP arrhythmias, 181
  inward rectifier (K_1/K_{11})
    functional and pharmacological properties, 188–190
    molecular genetics, 188
    resting membrane potential, 187
    α-subunits, 188
  voltage-dependent
    functional and pharmacological properties, 183–187
    molecular genetics, I_{to} and I_{K} channels, 181–183
Pro-convulsant assay, 94–95
PTZ. See Pentylenetetrazol (PTZ)
Pulse transit time (PTT), 259–262
Pulse wave analysis (PWA), 257, 259

Purkinje fibre
  canine, 212
dog, 209, 210, 213
His-Purkinje fibres, 159
isolation, 153–154
K+ channel, 186
pacemaker cells, nodal tissues, 166
rabbit, 153

Q
QT interval prolongation: project for database construction (QT PRODACT), 22–23
anaesthetised dog, 211
ciprofloxacin, 210
concentrations, 218
conscious dog and cynomolagus monkey, 211
evaluation, predictive values, 208–209, 212
human, 209
human free ETPC in vitro positive concentration, 212, 214–215
positive/negative in vitro results, 212–213, 216–217
JPMA and JACL, 208
NCE, 211–212
non-clinical QT assays, 212
outcomes, 213, 218
preclinical concentration exposure, 218
predictive biomarkers, 209–210
sensitivity and specificity, 209–210

R
RA. See Rheumatoid arthritis (RA)
Rat
  airway responsiveness, 140
  body temperature, 370, 371
  cardiac delayed-rectifying potassium current, 8
  cardiovascular assessments, drugs, 8
  HDO measurements, 255
  neurobehavioural systems, 367
  nonclinical safety program, 416
  PAK4-GI model, 314
  respiratory parameters, 367
  safety pharmacology assessments, 362–363
  sensor matrix, 368
  Tff3 mRNA, 342
  toxicology studies, 343
  unrestrained telemetry model, 224
Receptor tyrosine kinase (RTK), 455
Reduction, refinement and replacement (3Rs) benefit, 16, 308, 354, 396–397, 409
Repeat-dose toxicity studies. See also SP endpoints
drug classes, 358
emphasis and operational paradigms, 358, 360
histopathological examination, 355
in-life measurements and blood sampling, 355, 356
phase I clinical trials, 354
regulatory drivers, 357–358
regulatory toxicology studies, 355
renal/urinary measurements, 345
safety pharmacology assessments, 358
scientific drivers, 356–357
Resistance
airflow, 135, 136, 143
functional endpoints, 142
Penh and respiratory, 143
peripheral vascular, 223
pneumotachograph, 137
pulmonary, measurement, 398
rodents and non-rodents, spontaneous breathing, 141
unrestrained WBP, 142
Respiratory inductance plethysmography (RIP), 140–141
Respiratory rate, 132, 135, 138, 143
Respiratory system, 76–77, 133, 135, 136, 397–398
Rheumatoid arthritis (RA), 454
RIP. See Respiratory inductance plethysmography (RIP)
Risk assessment
and cardiovascular, 372
CNS, 92
vs. hazard identification, exploratory safety studies, 49–50
MTD/DRF studies, 372
NCE, 442
QTc effect, 458
seizure (see Seizure risk assessment)
Tdp, 152
RTK. See Receptor tyrosine kinase (RTK)
Ryanodine receptors (RYR2), 58
bacterial-and mammalian cell-derived oligonucleotides, 391
biopharmaceutical products, 357
and BPs, 393
CNS adverse effects, 85
new drugs, 7
nonclinical, 389, 390, 406, 424
ototoxicity, 279
pharmaceutical industry, 107
renal slice technology, 339
rodent and non-rodent species, 99–100
Safety pharmacology (SP)
anatomy and physiology, 327–333
auditory function (see Auditory function)
DIKI (see Drug-induced kidney injury (DIKI)) evaluation, BPs (see Biopharmaceuticals (BPs))
in vitro models, 338–340
in vivo mammalian models
glomerular function, 336
hemodynamic function, 337–338
tubular function, 335–337
in vivo non-mammalian models, 338
isolated perfused kidney preparations, 339
non-clinical research, HDO
conduct of study, 253
cuff, 254–256
data analysis, 255–259
pulse transit time measurement, 259–262
renal slice technology, 339
renal/urinary measurements, 345
repeat-dose toxicity studies, 345, 346
in silico models, 340–341
training, 253
urinary biomarkers, 334
urine and plasma analysis, 346
Seizure risk assessment
CDER and CBER, 93
convulsion-like motor behaviors, 93
drug-induced seizure, 93
EEG, 95–96
GABA neurotransmission, 93
ICH S7A guidelines, 93
in vitro electrophysiology, 96–99
Irwin/FOB, 94
non-blood-brain-barrier-penetrating drugs, 93
PTZ pro-convulsant assay, 94–95
Selective serotonin reuptake inhibitors (SSRIs), 117, 120
Self-administration, 119, 120, 122, 125–126, 129

S
SAD/MAD studies. See Single-ascending/multiple-ascending dose (SAD/MAD) studies
Safety assessment
Single-ascending/multiple-ascending dose (SAD/MAD) studies
“early QT assessment”, 437
ER models, 457
E14 time-matched approach, 460
TQT study, 460, 461
Small molecule anticancer agents
anthracyclines, 415
cardiovascular toxicities, 410
imatinib, 416–417
vs. large-molecule biopharmaceuticals, 407–409
rapidly dividing cancer cells, 409
sunitinib (Sutent), 417
tyrosine kinase inhibitors, 410–416
Sodium (Na+) channels
depolarisation, 167
molecular and pharmacological properties
activation/gating, 169
cryo-electron microscopic images, 169
depolarisation, 171
drugs, 169
α-helical intracellular linker, DIII–DIV, 171–172
heterotrimeric complexes, 169
inactivation gate, 171
ionic conductance, 171
local anaesthetic action, nerves, 172
mammalian voltage-gated, 169, 170
outward gating charge, 168–169
persistent/late, 172–173
pre-depolarising level, 173
protein, 169
resting membrane potentials, 171
safety, 172
S6 transmembrane-spanning region, 172
structure, 168
subtupes, voltage-gated, 169, 170
voltage sensor, 168
Xenopus laevis oocytes, 170, 171
permeability changes, 167
squid giant axon, 167
transmembrane movement, 167
Sodium current, 54, 56–57
Species selection, ototoxicity studies
albino and pigmented guinea pigs, 278
chinchillas, 278–279
large animals, safety assessments, 279
mouse, 277
preclinical abuse potential studies, 121–122
rat, 277–278
SP endpoints
application methods, 361–363
organ functions
body temperature, metabolic functions, 370–372
cardiovascular system, 363–365
gastrointestinal system, 368–369
nervous system, 365–367
renal system, 369–370
respiratory system, 367–368
QT interval, 361
routine and Ad Hoc Inclusion, 372–373
SSRIs. See Selective serotonin reuptake inhibitors (SSRIs)

Stem cells
and CIPA, 156–157
and embryonic, 28
hematopoietic stem cell transplantation, 312
high-throughput screening (HTS) methods, 157
human adult, 34
in vitro proarhythmia assay, 156
pluripotent, 28, 197

Study design and statistics, safety pharmacology
anaesthesia usage, 232–233
control group, 233–234
EKG and blood pressure values
beagle dogs, 229, 231
cynomolgus monkeys, 229, 230
rhesus monkeys, 229, 230
Sprague-Dawley rats, 229, 231
haemodynamic data interpretation
cautions, 238
dopamine administration, 238
drug-induced effects, 237–238
drug-induced vasodilation, 239
neurological stimulation, 238–239
parameters, 238
qualitative evaluation, 238
haemodynamic effects, 232
interpretation, 237–239
minimum detectable difference (MDD), 228–229
power analysis, 228
rodents, 233
sprague-dawley rats, 229, 231
sunitinib (Sutent), 417

T

Thorough QT/QTc (TQT) study
crossover-designed TQT studies, 445–446
design considerations, 442–445
early QT assessment, 461
ECG assessment, 451–453
E14 guidance, 438
ICH, 438
ICH E14 guidance, 461–432
and interval measurements, 451–453
IRT and sponsors, 446
IRT serves, 438
moxifloxacin, 446
negative TQT study, 446, 447
non-inferiority approach, 446
parallel-designed TQT 308 studies, 446
peak plasma concentration, 448
placebo-adjusted change-from-baseline QTc, 445
published in 2012, 438–441
PubMed search, 438
QT interval, heart rate changes, 450–451
sample size, 448–450
timing of, 442
Tidal volume, 132, 135, 136, 138, 139
Torsades de pointes (TdP)
antagonist, 187
arrhythmias and sudden cardiac death, 187
biomarkers, 209
description, 152
drug-induced, 152
idiopathic LQTS, 189
liability, 152, 155
QT prolongation, 209
TQT study, 156
Toxicology (Tox) studies. See Safety pharmacology (SP)
TQT study. See Thorough QT/QTc (TQT) study
Translational medicine, 65
Trastuzumab (Herceptin), 422–423
Tyrosine kinases (TKs) inhibitors, 410–416
U
The United States Environmental Protection Agency (EPA), 86
United States Food and Drug Administration (FDA), 9, 19, 21, 24, 25, 35, 117, 121, 252
V
Vascular system
arterial and venous components, 227–228
drug effects, 226
human, 226
physiological function, 226
regions, blood vessels, 226
tunic adventitia, 226–227
tunica intima, 226
tunica media, 226
vasa vasorum, 227
Vaughan Williams classification, 55
Voltage-gated ion channels
causes, resting membrane potential, 163
electrical activity, cardiac muscle, 163
genesis of cardiac AP, 164–167
Hodgkin-Huxley equations, 163–164
potassium (see Potassium (K⁺) channels)