Index

Abderhalden, Emil, 101
absolute oral bioavailability, 37
acquired copper deficiency, 202–203
active tubular secretion, 43
acute hereditary tyrosinemia, 115
adenosine triphosphate (ATP)
ATP7A, 203
distal hereditary motor neuropathy, 206–207
Menkes disease, 203
OHS, 206
nephropathic cystinosis, 103
agonists, 46
AKU. See alkaptonuria
AL deficiency. See argininosuccinate lyase deficiency
ALA. See aminolevulinic acid
alkaptonuria (AKU), 114, 118–121
cardiac involvement, 119–120
clinical presentation, 119
arthritis as, 119
diagnosis, 121
dietary therapies, 120
genetic factors, 121
HGA, 118–119
HPPD inhibition, 124
incidence rates, 118–119
nitrosamine therapy, 125
future developments, 130
side effects, 127
tyrosine levels, 129–130
pathophysiology, 121
renal transplants, 120
vitamin therapy, 120
Alpha-1 Foundation, 21
ambrisentan, 11
amino acylation products, 142–144
aminolevulinic acid (ALA), 117–118
Ammonul, 144–145
alternative therapy uses, 149
dosage, 146
overdose, 147
FDA status, 147
HIP, 144–145
long-term therapy results, 147–149
side effects, 147
antagonists, 46
apomorphine, 12
apoptosis, in cysteamine treatment, for nephropathic cystinosis, 103
apparent first-order kinetics, 40–41
apparent volume of distribution, 39
argininosuccinate lyase (AL) deficiency, 135
argininosuccinate synthetase (AS) deficiency, 135
AS deficiency. See argininosuccinate synthetase deficiency
ATP. See adenosine triphosphate
ATP7A, 203
distal hereditary motor neuropathy, 206–207
Menkes disease, 203
OHS, 206
basal ganglion diseases, 60
biotin therapy, 66
inheritance factors, 63
Bench-To-Bedside Research Program, 25
betaine, in homocystinuria treatment, 176–179
clinical evidence of, 176–177
development, 176–177
dosage, 177–178
FDA status, 179
future developments, 179
for remethylation disorders, 177
cblC disorder, 177
MTHFR, 177
side effects, 178–179
case studies, 178–179
Bickel, Horst, 76
bioavailability, of drugs, 37–38
absolute oral, 37
bioequivalence and, 38
relative, 37
studies, 37
bioequivalence, 38
FDA guidelines for, 38
biomarkers, in drug development, 49–50
Biopten. See sapropterin dihydrochloride
biotin, 64–66
biosynthetic pathways, 64
cGMP activity enhancement and, 62
dosing, 65
FDA recommendations, 65–66
gene transcription regulation, 61–62
metabolism of, responsive disorders and, 58–59
preparation for, 64–65
side effects, 65
structure, 64
UV light and, 64
biotin therapy, 66
basal ganglion diseases, 66
biotinidase deficiency, 66
HCS deficiency, 66
biotinidase deficiency, 60
biotin therapy, 66
inheritance factors, 63
biotin-responsive disorders, 57–64
basal ganglion diseases, 60
inheritance factors, 63
biotin metabolism, 58–59
biotin therapy, 66
biotinidase deficiency, 60
inheritance factors, 63
in children, 60–61
clinical presentation, 59–60
COA deficiency, 57
HCS deficiency, 57
clinical presentation, 59
inheritance factors, 63
hearing loss from, 61
immunological abnormalities, 61
inheritance factors, 62–64
MCD, 57
pathophysiology, 60–62
in brain tissue, 61
causative factors, 60
PCC deficiency, 57
screening programs, 62
symptoms, 59
bone marrow transplantation, for
lysosomal storage disorders, 156
bosentan, 11
Buphenyl. See sodium phenylbutyrate
carbamoyl phosphate synthetase (CPS)
deficiency, 135
cardiomyopathy, HT and, 129
carnitine deficiency disorders
L-carnitine therapy, 86–87
mortality rates, 94–95
for primary carnitine deficiency, 90–92
for secondary carnitine deficiency, 94–96
primary, 88–92
case reports, 89–90
definition, 88
incidence rate, 88–89
L-carnitine therapy for, 90–92
in muscles, 89
from OCTN2 deficiency, 90–92
secondary, 88, 92–96
clinical presentation, 92–94
clinical study history, 95
L-carnitine therapy for, 94–96
pathophysiology, 92
screening, 95
symptoms, 92
Carnitor, 94
chIC disorder, 175
betaine therapy, 177
CCO. See cytochrome c oxidase
CDME. See cystine dimethyl ester
CETT. See Collaboration, Education and
Test Translation program
cGMP. See cyclic guanosine
monophosphate
chemical chaperones, 156, 168
Fabry disease, 168
Gaucher disease, 167–168
children. See also neonates, Menkes disease
and
biotin-responsive disorders, 60–61
pharmacokinetic variables in, 51–52
Wilson disease in, zinc therapy for, 195
chitotriosidase, 165
chronic hereditary tyrosinemia, 115–116
chronic hyperammonemia, 138–139
clearance, of drugs, 39–40
elimination, 39–40
hepatic, mechanisms and determinants of, 40
blood flow and, 40
protein binding and, 40
intercompartmental, 39
renal, mechanisms and determinants of, 40
Fick principle, 40
GFR and, 40
Clinical and Translational Science Award
(CTSA), 25
COA. See β-methylcrotonyl-coenzyme A
CoA. See coenzyme A
cobalamin, 72–73
coenzymes, 69
deficiency, 72
mechanism of action, 73
metabolism, 69
as MMA treatment therapy, 70, 73
clinical effects, 73
dosage, 73
future developments, 74
natural forms, 69
pharmaceutical formulations, 72–73
Index

processing defects, 71–72
Cb1A, 71
Cb1B, 71
Cb1C, 71–72
Cb1D, 72
Cb1F, 72
Cockcroft-Gault equation, 50
coenzyme A (CoA), 86–87
Collaboration, Education and Test Translation (CETT) program, 22–23

genetic mutation information collection, 23

goals, 22

copper, as trace element, 202

copper chloride, 208

copper deficiency syndromes, 202–211
acquired, 202–203
distal hereditary motor neuropathy, 206–207
inherited, 203–207
Menkes disease, 202–205
animal models, 207
ATP7A, 203
brain pathology, 205
CCO activity, 205
clinical features, 204–205
clinical presentation, 203–204
diagnosis, 204
during neonatal period, 205
PAM deficiency, 204–205
phenotypes, 204
X-linked, 203
OHS, 206
molecular basis, 206
small copper complexes, in treatment therapies, 207–209
transport mechanisms to central nervous system, 209–210

copper gluconate, 207–209
copper histidine, 208
copper sulfate, 208
CPS deficiency. See carbamoyl phosphate synthetase deficiency
CTSA. See Clinical and Translational Science Award
cyclic guanosine monophosphate (cGMP), 62
CYP enzymes, 41–42
racial distribution, 42
Cystagon. See cysteamine
cysteamine, 104–106
cystine storage, 105
hygroscopic nature, 104
structure, 104
as treatment, for nephropathic cystinosis, 101–106, 111
apoptosis, 103
dosage, 107–108
FDA status, 109
future applications, 110–111
mutation inheritance, 104
renal failure from, 109
results, 109–110
side effects, 108
Stevens-Johnson syndrome from, 108
vomiting, 108
Cystic Fibrosis Foundation, 20–21

cystine dimethyl ester (CDME), 103
cystinosis. See nephropathic cystinosis
cystinuria, 101
cytochrome c oxidase (CCO), 205
distal hereditary motor neuropathy, 206–207
distribution, of drugs, 38–39
VD, 38–39
apparent, 39
drug absorption, 37
drug development, 47–50. See also pharmacodynamics;
pharmacokinetics
biomarkers, 49–50
dose-escalation schemes, 48–49
Fibonacci, 48
PGDE, 48–49
exploratory trials, with nonpharmacological doses, 49
FIH dosing estimates, 48
drug metabolism, 40–41
clinical approaches to, 41
enzymes for, 42
CYP, 41–42
kinetics, 40–41
apparent first-order, 40–41
saturable of Michaelis-Menten type, 41
reactions, 41
hepatic cells, 41
Phase I, 41
transport, 41–42
CYP enzymes, 41–42
genomics, 41–42
drug-dosing, pharmacokinetic principles, 43–45
continuous infusion, 44
design criteria, 45
multiple regimens, 44–45
plateau principle, 43–44
single regimens, 44
drug-receptor interactions, 46
agonists, 46
antagonists, 46
dose-response relationship, 46–47
drug efficacy, 46
elimination clearance, 39–40
EMEA. See European Medicines Agency
enzyme replacement therapy, for lysosomal storage disorders, 155–156, 168
epoprostenol, 12
European Medicines Agency (EMEA), 6
for neglected diseases, 30

FAA. See fumarylacetoacetate

Fabry disease, 155
for OTT, 30

chemical chaperones, 168
Gallin, John, 24

combination therapy for, 168
GARD. See Gaining Access to Research

enzyme replacement therapy, 155–156,
Discoveries

168
Gaucher disease, 155

synthesis inhibition therapy, 156–157
alternative small molecular entities,

Fanconi syndrome, 101, 109
165–168

MAA as factor, 117
miglustat, 165–168

Faucett, Andrew, 23
chitotriosidase as biomarker, 165

FDA. See Food and Drug Administration
combination therapy for, 168

FDAAA. See Food and Drug Administration
enzyme replacement therapy, 155–156,
Amendments Act

168
Genz-112638 in treatment therapy, 166

FDCA. See Federal Food, Drug, and
miglustat in treatment therapy, 166
Cosmetics Act
Phase II studies, 164

Federal Food, Drug, and Cosmetics Act
synthesis inhibition therapy, 156–157
(FDCA) (U.S.), 3
gene therapy, for lysosomal storage

Fibonacci scheme, 48
disorders, 156, 168
treatment, 79

Fick principle, 40
genetic disorders, orphan drugs for
first-in-human dose
clinical development of, 14
first-in-human (FIH) dose, 48
nonbiological, FDA approval of, 9, 12–15

Folling, Asbjorn, 76
Genz-112638, 163–165

Food and Drug Administration (FDA)
Gaucher disease therapy, 166
Amonul status, 147
miglustat v., as treatment therapy, 167

betaine status, in homocystinuria
GFR. See glomerular filtration rate
treatment, 179
glomerular filtration rate (GFR), 40
bioequivalence guidelines, 38
drug elimination and, 43
biotin recommendations, 65–66
glucosylceramide synthase inhibition,
cysteamine treatment, status under, 109
159–160
NDAs, 5, 12
glutamine hypothesis, 138
phases, 12
MAPK, 138
nitisinone status, 122
MPT, 138
nonbiological orphan drugs under
glutathione (GSH), 103–104
clinical studies, 13–15
glycol phenylbutyrate, 150
for genetic disorders, 9, 12–15
Groft, Stephen, xii
under Orphan Drug Act, 8–15
GSH. See glutathione
Orphan Drug Act under, 3–4
Haffner, Marlene, xii
marketing exclusivity, 4, 7–8
half-life, of drugs, 39
OOPD, 4
Hart, Suzanne, 23
written recommendations for
HCS. See holocarboxylase synthetase
investigation, 5
HDF. See hereditary tyrosinemia (HT)
Prescription Drug User Free Act under, 5
age of presentation as prognosis factor,
NDAs, 5
116
saroppterin dihydrochloride approval,
chronic, 115–116
80
dosage, 124
TM therapy for Wilson disease, status of,
newborn-screening programs, 117
197
genetic factors, 118
Food and Drug Administration
HPPD inhibition, 123–124
Amendments Act (FDAAA), 5–6
incidence rates, 115
Orphan Drug Act under, 8, 15
newborn-screening programs, 117
nitisinone therapy, 124–125, 127–130
administration, 124–125
administration, 124–125
cardiomyopathy complications, 129
in children, 127
dosage, 124
future developments, 130

Gahl, William, 23–24
Gaining Access to Research Discoveries
(GARD), 29–30
functions, 29
Internet applications, 29
Index

growth and development complications, 129
hepatic complications, 127–128
neurologic complications, 128
renal tubular dysfunction, 128
side effects, 125–127
tyrosine levels, 129
pathophysiology, 117–118
ALA, 117–118
FAA, 117
MAA, 117
SA, 117
screening for, 116
in diagnosis, in newborns, 117
HGA. See homogentisic acid
HIP nitrogen. See hippurate nitrogen
hippurate (HIP) nitrogen, 140
Ammonul, 144–145
holocarboxylase synthetase (HCS) deficiency, 57
biotin therapy, 66
clinical presentation, 59
inheritance factors, 62–63
homocystinurias, 173–179
betaine treatment, 176–179
clinical evidence of, 176–177
development, 176–177
dosage, 177–178
FDA status, 179
future developments, 179
remethylation disorders, 177
for remethylation disorders, 177
side effects, 178–179
methionine metabolic pathways, 176–177
pathogenesis, 174–175
presymptomatic therapy, 175
remethylation disorders, 175–176
betaine therapy, 177
chCIC disorder, 175
MTHFR deficiency, 176
transsulfuration disorder, 174–175
homogentisic acid (HGA), 118–119
HPPD. See hydroxyphenylpyruvate dioxygenase
HT. See hereditary tyrosinemia
hydroxyphenylpyruvate dioxygenase (HPPD), 123–124
AKU and, 124
HT and, 123–124
hyperammonemia, 136–137
chronic, 138–139
treatment therapies, 140
hypothyroidism, 102, 109
iloprost, 12
In Need of Diagnosis (INOD), 25
IND applications. See investigational new drug applications
infants, nephropathic cystinosis, development of, 101–102
INOD. See In Need of Diagnosis
intercompartmental clearance, 39
investigational new drug (IND) applications, 163. See also New Drug Applications
kidneys
drug clearance, mechanisms and determinants of, 40
Fick principle, 40
GFR and, 40
drug elimination, 43
active tubular secretion, 43
GFR, 43
passive tubular secretion, 43
HT and, nitisinone therapy for, 128
PTD, 128
L-carnitine
in carnitine deficiency disorders therapy, 86–87
clinical study history, 95
mortality rates, 94–95
for primary carnitine deficiency, 90–92
for secondary carnitine deficiency, 94–96
CoA, 86–87
primary sources, 87
synthesis, 86
liver
drug clearance, mechanisms and determinants of, 40
blood flow and, 40
protein binding and, 40
Wilson disease, zinc therapy and, 195
lysosomal storage disorders, 153–169
discovery of, 154–155
Fabry disease, 155
chemical chaperones, 168
combination therapy for, 168
enzyme replacement therapy, 155–156, 168
synthesis inhibition therapy, 156–157
Gaucher disease, 155
alternative small molecular entities, 165–168
chitotriosidase as biomarker, 165
combination therapy for, 168
enzyme replacement therapy, 155–156, 168
synthesis inhibition therapy, 156–157
Gaucher disease, 155
Genz-112638 in treatment therapy, 166
miglustat in treatment therapy, 166
Phase II studies, 164
synthesis inhibition therapy, 156–157
IND applications, 163
nephropathic cystinosis, 103
cysteamine, as treatment, 101–106, 111
Index

lyosomal storage disorders (cont.)
cystinuria, 101
diagnosis, 102
hypothyroidism, 102, 109
inheritance, 104
mortality rates, 102
natural history, 101–102
pancreatitis, 102
pathophysiology, 102–104
phenotypes, 102–104
restrictive pulmonopathy, 102
additional activities, 161
as cationic amphiphilic drug, 160–161
combination therapy with, 168
functional groups, 158
glucosylceramide synthase inhibition, 159–160
homologue development, clinical trials for, 162–163
Phase studies, 163–165
Gaucher disease, 164
I, 163–164
II, 164–165
sphingolipids, 153–154
synthesis inhibition therapy, 156–157

treatment strategies, 155–156
bone marrow transplantation, 156
chemical chaperones, 156, 168
enzyme replacement, 155–156, 168
gene therapy, 156, 168
MAA. See maleylacetoacetate
maleylacetoacetate (MAA), 117
Fanconi syndrome, 117
MAPK. See mitogen-activated protein kinases
MCD. See multiple carboxylase deficiency
MDRD equation. See Modification in Diet in Renal Disease equation
medically plausible subsets, under Orphan Drug Act, 7, 17
definition of, 7
for Parkinson disease, 12
therapeutic orphans, 7, 16
Menkes disease, 202–205
animal models, 207
ATP7A, 203
brain pathology, 205
CCO activity, 205
clinical features, 204–205
clinical presentation, 203–204
diagnosis, 204
during neonatal period, 205
PAM deficiency, 204–205
phenotypes, 204
N-linked, 203
metabolism. See also drug metabolism of biotin, responsive disorders and,
58–59
cobalamin, 69
secondary carnitine deficiency, 93
methionine metabolism, 191
methionine metabolic pathways, 173
β-methylcrotonyl-coenzyme A (COA), 57
methylene-tetrahydrofolate reductase (MTHFR) deficiency, 176
betaine therapy, 177
methylmalonic acidemia (MMAs), 68–74.
See also cobalamin
covalamin as treatment therapy, 70, 73
clinical effects, 73
dosage, 73
future developments, 74
cobalamin-processing defects, 71–72
Cb1A, 71
Cb1B, 71
Cb1C, 71–72
Cb1D, 72
Cb1F, 72
early clinical reports, 68–69
mutase deficiency, 69–71
diagnosis, 70
treatment, 70–71
pathophysiology, 68
miglustat, 165–167
Gaucher disease therapy, 166
Genz-112638 v., as treatment therapy, 167
mitochondrial permeability transition (MPT), 138
mitogen-activated protein kinases (MAPK), 138
MMAs. See methylmalonic acidemia
Modification in Diet in Renal Disease (MDRD) equation, 50–51
Molecular Libraries initiative, 31–32
MPT. See mitochondrial permeability transition
MT induction. See methallothionein induction
MTHFR deficiency. See methylene-tetrahydrofolate reductase deficiency
multiple carboxylase deficiency (MCD), 57
Muscular Dystrophy Association, 21
mutase deficiency, 69–71
diagnosis, 70
treatment, 70–71
N-acetylglutamate synthetase (NAGS) deficiency, 135
NAGS deficiency. See N-acetylglutamate synthetase deficiency
National Center for Research Resources (NCRR), 25
National Commission on Orphan Diseases, xii
Index

National Institutes of Health (NIH), 19–34.
See also Office of Rare Diseases Research
ORDR, 19–34
CETT program, 22–23
collaborative research efforts, 25
development of, 19–20
function of, 20
GARD, 29–30
goals of, 20
orphan drug development and, 20–21
PAGs and, 29
RDCRN, 26–28
scientific conferences support, 21–22
PAGs as collaborators, 28–29, 34
ORDR and, 29
research initiatives, 31, 34
Molecular Libraries, 31–32
RAID program, 32
TRND program, 32–33
Roadmap for Medical Research, 30–31
UDP, 23–25
National Library of Medicine/National Center for Biotechnology Information (NLM/NCBI), 23
National Organization for Rare Disorders (NORD), 25
natural history of disease studies, 24
NCRR. See National Center for Research Resources
NDAs. See New Drug Applications
neglected diseases, 30
neonates, Menkes disease and, 205
neoplastic cystinosis
cysteamine, as treatment, 101–106, 111
apoptosis, 103
cystine storage, 105
dosage, 107–108
FDA status, 109
future applications, 110–111
hygroscopic nature, 104
mechanism of action, 106–107
mutation inheritance, 104
renal failure from, 109
results, 109–110
side effects, 108
Stevens-Johnson syndrome from, 108
structure, 104
vomiting, 108
cystinuria, 101
diagnosis, 102
hypothyroidism, 102, 109
inheritance, 104
gene location, 104
mortality rates, 102
natural history, 101–102
Fanconi syndrome, 101, 109
infant development, 101–102
late complications, 102
urinary volume, 102
pancreatitis, 102
pathophysiology, 102–104
aberrant energy production, 103
ATP production, 103
CDME, 103
cystine content, 103
PKC, 103
phenotypes
aberrant energy production, 103
development, 102–103
GSH, 103–104
lysosomal storage, 103
restrictive pulmonopathy, 102
New Drug Applications (NDAs), 5
definition criteria, 18
lysosomal storage disorders, 163
phases, 12
substantial evidence of effectiveness as criteria, 13
well-controlled investigations, 13
NGCC. See NIH Chemical Genomics Center
NIH Chemical Genomics Center (NGCC), 33
nitisinone, 121–123
for AKU, 125
future developments, 130
side effects, 127
tyrosine levels, 129–130
FDA status, 122
half-life, 123
HPPD, 123–124
AKU and, 124
HT and, 123–124
for HT, 124–125, 127–130
administration, 124–125
cardiomyopathy complications, 129
in children, 127
dosage, 124
future developments, 130
growth and development complications, 129
hepatic complications, 127–128
HPPD, 123–124
neurologic complications, 128
renal tubular dysfunction, 128
side effects, 125–127
tyrosine levels, 129
mechanism of action for, 123–124
pharmacokinetics of, 122–123
side effects, 125–127
toxicity, 125–127
NLM/NCBI. See National Library of Medicine/National Center for Biotechnology Information
nonbiological orphan drugs, 8–15
FDA approval, for genetic disorders, 9, 12–15
clinical studies, 13–15
market exclusivity of, 11
timeline, 10–11
NORD. See National Organization for Rare Disorders

occipital horn syndrome (OHS), 206
molecular basis, 206
ochronosis, 119
OCTN2 deficiency, 89–90
Office of Rare Diseases Research (ORDR), 19–34
CETT program, 22–23
genetic mutation information collection, 23
goals, 22
collaborative research efforts, 25
Bench-To-Bedside Research Program, 25
development of, 19–20
function of, 20
GARD, 29–30
functions, 29
Internet applications, 29
for neglected diseases, 30
OTT, 30
goals of, 20
orphan drug development and, 20–21
PAGs and, 29
RDCRN, 26–28
corpora of organizations, 26
goals of, 26
patient participation, 26–28
researched diseases, 26
scientific conferences support, 21–22
Office of Technology Transfer (OTT), 30
OHS. See occipital horn syndrome
OOPD. See Orphan Products Development
ORDR. See Office of Rare Diseases Research
ornithine transcarbamylase deficiency, 135
neonatal onset, 149
orphan disease, 3
orphan drug(s)
clinical superiority of new drugs, 8
definition of, 4
designation, 6–7
for genetic disorders, clinical
development of, 14
information criteria for, 6
nonbiological, 8–9, 15
FDA approval, for genetic disorders, 9, 12–15
market exclusivity of, 11
timeline, 10–11
ORDR coordination, 20–21
revocation of designation, 7
Orphan Drug Act (U.S.), xi, 3–16
under FDA, 3–4
OOPD, 4
orphan drug designation, 6–7
written recommendations for investigation, 5
incentives, 4–6, 15
marketing exclusivity, 4
open treatment protocols, 5
product grants, 4–5
tax credits, 5, 16
waiver of use fees, 5–6
written recommendations for investigation, 5
marketing exclusivity under, 4
for clinical superiority of new drugs, 8, 17
protections, 7–8
medically plausible subsets, 7, 17
definition, 7
therapeutic orphans, 7, 16
orphan drugs
clinical superiority of new drugs, 8
definition of, 4
designation, 6–7
information criteria for, 6
nonbiological, 8–9, 15
revocation of designation, 7
Orphan Products Development (OOPD), 4
OTC deficiency. See ornithine transcarbamylase deficiency
OTT. See Office of Technology Transfer

PAGN nitrogen. See phenylacetylglutamine

nitrogen
Pagon, Roberta, 23
PAGs. See patient advocacy groups
PAH. See phenylalanine hydroxylase
PAM deficiency. See peptidylglycine alpha-amidating monooxygenase deficiency
pancreatitis, 102
Parent Project for Duchenne Muscular Dystrophy, 21
Parkinson disease, medically plausible subsets for, 12
passive tubular secretion, 43
patient advocacy groups (PAGs), 20
NIH collaboration, 28–29, 34
ORDR and, 29
Patrick, A.D., 102
PCC. See propionyl-CoA carboxylase
PDMP. See 1-phenyl-2-decanoylamino-3-morpholinopropan-2-one inhibitors
penicillamine, 189–190
peptidylglycine alpha-amidating monooxygenase (PAM) deficiency, 204–205
PET. See positron emission tomography
(PET), in drug development
PGDE scheme. See pharmacologically guided dose escalation scheme
pharmacodynamics, 35–52
clinical approach, 50–52
definition, 36
Index

drug development and, 47–50
key abbreviations, 36
principles, 45–47
antagonism, 47
drug-receptor interactions, 46
synergism, 47
tolerance, 47
pharmacokinetics, 35–52. See also
bioavailability, of drugs; clearance, of drugs; drug metabolism
children and, variables for, 51–52
clinical approach, 50–52
definition, 36
drug development and, 47–50
drug-dosing, 43–45
continuous infusion, 44
design criteria, 45
multiple regimens, 44–45
plateau principle, 43–44
single regimens, 44
key abbreviations, 36
of nitisinone, 122–123
principles, 37–43
alternative administrations, 37
bioavailability, 37–38
clearance, 39–40
drug absorption, 37
drug distribution, 38–39
elimination routes, 42–43
half-life, 39
metabolism, 40–41
for UCDs, 144–145
sodium benzoate, 144–145
sodium phenylacetate, 144–145
pharmacologically guided dose escalation (PGIDE) scheme, 48–49
1-phenyl-2-decanoylamino-3-morpholino-propanol (PDMP) inhibitors, 157–163
additional activities, 161
as cationic amphiphilic drug, 160–161
phospholipase A2 inhibition, 161
combination therapy with, 168
functional groups, 158
glucosylceramide synthase inhibition, 159–160
in vitro/in vivo proof-of-concept studies, 161–162
homologue development, clinical trials for, 162–163
Genz-112638, 163–165
miglustat, 165–167
phenylacetylglutamine (PAGN) nitrogen, 140
phenylalanine hydroxylase (PAH), 76
inheritance factors, 79
phenylketonuria (PKU), 76–79
clinical presentation, 76–77
long-term consequences, 78
PAH deficiency, 76
inheritance factors, 79
pathophysiology, 76
central nervous system dysfunction, 79
pregnancy and, 78–79
sapropterin dihydrochloride as treatment therapy, 79–80
with diet, 77–78, 82–83
FDA approval, 80
future developments, 83
primary benefits, 82
responsiveness testing, 80–82
results of, 80–83
side effects, 80
synthesis, 79–80
screening tests, 77
severity spectrum, 77
treatment outcomes, 78
phosphocysteamine, 111
phospholipase A2, 161
PKU. See phenylketonuria
plateau principle, drug-dosing, 43–44
steady-state concentrations, 43–44
directly proportional, 44
inversely proportional, 44
positron emission tomography (PET), in
drug development, 50
pregnancy
PKU and, 78–79
Wilson disease during, zinc therapy and, 195
Prescription Drug User Free Act (U.S.), 5
primary carnitine deficiency, 88
case reports, 89–90
definition, 88
incidence rate, 88–89
L-carnitine therapy for, 90–92
in muscles, 89
from OCTN2 deficiency, 89–90
Progeria Research Foundation, 21
propionyl-CoA carboxylase (PCC), 57
protein kinase C (PKC), 103
proximal tubular dysfunction (PTD), 128
PTD. See proximal tubular dysfunction
Radin, Norman, 156, 168
RAID. See Rapid Access to Interventional Development program
Rapid Access to Interventional Development (RAID) program, 32
Rare Diseases Clinical Research Network (RDCRN), 26–28
consortia of organizations, 26
goals of, 26
patient participation, 26–28
researched diseases, 26
RDCRN. See Rare Diseases Clinical Research Network
Reagan, Ronald, 3
Index

relative bioavailability, 37
remethylation disorders, 175–176
betaine therapy, 177
cblC disorder, 175
betaine therapy, 177
MTHFR deficiency, 176
betaine therapy, 177
renal failure, from nephropathic cystinosis, 109
restrictive pulmonopathy, 102
Roadmap for Medical Research, 30–31
SA. See succinylacetocetate
sapropterin dihydrochloride, in PKU therapy, 79–80
with diet, 77–78, 82–83
FDA approval, 80
future developments, 83
primary benefits, 82
responsiveness testing, 80–82
results, 80–83
side effects, 80
synthesis, 79–80
saturable kinetics of Michaelis-Menten type, 41
Schwartz equation, 51
secondary carnitine deficiency, 88, 92–96
clinical presentation, 92–94
inborn errors of metabolism, 93
L-carnitine therapy, 94–96
clinical study history, 95
pathophysiology, 92
screening, 95
symptoms, 92
selegiline, 12
small copper complexes, in treatment therapies, 207–209
sodium benzoate, 144–145
sodium phenylacetate, 144–145
sodium phenylbutyrate, 144
sphingolipids, 153–154
biological functions, 154
definition, 153
Spinella, Giovanna, 23
Stevens-Johnson syndrome, 108
succinylacetocetate (SA), 117
SWAN. See Symptoms Without a Name
Symptoms Without a Name (SWAN), 25
synergism, 47
synthesis inhibition therapy, for lysosomal storage disorders, 156–157
synthetic porcine secretin, 8
tax credits, under Orphan Drug Act, 5, 16
Tay-Sachs disease, 157
tetrathiomolybdate (TM), for Wilson disease, 190–191
zinc therapy with, 195–196
TRND. See Therapeutics for Rare and Neglected Diseases
UCDs. See urea cycle disorders
Ucephan, 8
UDP. See Undiagnosed Diseases Program
ultraviolet (UV) light, 64
Undiagnosed Diseases Program (UDP), 23–25
goals, 24
natural history of disease studies, 24
urea cycle disorders (UCDs), 135–139. See also waste nitrogen disposal therapies, for UCDs
AS, 135
AL, 135
clinical presentation, 136
CPS, 135
hyperammonemia, 136–137
chronic, 138–139
treatment therapies, 140
incidence rates, 135
inheritance factors, 139
molecular genetics of, 139
mortality/morbidity rates, 136
NAGS, 135
OTC, 135
pathophysiology, 136–139
ammonium ions, 138
glutamine hypothesis, 138
hyperammonemia, 136–137
waste nitrogen disposal therapies, 140–143, 150
alternative pathway, 148–149
aminoacylation products, 142–144
dosage, 145–146
FDA status, 147
future developments, 149–150
glycol phenylbutyrate, 150
HIP nitrogen, 140
long-term results, 144, 147–149
mechanism of action, 140–145
PAGN nitrogen, 140
pharmacokinetics of Ammonul, 144–145
side effects, 146–147
urea cycle intermediates, 141–142
Index

UV. See ultraviolet light

VD. See volume of distribution
vitamin B12. See cobalamin
Vitamin C, 120
volume of distribution (VD), 38–39
apparent, 39
vomiting, as side effect
of Ammonul therapy, 147
of cysteamine treatment, 108

waste nitrogen disposal therapies, for
UCDs, 140–143, 150
alternative pathway, 148–149
amino acylation products, 142–144
Ammonul, pharmacokinetics of, 144–145
alternative therapy uses, 149
dosage, 146
FDA status, 147
HIP, 144–145
long-term therapy results, 144, 147–149
side effects, 147
dosage, 145–146
FDA status, 147
future developments, 149–150
glycol phenylbutyrate, 150
HIP nitrogen, 140
long-term results, 147–149
mechanism of action, 140–145
PAGN nitrogen, 140
side effects, 146–147
urea cycle intermediates, 141–142
Waxman, Henry, xi, 3
Wilson disease, 185–198. See also
tetrahydrobiopterin (BH4), for Wilson
disease; zinc therapy, for Wilson
disease
clinical presentation, 185–186

hepatic, 185–186
neurologic, 186
diagnosis, 186–189
criteria, 188
tests for, 187
inheritance factors, 187
liver failure presentation, 195
therapeutic treatment therapies, 190
anticopper drugs, 189
future developments, 198
long-term results, 193
penicillamine, 189–190
TM therapy, 192–193
case studies, 196
dosage, 193
FDA status, 197
mechanism of action, 192
side effects, 197
trientine therapy, 190–191
zinc therapy with, 195–196
zinc therapy, 191–192
dosage, 194
efficacy monitoring, 192
failure reports, 194
MT induction, 191
in pediatric patients, 195
during pregnancy, 195
in presymptomatic patients, 195
side effects, 192
with trientine, 195–196
zinc therapy, for Wilson disease, 191–192
dosage, 194
efficacy monitoring, 192
failure reports, 194
MT induction, 191
in pediatric patients, 195
during pregnancy, 195
in presymptomatic patients, 195
side effects, 192
trientine therapy and, 195–196