Index

Note: Italicized page locators indicate figures; tables are noted with t.

Abbreviated New Drug Application, 352
Abdominal skin, human skin studies and, 192
Ablative technologies, 52–57
Absolute recovery, 140
Acceptable operator exposure level, to pesticides, 186
Acceptor solutions, in vitro skin permeation and, 89
ACD, in vitro assays for, 312t, 326–327
Acetone vehicle, IVIV comparison for 12 organic compounds applied in, 168
Acetyl ethyl tetramethyl tetralin, receptor solutions and permeation of, 89, 90t
Acetylsalicylic acid
age-related differences in percutaneous absorption of, 93t
race-related differences in percutaneous absorption of, 95t
in vitro and in vivo absorption values for, 171t
Acid sphingomyelinase, 371
Acne, aqueous gel formulations and, 270
Acne vulgaris, barrier function and, 13
Acrylic pressure-sensitive adhesives, 296, 297
Active compounds, delivering to skin, goals related to, 23
Active pharmaceutical ingredient, 178, 292
Active topical local drug delivery, 364–365
Active transdermal systemic drug delivery, history behind, 362

Acyclovir
dermal concentrations in rabbit skin, after iontophoretic administration at various time intervals, 143
DMD, tape stripping and penetration of, on disrupted skin barrier, 143
indication/action for, 363t
skin abrasion and skin delivery of, 50
Acyclovir cream, iontophoretic application of, 71–72
AD. See Atopic dermatitis
Adapalene, indication/action for, 363t
Additives, stabilization of supersaturated systems and, 31–32
Adhesion, patch, sample diary page for, 225
Adhesion failure, transdermal products and, 294
Adhesion properties, assessment of, 224
Adhesive modifiers, 299
drug delivery and, 302
drug diffusion and, 301
excipient compatibility and, 303
irritation/sensitization and, 306
performance parameters and, 301t
stability and, 305
wear properties and, 304
Adhesives
delivery vs., 300
excipient compatibility and, 303
irritation/sensitization and, 305
for liquid/gel reservoir transdermal patch, 288
performance parameters and, 301t
for solid matrix transdermal patch, 288
stability and, 305
types of, 297
wear properties and, 304
Aeroallergens, atopic dermatitis and, 384
Aerosol sprays, 287
AETT. See Acetyl ethyl tetramethyl tetralin
Age
percutaneous absorption and, 92–94, 93
skin barrier and, 11–12
Aggressive adhesion, transdermal products and, 295
Agricultural chemicals, aqueous dilutions of, immersion assay and, 330
Agrochemical products
skin exposure to, safety issues and, 187
of unknown dermal absorption, tree for performance of in vivo/in vitro studies for, 188–189
ALA. See Aminolevulinic acid
Albumin, 137, 194
Alclometasone cream, comparing BE of, as determined by in vivo VC assay and in vitro excised skin model, 179
Alclometasone dipropionate, 180
Alclometasone ointment, comparing BE of, as determined by in vivo VC assay and in vitro excised skin model, 179
Alcohols, 265, 266
Alkyl gallates, 266
Allergens, pressure wave-mediated delivery and, 54
Allergic contact dermatitis, 13, 310
Allergic rhinitis, 367, 381
Allergic skin sensitization, 241–242
Alniditan, iontophoresis and, 76
Alpha-2 macroglobulin-like 1, 369
Altea PassPort system, substances under trial for delivery with, 52
Altea Therapeutics Corp., PassPort system from, 52
Alternaria alternata
atopic dermatitis and, 384
PAR2 activation and, 377
subclinical inflammation and, 379
Alza Corporation, 44, 176, 214, 289
Alzheimer’s disease, 361
Exelon and, 351–352, 352
Aminolevulinic acid, iontophoretic delivery of, 72
Amorolline, indication/action for, 363
AMP. See Antimicrobial peptides
Analytical methods, topical formulations and, 267
Anatomic site
skin barrier and, 12
skin impedance and, 162
ANDA (Abbreviated New Drug Application) process, 205, 211, 214
AndroGel, 347, 361, 362
Paragraph IV filing and, 353
transference and, 222
Androgens, transdermal, 287
Anesthetics, iontophoresis and fast onset of action for, 68–70
Angiotensin II, skin abrasion and skin delivery of, 50
Animal models, 246
Animals
experimental, local tolerance testing requirements for, 223
irritation tests in, 312r, 328–331
Animal skin, in vitro skin permeation studies and, 278–279
Animal testing, humane objections to, 334
Anionic surfactants, 266
ANNs. See Artificial neural networks
Antiemetics, 78, 350
Antifungal drugs, tape stripping, DPK approach and, 121–122
Antigen-presenting cells, 381
Antimicrobial peptides, 4–5, 372
Antimicrobials, in topical formulations, 266
Antimigraine drugs, iontophoresis and, 76–77
Antioxidants, excipients and use of, 266
Antiseptics, tape stripping, DPK approach and, 122
AOEL. See Acceptable operator exposure level
APCs. See Antigen-presenting cells
API. See Active pharmaceutical ingredient
Apocrine sweat glands, 4, 10, 11
Apotex Fentanyl Transdermal Systems, 300
Appendages
in dermis, 10–11
skin permeation via, 14–15
Application site, dermal toxicology studies and, 252
Aqueous cream, 387, 388, 391
Aqueous emulsions adhesives, 296
Aqueous gels, 265, 270
Aqueous solutions, drugs in, 265–266
Aqueous surfactant solutions, irritant potential of, immersion assay and, 312f, 330
Area under the curve
drug development programs and, 206
iontophoretic treatment for migraine, 77
rate and extent of drug delivery and, 293
Arm immersion model of compromised skin, 334
Artificial neural networks, 260
Aryl hydrocarbon hydroxylase activity, enzymic activity, skin permeation and, 102
Asthma, 367, 381
Athlete’s foot, barrier function and, 13
Atopic dermatitis, 373–381
barrier function and, 13
chronic flares/remission in, 383–384
clinical disease, 380–381
genetic susceptibility to defective skin barrier, 374–376, 390
immune system defects and, 379
lipid defect associated with, 377
multifactorial nature of, 390
preventing emergence of, 391
progression and treatment of, 382
role of skin barrier in development of, 367
serine protease-PAR2 axis and, 372
skin assessment throughout course of, 388
skin characteristics of, 373–374
subclinical inflammation, 378–380
subclinical skin barrier defect, 376–378
subtypes of, 381
thickness of stratum corneum and, 370
treating underlying skin barrier defect in, 390–391
treatment of, 381–387
positive environment, 384–386
proactive inflammatory treatment, 383–384
reactive inflammatory treatment, 381–383
skin barrier repair, 386–387
washing the skin and, 385–386
Atopic march, 381, 391
ATR-FTIR analysis. See Attenuated total reflectance-Fourier transform infrared analysis
ATR-FTIR spectroscopy. See Attenuated total reflectance-Fourier transform infrared spectroscopy
Attention deficit hyperactivity disorder (ADHD), Daytrana for, 360
Attenuated total reflectance-Fourier transform infrared analysis
impedance and, 162
quantification of terbinafine and cyanophenol by, 125
tape-stripping technique and, 121
Attenuated total reflectance-Fourier transform infrared spectroscopy, 156
experimental set-up for in vitro membrane diffusion experiment, 157
AUC. See Area under the curve
AUC<sub>tumor/tissue</sub>, estimating, drug development and, 141
Australia, labeling of transdermal products and, 224
Autoimmune disease products, mandatory centralized procedure for, 213
Auxilium Pharmaceuticals, Inc., 353, 354
Aveva, 290
Axiron, 362
Azelaic acid, indication/action for, 363t
Azone, 33, 34, 34, 36, 157, 265
BA/BE. See Bioavailability and bioequivalence (BA/BE)
Backings films, 297–298
adhesion to matrix and, 297
appropriate occlusivity/permeability for, 298
comfortable and aesthetically acceptable, 298–299
drug delivery and, 300–301
excipient compatibility and, 303
irritation/sensitization and, 305–306
for liquid/gel reservoir transdermal patch, 288
nonirritating, 298
nonreactive, 297–298
performance parameters and, 301t
for solid matrix transdermal patch, 288
Backig films (cont'd)
stability and, 305
wear properties and, 304
Bacterial allergens, atopic dermatitis and, 384
Barratt model, prediction of dermal absorption and, 258, 259
Barrier creams, preventing relapses of AD and, 385
Barrier disruption, consequences of, 371
Barrier reduction, penetration of topically applied substances after treatment with, 44
Basal cell carcinomas, iontophoretic delivery of cisplatin and, 72
Basal TEWL, assessment of human skin barrier structure/function and, 389
BCCs. See Basal cell carcinomas
Benzalkonium chloride, 266
indication/action for, 363
Benzene
total absorption from IVIV studies conducted under harmonized protocol, 170
in vitro and in vivo absorption values for, 171
Benzoic acid
age-related differences in percutaneous absorption of, 93
interlaboratory comparison of, using human epidermal membranes, 196
in OECD guidance, 195
race-related differences in percutaneous absorption of, 95
total absorption from IVIV studies conducted under harmonized protocol, 170
in vitro and in vivo absorption values for, 171
Benzyol benzoate, indication/action for, 363
Benzydamine, indication/action for, 363
Benzy alcohol, 265, 266
Bertek/Mylan Technologies, 289
Betamethasone, indication/action for, 363
Betamethasone valerate, 179
Betamethasone 17-valerate, experimental and predicted values of, in SC, vs. time following delivery from MCT and ME vehicles, 118
ß-glucocerebrosidase, 371
Bifonazole, indication/action for, 363
“Big Pharma,” collaborations between transdermal companies and, 347
Binary cosolvent system, solubility of drug in, 27
Bioavailability
defined, 110
DMD and monitoring changes in, 142–144
blood circulation, 143–144
damaged skin barrier, 142–143
effect of iontophoresis, 143
increasing local, iontophoresis and, 68–73
anesthetics, 68–70
dermatological applications, 71–73
diagnostic application, 73
pain management, 70–71
innovative technologies to improve existing drugs and, 346
local, tape stripping and assessment of, 109
of transdermal products, 221–222
in vitro-in vivo correlation, 177–180
Bioavailability and bioequivalence
(BA/BE)
methods for skin permeation assessment in terms of, III
of topical products:
dermatopharmacokinetic approach, 110–122
Bioengineering methods in model development, 321, 334
Bioequivalence
demonstrated clinical efficacy and, 229
demonstrating for locally acting dermal products, 222
regulatory authorities, drug development and, 148
of topically administered drugs, 144–145
microdialysate concentration data from 2 separate experiments, 145
study size estimates, 145
topical ketoprofen gel study, 146
of transdermal products, 221–222
in vitro-in vivo correlation, 177–180
Bioequivalence testing, Phase I-type trials, 207
Biosimilar products, 205
Biotechnology processes, mandatory centralized procedure for, 213
Black box warnings, on U.S. nonocclusive transdermal testosterone products, 207, 364
Blockbuster drugs
exclusivity and, 205
expiring patent life of, 345

Blood circulation, DMD and, 143–144
Blood samples, 131
BMV. See Betamethasone 17-valerate
Borax, in vitro and in vivo absorption values for, 171t
Boric acid, in vitro and in vivo absorption values for, 171t
Bovine corneal opacity and permeability (BCOP) assay, 241
Bowen’s disease, 72
Buehler’s test, 242
Buehler’s test (BT), 310, 312t, 314
Bufexamac, indication/action for, 363t
Bulk-solid adhesives, 296
Buprenorphine
indication, U.S. approval, and EU marketing, 358t
pharmacokinetic and physicochemical properties of, 359t
Business cases for products, key attributes in, 348
BuTrans (LTS), 289, 360
Butylated hydroxyanisole, 266
Butylated hydroxytoluene, 266

Caffeine
age-related differences in percutaneous absorption of, 93t
in vitro and in vivo absorption values for, 171t–172t
interlaboratory comparison of, using human epidermal membranes, 196t in OECD guidance, 195
race-related differences in percutaneous absorption of, 95t
skin abrasion and skin delivery of, 50 total absorption from IVIV studies conducted under harmonized protocol, 169t, 170t
Calcein, thermal ablation and, 52–53
Calcitonin, iontophoretic delivery of, 78
Calcium ion chelators, optimal cleansing, skin barrier and, 386
Calcium ions, gradient of, across epidermis, 371
Calibration, microdialysis and, 139–140
Camphor, indication/action for, 363t
Cancer pain, transdermal drug delivery and, 347
Cancer products, mandatory centralized procedure for, 213
Canola oil, skin barrier and biological effects of, 387
Capillary electrophoresis, analytical aspects of DMD studies and, 146
Capsaicin, indication/action for, 363t
Carbomers, 271
Carboxymethylcellulose, dry-coated microneedles and, 47
Carcinogenicity, 233, 238–239
Catarpres-TTS (Alza), 289
flux, therapeutic dose range, and patch size, 292t
Cathepsin D, 369
Cathepsin L2, 369
Cavitational technologies, 52–57
penetration of topically applied substances after treatment with, 44
CDER. See Center for Drug Evaluation and Research
CE. See Cornified envelope
Celluloses, 271
Center for Drug Evaluation and Research (FDA), 243
Center lift, transdermal products and, 294
Centralized procedure
mandatory product types subject to, 213 for product approval in EU, 212
CER1, stratum corneum and, 8, 9
CER4, stratum corneum and, 8
CER9, stratum corneum and, 8
Ceramidase, bacterially-derived, defective skin barrier and, 377
Ceramide dominant SC lipids, atopic dermatitis and, 377
Ceramide insufficiency, in atopic dermatitis, 374, 377
Ceramides, 155
aging skin and, 11
molecular structure of, in stratum corneum, 8
Cetrimide, 266
   indication/action for, 363t
Chamber scarification test, 312t, 333
Charitable organizations, 204
Chemical analysis, assessment of human skin barrier structure/function and, 390t
Chemical irritation, transdermal products and, 296
Chemical permeation enhancers, 32–35 ideal, properties of, 32t
   mechanisms of action for, 32–35, 34
   typical use of, in transdermal delivery, 33t
Chemical structure, drug pharmacological activity and, 302
Chemistry, manufacturing and controls
drug product, 209–210
drug substances, 209
Chemotherapy, 350
Chloramphenicol, in vitro and in vivo absorption values for, 172t
Chlorhexidine, indication/action for, 363t
Chlorocresol, 266
Chloroform, in vitro and in vivo absorption values for, 172t
Chlorpyrifos, in vitro and in vivo absorption values for, 172t
CHMP. See Committee for Medicinal Products for Human Use
Cholesterol
   aging skin and, 11
   skin structure and, 155
Ciba-Geigy, 289
Ciclopirox, indication/action for, 363t
Cinnamyl anthranilate, receptor solutions and permeation of, 89, 90t
Cisplatin, iontophoretic delivery and, 72
Citizen’s petitions, 214
Class labeling changes, 214
Cleansing, atopic dermatitis and, 385–386
Clearance phase, dermato-pharmacokinetic approach, drug distribution across SC and, 112, 117–118
Climara Pro (3M), 289
Clindamycin, indication/action for, 363t
Clinical disease, 368
Clinical Trial Authorisation, 212, 219
Clinical Trial Exemption (CTX) scheme, 219
Clinical Trial Notification (CTN) scheme, 219
Clinical trials, 206–209 conducting, requirements for, 219
   entering into, 206
   505(b)(2) regulatory approval process and, 346
   Phase 0, 206
   Phase I, 206–208
   Phase II, 208
   Phase III, 208
   Phase IV, 209
Clobetasone, indication/action for, 363t
Clonidine
   flux, therapeutic dose range, and patch size, 292t
   indication, U.S. approval, and EU marketing, 358t
   irritation/sensitization issues and, 305
   pharmacokinetic and physicochemical properties of, 359t
Clonidine patch, 290, 361
Clonidine transdermal product, manufacturer, transdermal flux, therapeutic dose, and patch size, 292t
Clotrimazole, indication/action for, 363t
Cmax, drug delivery and, 293
CMC. See Chemistry, manufacturing and controls
Coating technologies, microneedles and, 47
Cockroach allergens, skin barrier breakdown and, 377
Code of Federal Regulations, 222
Cold flow, transdermal products and, 295
Cold sores, barrier function and, 13
COLIPA guidance, 184
Collagen, aging skin and, 11
Collagen fibrils, in dermis, 10
Colsolvent systems, mixed, 26–27, 30
Combinatorial chemistry, drug candidate selection and developments in, 256
Commercial product development function over form/time-money/research vs. development, 291
   philosophy behind, 290
Committee for Medicinal Products for Human Use, 212, 213, 243
Compatibility, formulation development and, 267–268
Complete Response Letter, 362
Complex formulations, dermal absorption, good practice across industry sectors and, 190–191
Compliance, innovative technologies and, 346
Concentric probes, 132, 134, 135, 136, 139
Confocal laser scanning microscopy, 59
Confocal Raman spectroscopy, 60
Congress, patent act of 1790 and, 205
Consumer Product Safety Commission, 309
Contact dermatitis, 241
barrier function and, 13
epidermal Langerhans cells and, 310
role of skin barrier in, 367
serine protease-PAR2 axis and, 372
Contraceptive transdermal patches, 289
Controller, LidoSite lidocaine delivery system, 69
Conventional vaccines, microneedle delivery and, 45
Corium, 290
Corneocytes, 155
morphology of, 368, 389t
stratum corneum and, 7
Corneodesmosin, 369
Corneodesmosomes, 369, 377
Cornification, thickness of SC and, 370
Cornified envelope, 33, 368
Cornulin, 375
Corrosion
skin irritation and, 327–328
in vitro assays of, 312r, 334–336
Corrositex, 335–336
Corticosteroids, topical dermatological, special considerations, 226–227, 227
Cosmetic topical formulations, regulation of, 264–265
Cosolvents, pre-formulation study and, 268
Coumarin, in vitro and in vivo absorption values for, 172r
CPES. See Chemical permeation enhancers
CPEX Pharmaceuticals, Inc., 353
CPSC. See Consumer Product Safety Commission
Creams, 270
formulations of, 270–271
topical dosage forms, 263
“Critical Path Initiative” (FDA), 148
CRL. See Complete Response Letter
Cronin model, prediction of dermal absorption and, 259r, 260
Crop protection products, European Commission SANCO 222/2000 rev. 7 and, 187
Crop protection product studies, dislodgeable dose and, 196
Crystal formation, additives, supersaturated systems and, 31
Crystalline packing, stratum corneum and, 9, 9
CTA. See Clinical Trial Authorisation
“Cuff-off value,” of probe, 136
Cumulative irritation assays, 312r, 330
Cumulative irritation testing, 312r, 333
Cyanophenol, ATR-FTIR and quantification of, 125
Cycloextrins, increased MD relative recovery and, 137
CYP450, 237
Cypermethrin, receptor solution and permeation of, 90–91
Cystatin A, stratum corneum and, 7
Cystatin protease inhibitors, A, C, and M/E, 369
Cystic fibrosis, pilocarpine iontophoresis and diagnosis of, 73
Data interpretation, dermal absorption, good practice across industry sectors and, 195–198
Data processing, drug distribution profile inside SC and, 126–127
Daytrana (Noven), 289, 302, 349, 360
DDT. See Dichloro-diphenyl-trichloroethane
Decentralized procedure, for product approval in EU, 212–213
Decylmethyl sulfoxide, 161
Degradation products, formulation characterization and, 281
Degree of saturation, calculating, 27
Delayed-contact sensitization, 296
Delivery method, 140
Delivery rate, of API through skin, 301
Dendritic cells, thymic stromal lymphopoietin and, 379
Department of Transportation, 309
Depth profiling, 159
DEREK database, 241–242
Dermal absorption development of OECD test guidelines for, 184–185
estimating in man, models for, 183–184
summary of QSPRs for prediction of, 259
Dermal dosage forms, pharmacokinetic evaluation of, 220–221
Dermal marketing supporting nonclinical program, 236
Dermal microdialysis methodology, 131, 132
Dermal papilla, 4
Dermal Phase I clinic supporting nonclinical program, 235
Dermal Phase II clinic supporting nonclinical program, 236
Dermal Phase III clinic supporting nonclinical program, 236
Dermal products locally acting, demonstrating bioequivalence for, 222
pharmaceutics of, 219–220
regulatory agencies and full characterization of, 228–229
regulatory aspects of drug development for assessment of adhesion properties, 224
labeling aspects and, 224
local tolerance testing requirements in experimental animals and humans, 223
pediatric use and, 225–226
photosafety testing requirements, 224
topical dermatological corticosteroids, 226–227
topical fentanyl products, 227–228
topical lidocaine products, 227
topical products for psoriasis, 226
transference studies, 222–223
washing studies and interference from other applied products, 223
regulatory aspects of drug development of, 217–229
clinical trials and, 219
pharmaceutics, 219–220
specification of delivered amounts, 220
Dermal toxicology studies, 233–253
allergic skin sensitization, 241–242
animal models, 246
carcinogenicity, 238–239
excipients, 244–245
exposure, 249–250
genotoxicity, 237–238
life cycle management, 245–246
local skin irritation, 240–241
photosafety, 242–244
practical considerations, 250–252
reproductive toxicity, 239
safety pharmacology, 239–240
species selection, 246–249
standard testing for NCEs or excipients and, 252–253
Dermaportation, 57–58
Dermatitis emollients and, 265
occlusive formulations for, 270
overexpression of SCCE and, 6
Dermatopharmacokinetic approach, 110–122, 310–311. See also Tape stripping
drug distribution profiles across SC, 113–118
clearance phase, 112, 117–118
uptake phase, 112, 114–115, 117
FDA draft guidance, 111–112
opportunities to improve, 113–120
perspective and limitation of tape stripping and, 121–122
schematic representation of, as proposed by FDA, 113
tape stripping, bioavailability/ bioequivalence of topical products and, 110–122
topically administered drugs and, 144
“two-time” approach, 119–120
Dermatosis, role of skin barrier defect in, 384
Dermis, 3, 5
   appendages in, 10–11
   description of, 10
   guide cannula and probe inserted in, 135
   MD probe placement in, 134
   vascular network in, 10
Desmoglein 3, 380
Desmosomes, stratum corneum, 7
Desquamation, 369
   antimicrobial peptides and, 372
   atopic dermatitis and increased rate of, 374
   serine proteases and, 378–379
   in vivo and in vitro dermal absorption studies and, 197
Detergents, atopic dermatitis and, 385–386
DEWSI, formulation design and, 292
Dexamethasone, iontophoresis and delivery of, 71
Dexpanethanol, indication/action for, 363
Diabetes products, mandatory centralized procedure for, 213
Diazinon, in vitro and in vivo absorption values for, 172
   assays with, in guinea pigs, 327
Dip coating, 47
Direct injection, 44–48
   microneedles for vaccine delivery, 44–48
   penetration of topically applied substances after treatment with, 44
Discovery phase, drug development and, 217
Disease, fundamental aspects/stages of, 368
Dishesion, transdermal products and, 294
Dislodgeable dose, crop protection product studies and, 196
Disodium octaborate, in vitro and in vivo absorption values for, 171
Dissolvable polymer microneedle patches, 46
Dithranol, indication/action for, 363
Divigel, 361
DNCB. See Dinitrochlorobenzene
DMD. See Dermal microdialysis methodology
DMPBS. See Dulbecco modified phosphate-buffered saline
DMSO. See Dimethyl sulfoxide
DNA, electroporation and delivery of, 57
DNA vaccines, microneedle delivery and, 45
DNCB. See Dinitrochlorobenzene
Donepezil patch, 361
Dosage forms, topical, classification of, 263
Dose levels
   innovative technologies to improve existing drugs and, 346
   in regulatory toxicology studies, 251–252
Dosing area, size of, 251–252
DOT. See Department of Transportation
DPK. See Dermatopharmacokinetic approach
Draize criteria, evaluating irritancy of skin and, 223
Draize-FHSA scoring system, 329
Draize human sensitization test, 323, 324, 326
Draize primary erythema scale, 316
Draize rabbit model, 312
interpretation of PII value, 329, 329
procedure, 328–329
Draize test, 310, 312, 313
Driving force technologies
dermaporation, 57–58
iontophoresis, 58–59
Drug candidate selection, 256
Drug concentration, topical efficacy and,
262–263
Drug content and uniformity, formulation
characterization and, 281
Drug delivery
active pharmaceutical ingredient and, 292
rate and extent of, 292
Drug delivery products, number of new
launches for, 346
Drug delivery technology, promise of,
345–346
Drug development process
overview of, 218
regulatory process and, overview,
217–218
typical sequence of active meetings in,
218
Drug discovery, formulation, toxicology
testing and, 205–206
Drug partitioning, DPK parameters and, 115
Drug physicochemical properties,
formulation development decision tree
based on, 273
Drug Price Competition and Patent Term
Restoration Act (Hatch-Waxman Act),
205
Drug reservoir, LidoSite lidocaine delivery
system, 69
Drugs
delivery vs., 300
excipient compatibility and, 302–303
irritation/sensitization vs., 305
stability vs., 304–305
wear vs., 304
Drug salt forms, pre-formulation studies
and, 262
Dry-coated microneedle arrays, 46
Dry-coated microneedles, 47
DS. See Degree of saturation
DSC. See Differential scanning calorimetry
DT. See Draize test
Duhring chambers, 325, 333
Dulbecco modified phosphate-buffered
saline, 89, 103
Dupel iontophoretic system, 70
Duragesic, 157, 288, 289, 347
citizens petitions and, 214
fentanyl patches, 358–359
Eccrine sweat glands, 4, 10, 11
Econazole, indication/action for, 363
Econazole creams, BE assessment of, 119,
119–120
ECPA. See European Crop Protection
Association
Eczema
barrier function and, 13
emollients and, 265
occlusive formulations for, 270
Edema, intercellular, atopic dermatitis and,
380
EDETOX, 195
Edge lift, transdermal products and, 294
EEC. See European Economic Community
Efficacy, innovative technologies and, 346
Efficiency, of delivery rate from patch, 293
Elafin, 7, 369
Elan, 289
Elastin, aging skin and, 11
Electrical impedance, 162
Electrical resistance
acceptance values for T,0 permeability
coefficient and, using standard
diffusion cells for skin preparations,
193
skin integrity measurement and, 191,
192
Electric current, history behind use of, 67
Electromagnetic spectrum, 156
Electronic spectroscopic methods, 160–163
NMR, 160–161
UV and fluorescence, 160
Electron spin resonance, 161
Electroporation
tissue damage concerns with, 57
for transdermal delivery, 55, 57
Elestrin, 361
Eli Lilly, 362
Elimination profile, pesticide products and,
198
EMLA cream
formation of, 37
local anesthesia and, 69
Tegaderm dressing with, 18
Emollients, 265, 270, 388
for atopic dermatitis, 386–387, 391
EMSAM (Bertek/Mylan Technologies), 289
Emsam patch, 360
Emgels, 270
Emulsifier-free approaches, 271
Emulsifiers, 266
Encapsin, modifying perfusate by, 137
Endo Pharmaceuticals, 364
Environmental factors, atopic dermatitis and, 384–386
Environmental Protection Agency, 184
Health Effects Test Guideline OPPTS 870.7600, 187
Enzyme assays, human skin barrier structure/function and, 389
Enzymic activity, in vitro skin permeation and factors affecting, 102–103
Epi-Derm, description of, 335
Epidermal-dermal junction, skin permeation, aging and flattening of, 93–94
Epidermal hyperplasia
atopic dermatitis and, 380
repeated barrier disruption and, 367
Epidermal thickness, human skin barrier structure/function and, 389
Epidermis, 3, 4–10, 5
defined, 4
gradient of calcium ions across, 371
multiphoton microscopy and fluorescence lifetime imaging of, 7
renewal of, 369
stratum basale, 5, 5–6
stratum corneum, 5, 7–10
stratum granulosum, 6
stratum lucidum, 6
stratum spinosum, 5, 6
viable, 4
Erector pilorum muscle, 11
Er-YAG laser, 53
Erythema, human skin barrier structure/function and, 389
Erythematosus lesions, atopic dermatitis and, 380
Erythromycin, indication/action for, 363
ESR. See Electron spin resonance
Estraderm (Alza), 289
Estradiol
age-related differences in percutaneous absorption of, 93
flux, therapeutic dose range, and patch size, 292
indication, U.S. approval, and EU marketing of, 358
manufacturer, transdermal flux, therapeutic dose, and patch size, 292
pharmacokinetic and physicochemical properties of, 359
rate of absorption of testosterone and, from excised skin and in human subjects, 177
transdermal delivery and use of, 33, 176
Estradiol and norethindrone acetate, indication, U.S. approval, and EU marketing of, 358
Estradiol patches, generic versions of, 290
Estrasorb, 361
Estrogel, 223, 361
Estrogens
transdermal, 228, 287
U.S. package inserts for, 220
Ethanol, 266
drug solubility and, 265
as penetration enhancer, 157
solubilization effect and, 26
Ethinyl estradiol
pharmacokinetic and physicochemical properties of, 359
transdermal delivery and use of, 33
Ethinyl estradiol and norelgestromin, indication, U.S. approval, and EU marketing of, 358
Ethnicity, skin barrier and, 12–13
E-TRANS electrotransport technology, 74, 75
E2, itch and PAR2-induced release of, 383
Europe, modern patent system in, 205
European Centre for Ecotoxicology and Toxicology of Chemicals, 184
European Centre for the Validation of Alternative Methods, 184
European Commission SANCO 222/2000
rev. 7, crop protection products and, 187
European Community, Annex I or Directive 91/414 of, 186
European Crop Protection Association, Toxicology Expert Group of, 184
European Economic Community, 309
European Medicines Agency (EMEA), 208, 217, 219, 221, 222, 360, 362
Committee for Medicinal Products for Human Use, 243
labeling of transdermal products and, 224
local tolerance testing and, 223
pediatric transdermal formulations and, 226
photosafety testing requirements of, 224
psoriasis treatment and, 226
regional guidelines available from, 234
topical dermatological corticosteroids, 226–227
European Union, 184
ethics committee approval in, 219
product approval system in, 212–213
risk assessment relating to pesticides in, 186–187
European Union Conformité Européene, MD probes approved by, 131
EUROPOEM, 186
Eutectic mixtures, 37
EVA films, 298
Evamist, 361
Excimer-type lasers, 162
Excipient/drug compatibility, classifying, 269
Excipient/excipient compatibility, classifying, 269
Excipients
adhesive modifiers, 299
adhesives, 296–297
backing films, 297–299
carcinogenicity and, 238–239
compatibility of acceptability and, 294
fundamental requirements for, 302–303
defined, 268, 296
dermal applications and standard testing program for, 252–253
genotoxicity and, 237–238
local skin irritation and, 240–241
permeation enhancers, 300
photosafety and, 242–244
release liners, 299
role of, 265–266
safety issues related to, 244, 245
selection of, 263–267
product “in use” considerations, 267
regulatory perspective, 263–265
topical formulations and, 118
Excised human skin
in vitro–in vivo correlation: bioavailability and bioequivalence, 177–180
in vitro–in vivo correlation: transdermal delivery, 176
Excised skin model
other validation studies and, 169–170
validity of, summary remarks, 180
Exelon, 289
Alzheimer’s disease and, 351–352, 352
Exfoliative toxins, 377
Exposure, toxicity linked to, 249–250
Extended release oral drug delivery, 351
Extrinsic atopic dermatitis, 381
ExtroGel, transference and, 222
Exubera, 351
Exudate, 296
ex vivo animal models, new drug development and, 131
Eye irritation, dermal products evaluated for, 241
Fatty acids, 11, 265
FCA. See Freund’s complete adjuvant
FCAT. See Freund’s complete adjuvant test
FDA. See Food and Drug Administration
Federal Hazardous Substance Act, Draize rabbit model and, 328
Fentanyl
electroporation and delivery of, 55
flux, therapeutic dose range, and patch size, 292
indication, U.S. approval, and EU marketing of, 358
pharmacokinetic and physicochemical properties of, 359
topical, special considerations with, 227–228
transdermal delivery and use of, 33t
transdermal delivery of, specified doses for, 220
transdermal iontophoresis and, 74, 76
transference for, 222
Fentanyl ITS, fully integrated, application of, 74
Fentanyl patches, generic, 290
citizen’s petitions and, 214
in U.S. market, 359
Fentanyl transdermal product, manufacturer,
transdermal flux, therapeutic dose, and patch size, 292t
Fertility, new drug products and, 239
FHSA. See Federal Hazardous Substance Act
Fibroblasts, 10
Fibronectin, 10
Fick’s laws of diffusion
first, baseline TEWL across unstripped SC of thickness L and, 126
second
drug profiles fitted to appropriate solution of, 127
uptake phase and, 114–115
skin permeation and, 17
tape stripping and, 48
Filaggrin, 368, 380
AD and reduced expression of, 375
deficiency of, 374
skin barrier function and, 376
Firestone, Harvey, 203
Firestone Tire and Rubber Company, 203
Fischer’s exact test, 316
Fiserova-Bergerova model, skin permeation and, 258, 259t
FITC-dextran 40, LTR formation in full-thickness rat skin with, 54
“Fit-for-purpose” methods, 267
5-ALA, electroporation and delivery of, 55
5-aminolevulinic acid dermaporation and, 58
skin abrasion and skin delivery of, 50
505(b)(1) applications, description of, 211
505(b)(2) applications, description of, 211
505(b)(2) regulatory approval process, with FDA, 346
5-fluorouracil (5-FU)
iontophoretic treatments with, for Bowen’s disease, 72
skin abrasion and skin delivery of, 50
5-HT, 350, 360
Fixed combination products, nonclinical safety programs for, 246
Flares, reducing in atopic dermatitis, TCS, TCI and, 384
FLG gene, atopic dermatitis and, 375
FLG loss-of-function mutations, AD and, 376, 377
FLIM. See Fluorescence lifetime imaging
Flow-through diffusion cell design, 86, 87, 88
Fluazifop-butyl
in vitro absorption of three doses of, through isolated human epidermis, vs. in vivo absorption with different receptor media, 91, 91t
in vitro and in vivo absorption values for, 172–173t
Fluid packing, stratum corneum and, 9, 9
Fluorescein isothiocyanate (FTC)-coated dextran beads, 48
Fluorescence lifetime imaging, 58, 59
Fluorescence spectroscopy, 160
Fluorocarbon- or fluorosilicone-coated release liners, 303
Flynn data set, percutaneous absorption prediction and, 258
Foam products, topical, development of, 255
Follicular delivery, skin stretching and, 49
Food allergies, 367
atopic dermatitis and, 384
atopic march and, 381
Food and Drug Administration, 184, 222, 309, 353, 358, 360, 362, 365
bioequivalence described by, 144
black box warning on nonocclusive testosterone transdermal products, 207
branded transdermal patches approved by, 290
citizen’s petitions and, 214
conducting clinical trials and, 219
“Critical Path Initiative,” 148
Exubera approved by, 351
Food and Drug Administration (cont’d)
505(b)(2) regulatory approval process with, 346
LidoSite Topical System approved by, 69
list of inactive ingredients, 241, 245
MD probes approved by, 131
most common types of submission to, for product approval, 211
New Drug Applications approved by, 347
photosafety testing requirements, 224
regional guidelines available from, 234
topical fentanyl products, 227
transdermal product labeling and, 224
Transderm Scop approved by, 289
Zelrix launch and, 362
Formaldehyde-releasing preservatives, 244
Form-fill seal, 287
Formulation application, skin surface cleaning and, 122–123, 123
Formulation approaches, skin permeation via appendages, 15
Formulation characterization drug content and uniformity, related substances, and degradation products, 281
ICH stability and, 280
macroscopic/microscopic appearance and odor, 281
microbial quality or MLT and PET, 282–283
pH, 281–282
preservative content, 281
rheology and viscosity, 282
sterility, 283
Formulation development, description of, 269–270
Formulation of drugs, drug discovery, toxicology testing and, 205–206
Formulation optimization, 279–280
drug recovery from epidermal layer after mass balance study and, 279–280
factorial designs and, 279
Formulation selection, 280
Formulation type, formulation development decision tree based on, 272
Fougaro, 361
Fourier transform infrared (FTIR) spectroscopy, 58, 157
Fourier transform infrared (FTIR) studies, of chemical permeation enhancers, 34, 35
Framycetin, indication/action for, 363
Franz cell, 87
representation of, 277
in vitro skin permeation studies and, 278
Franz cell system, in vitro release method for topical dosage forms and, 277
Free fatty acids, 8
Freund’s complete adjuvant, guinea pig maximization test and, 242
Freund’s complete adjuvant test, 310, 312
induction phase, challenge phase, and evaluation, 315
modifications, 314
FTIR spectroscopy. See Fourier transform infrared (FTIR) spectroscopy
FTS, flux, therapeutic dose range, and patch size, 292
Funding, ideas and, 203–204
Fungal infections, barrier function and, 13
Gas chromatography-flame photometric detector, analytical aspects of DMD studies and, 146
Gas chromatography-mass spectrometry, analytical aspects of DMD studies and, 146
Gas-jet coating, 47
Gaussian processes (GP) modeling, QSRR modeling vs., 260
GC-FPD. See Gas chromatography-flame photometric detector
GC-MS. See Gas chromatography-mass spectrometry
Gelnique, 361
Gels, 270
size of dosing area with, 251
topical dosage forms of, 263
Gender
skin barrier and, 13
skin impedance and, 162
Generally recognized as safe, chemical permeation enhancers and, 32
Genetic susceptibility, disease and, 368
Gene transfer, pressure wave-mediated delivery and, 54
Genotoxicity, 233, 237–238
Genotyping, assessment of human skin barrier structure/function and, 390t
Glass, diffusion cell design and, 88, 89
Glazing, 296
GLP. See Good laboratory practice
Glycerides, 266
Glycerol, 265
Glycols, 265
Glycosaminoglycans, aging skin and, 11
GM-CSF. See Granulocyte-macrophage colony-stimulating factor
GMP. See Good manufacturing practice
Good laboratory practice, 190, 233–234
Good manufacturing practice, 283
Government, 204. See also Food and Drug Administration
GPMT. See Guinea pig maximization test
Granisetron
indication, U.S. approval, and EU marketing of, 358t
pharmacokinetic and physicochemical properties of, 359t
Granisetron hydrochloride, thermal ablation and penetration of, 53
Granulocyte-macrophage colony-stimulating factor, skin barrier disruption and, 378
GRAS. See Generally recognized as safe
Gravimetric approach, tape stripping, quantifying removal of SC and, 124
Growth-hormone-releasing hormone, iontophoretic delivery of, 78
Guinea pig maximization test, 312t
classification of materials, 318t
drawbacks to, 242
induction phase, challenge phase, and evaluation, 317
Guinea pig sensitization tests, 311–318, 312t
Buehler’s test, 312t, 314
Draize test, 312t, 313
Freund’s complete adjuvant test, 312t, 314–315
guinea pig mazimization test, 312t, 317
open epicutaneous test, 312t, 313–314
optimization test, 312t, 315–316
split adjuvant test, 312t, 316–317
Guinea pig skin, acceptance values for T2O permeability coefficient and electrical resistance, using standard diffusion cells for, 193t
Guinea pig repeat irritation test, 330
Habitrol (Pharmatrix), 289
Hair follicles, 4, 10–11
Halobetasol cream, comparing BE of, as determined by in vivo VC assay and in vitro excised skin model, 179t
Halobetasol ointment, comparing BE of, as determined by in vivo VC assay and in vitro excised skin model, 179t
Hatch-Waxman Act, 205, 352, 353
Hazards, addressing, regulatory programs and, 233
Health Canada, 184
Health-care budgets, global pharmaceutical industry and, 345
Heparin, FITC-labeled, microscopic images of permeation of, across hairless rat skin at various depths, 56
HEPES-buffered Hanks’ balanced salt solution, 89, 103
Herpes orolabialis, iontophoresis of vidarabine monophosphate and acyclovir for efficacy against, 71–72
Herpes simplex infections, barrier function and, 13
Hexacosanoic acid (C26), in stratum corneum, 8
Hexagonal lattice lipid packing, stratum corneum and, 9
HHBSS. See HEPES-buffered Hanks’ balanced salt solution
High-performance liquid chromatography, quantification of drugs in tape strips by, 125
High throughput screening, drug candidate selection and developments in, 256
Hill Top Chambers, semisolid formulations applied with, 122
Hippuric acid
total absorption of, from IVIV study conducted under harmonized protocol, 169t
in vitro and in vivo absorption values for, 173t
Hisamitsu, 289
HIV/AIDS products, mandatory centralized procedure for, 213
“Hollow fibers,” MD technique, 132
Hollow microneedles, 45, 46–47
Homeostasis, skin barrier and, 371–372
Hormone products, transdermal, 287
Hormone replacement therapy patches and, 361
transdermal drug delivery and, 347
Hornerin, 375
House dust mites, skin barrier breakdown and, 377, 384
HPC. See Hydroxypropylcellulose
HPLC. See High-performance liquid chromatography
HPMC. See Hydroxypropyl methylcellulose
Human maximization test, 312
challenge phase and evaluation, 326
induction phase, 325–326
Human MD experiments, preparation of, necessary steps in, 134
Human Research Ethics Committee, 219
Humans irritation tests for, 312, 331–336
local tolerance testing requirements for, 223
Human sensitization assays, 312
human maximization test, 312, 325–326
modified Draize human sensitization test, 312, 326
precautions taken with, 322
RIPT, 312, 323–325
S-P tests, 312, 322–323
Human skin acceptance values for T2O permeability coefficient and electrical resistance, using standard diffusion cells for, 193
as gold standard for assessing dermal absorption of pesticide products, 191
porcine skin and, 247
in vitro skin permeation studies and, 278–279
Human skin permeation assessment comparison of in vitro and in vivo absorption values for 97 data sets, 171–174
IVIV comparison for 11 data sets, performed on skin from same anatomical site, with fully harmonized protocols, 175
IVIV comparison for 92 data sets on 30 organic compounds, 175
IVIV comparison for 12 organic compounds applied to acetone vehicle, 168
total absorption from IVIV study conducted under harmonized protocol, 169
in vitro-in vivo correlation: bioavailability and bioequivalence, 177–180
other validation studies, 169–170
validating the model, 167–169
in vitro-in vivo correlation: transdermal delivery, 176
Humectants, 265, 368
Hydration assessment of human skin barrier structure/function and, 389
in healthy and diseased skin states, 10 permeability and, 18, 157
Hydrocortisone age-related differences in percutaneous absorption of, 93
indication/action for, 363
Hydrocortisone iontophoresis, 78
Hydrogen bonding, skin permeation and, 258
Hydrophobic lipid tails, CPE insertion between, 34
Hydrophilic compounds, laser technology and, 53
Hydrophilic drugs, 53
Hydrophilic molecules, skin abrasion and skin delivery of, 50
Hydrophilic polymers, stabilization of supersaturated systems and, 31
Hydrophobic lipid tails, CPE insertion between, 34
Hydroxy-benzoates, 266
Hydroxypropylcellulose, 275
Hydroxypropyl methylcellulose, growth inhibition of hydrocortisone acetate crystals by, 31
Hyperkeratosis, atopic dermatitis and, 380
Hypodermis, 11
Ibuprofen
indication/action for, 363
theoretical SC concentration-depth
profiles for, 116
ICCVAM. See Interagency Coordination
Committee on the Validation of
Alternative Methods
ICH. See International Conference on
Harmonisation
Ichthyosis
barrier function and, 13
role of skin barrier in, 367
serine protease-PAR2 axis and, 372
Ideas, money and, 203–204
IDECs. See Inflammatory dendritic
epidermal cells
Idoxuridine iontophoresis, 71
IL-1, KLK7 and, 372
IL-4, subclinical inflammation and, 380
IL-6, normal skin barrier repair and, 372
IL-10, subclinical inflammation and, 379
IL-13, subclinical inflammation and, 380
IL-18, subclinical inflammation and, 379
Immersion assay, 312t, 330
Immersion test, 312t, 333–334
– 334
Immune system defects, atopic dermatitis
and, 379
Immunogenicity, microneedles and, 47
IMPD. See Investigational Medicinal
Product Dossier
Impedance spectroscopy, basis of, 162
Impetigo, barrier function and, 13
IND, 212
clinical trials requirements and, 219
Infinite-dose studies, in vitro permeation
and, 98–99, 99
Inflamed skin, chronic, characteristics of,
381
Inflammation
repeated barrier disruption and, 367
subclinical, AD and, 378–380
Inflammatory dendritic epidermal cells, 381
Influenza vaccine, microneedles,
immunogenicity and, 47–48
Infrared, skin probing and, 156
Infrared (IR) radiation, 53
Infrared spectrum, of skin, 156
Infrared surface thermometers, for
measuring skin surface temperature, 98
Injections, fear around, 69–70
Innovative technologies, to improve
existing drugs, 346
Institutional review boards, 219
Insulin
iontophoretic delivery of, 78
pressure wave-mediated delivery and,
54
sonophoresis and transdermal delivery of,
55
Intellectual property, 347, 352–354
Interagency Coordination Committee on
the Validation of Alternative Methods,
336
Intercellular junctions, CPE interactions
and, 33
Intercellular route, 23, 24
permeation via stratum corneum and, 16
Interconnect tab, LidoSite lidocaine
delivery system, 69
International Conference on Harmonisation,
223, 234
guidelines, 267
carcinogenicity, 238
genotoxicity, 238
safety pharmacology, 239
stability tests
formulation characterization, 280
topical product formulation
development, 283
Intralipid, modifying perfusate by, 137
Intrinsic atopic dermatitis, 381
Investigational Medicinal Product Dossier,
219
Investments, protecting, strategies for,
204–205
Investors, new product development and,
348–349
in vitro animal models, new drug
development and, 131
In vitro assays
for ACD, 312t, 326–327
of skin irritation and corrosion, 312t,
334–336
of skin irritation and corrosion,
approaches to, 335
in vitro calibration, 139
in vitro dermal absorption studies,
compartments test chemicals for, 197
in vitro drug release studies, topical product formulation and, 276–277
in vitro excised skin model, validating, earliest attempt, 167–168
in vitro release testing, use for, 277
In vitro skin permeation methodology, 85–104
analysis of data, 98–100
concluding remarks, 103–104
diffusion cell design, 86–89
impact of skin metabolism, 100–103
detection of metabolism, 101
factors affecting enzymic activity, 102–103
modeling, 103
nature of enzymes, 100–101
prodrugs, 101
site of metabolism, 101–102
introduction, 85
permeation experiment, 96–98
application of test material, 96–97
duration of experiment, 97
membrane integrity, 96
number of replicates, 98
sample interval, 97–98
temperature, 98
receptor chamber and medium, 89–92
selection, variation, and preparation of skin membranes, 92–96
donor age effects, 92–94
intra- and intersubject variation, 92
membrane preparation, 95–96
racial differences, 94
storage conditions, 95
in vitro skin permeation studies, 278–279
In vitro tape-stripping, for research purposes, 120–121
in vivo calibration, 139
in vivo dermal absorption studies, compartments test chemicals for, 197
in vivo skin permeation testing, 206
In vivo tape-stripping, for research purposes, 120–121
Involucrin, 7, 368, 380
Iogel electrodes, 77
Iomed Inc., 69
Ion gradients, maintenance of, across epidermis, 371
Ionization, permeant and, 25
Ion pairs
defined, 37
permeation and formation of, 37
Ionsys fentanyl iontophoretic device, 362
Ionsys system, 74, 76
Iontophoresis, 58–59
anesthetics, 68–70
antiemetics, 78
anti-migraine drugs, 76–77
dermatological applications, 71–73
diagnostic application, 73
DMD and effect of, 143
electroporation combined with, 57
FDA-approved products and, 79
future developments with, 79–80
“how” and “why” of, 67–68
local bioavailability increased with, 68–73
opioids, 73–76
pain management and, 70–71
peptides and proteins, 78–79
treatment of neurodegenerative diseases, 77–78
Iontophoresis System, 69
Iontophoretic devices, first-generation, 69
Iontophoretic patch system
components of, 68
schematic representation of, 68
Iontophoretic skin transport, mechanisms related to, 59
IP. See Intellectual property
IPM. See Isopropyl myristate
IR, skin disorder diagnosis and, 158
IRBs. See Institutional review boards
Irritation
local, evaluating, 223
testing, 206
transdermal products and, 295–296
Irritation/sensitization
adhesive modifiers and, 306
adhesives and, 305
backing film and, 305–306
drugs and, 305
permeation enhancers and, 306
release liners and, 306
Irritation tests in animals, 312r, 328–331
cumulative irritation assays, 312r, 330
Draize rabbit model, 328–329
immersion assay, 312t, 330
mouse ear model, 312t, 331
Irritation tests in humans, 312t, 331–336
bioengineering methods in model
development, 312t, 334
chamber scarification test, 312t, 333
cumulative irritation test, 312t, 333
human patch test grading scales, 332t
immersion tests, 312t, 333–334
single-application patch testing, 312t,
331–332
Isophenos, *in vitro* and *in vivo* absorption
values for, 173t
Isopropyl alcohol, drug solubility and, 265
Isopropyl myristate
mechanism of action for, 36
permeation enhancement and, 36–37
*in vitro* rate of absorption profiles of
ketoconazole cream, with varying
levels of, 178
Isotretinoin, indication/action for, 363t
Itching, leukotriene B4, E2 and, 383
Johnson & Johnson, 214, 358
Juvenile toxicity, 233, 245
Kallikrein-related peptidases, 369
Kaposi’s sarcoma, iontophoretic delivery of
vinblastine solution and, 73
Keloid formation, DMD and, 139
Keratin, 155
Keratin immediate filaments, stratum
corneum and, 7
Keratinocytes, 5, 6, 371
Keratolytics, tape stripping, DPK approach
and, 122
Ketoconazole, indication/action for, 363t
Ketoconazole cream
*in vitro-in vivo* correlation: bioavailability
and bioequivalence, 177–178
*in vitro* rate of absorption profiles of test
formulations of, with varying levels of
PG and IPM, 178
Ketoprofen
indication/action for, 363t
iontophoresis and delivery of, 70
Ketorolac, iontophoresis and delivery of,
70
Key Pharmaceutical, 289
Kirchner data set, prediction of dermal
absorption and, 259t, 260
KLK1, 369
KLK3, 369
KLK5, 369, 372, 374, 376, 379
KLK6, 369
KLK7, 369, 372, 374, 375, 379
KLK8, 369
KLK9, 369
KLK10, 369
KLK11, 369
KLK13, 369
KLK14, 369, 372, 374, 376
KLK7 gene, 375
Kytril, 350
Labeling
changes in, 214
of transdermal products, 224
Lactic acid, in corneocytes, 368
Lamellar bodies, 369
Lamellar phases, stratum corneum and, 9
Laminin, in dermis, 10
Langerhans, Paul, 309
Langerhans cells, 5, 5, 6, 381
aging skin and, 11
skin abrasion and, 51
thymic stromal lymphopoetin and, 379
Laser-induced breakdown spectroscopy, 162
Laser technology, commercial applications
with, 53–54
Latex, skin sensitivity issues with, 305
Lavipharm, 290
LBs. See Lamellar bodies
LC-MS. See Liquid chromatography-mass
spectrometry
LEKT1, 374
composition of, 369
subclinical inflammation and, 379
LEKT1-2, 369
Lesions, 296
Leukotriene B4, itch and PAR2-induced
release of, 383
Leuprolide, iontophoretic delivery of,
78–79
LHRH. See Luteinizing-hormone-releasing
hormone
LIBS. See Laser-induced breakdown
spectroscopy
Lidocaine, 68, 229, 364
pH and skin enhancement of, 262
scales in FDA guidance on, 223
topical products, special considerations, 227, 228
Lidocaine iontophoresis, in dermal anesthesia, 69
Lidoderm, 364
LidoSite lidocaine delivery system, 69, 69–70, 364
Life cycle management, 245–246
Lignoceric acid (C24), in stratum corneum, 8
Lindane, in vitro and in vivo absorption values for, 173t
Linear methods, predictions of skin absorption and, 260–261
Linear probes, 134, 135, 135, 139
MD sampling by, 132
Line extension, 245
Linoleic acid, skin barrier and biological effects of, 387
Lipid analysis, human skin barrier structure/function and, 390t
Lipid envelope, stratum corneum and, 7
Lipid lamellae, components of, 369
Lipid structure, human skin barrier structure/function and, 389t
Lipophilic chemicals, in vivo and in vitro dermal absorption studies and, 197–198
Lipophilic compounds
impedance values and, 162
laser technology and, 53
solubility of, 18
Liposomes, in pharmaceuticals and cosmetics, 271
Liquid chromatography-mass spectrometry, analytical aspects of DMD studies and, 146
Liquid/gel reservoir patch
advantages and disadvantages with, 288
description of, 287–288
transdermal, schematic, 288
Liquid lattice lipid packing, stratum corneum and, 9
 Liquids, topical dosage forms, 263
LLNA. See Local lymph node assay
LLOQ. See Lower limit of quantification
Localized transport regions, ultrasound and, 54
Local lymph node assay, 242, 310, 312t
materials required, 320
procedure, 320–321
Local skin irritancy, 240–241
Local tolerance testing, for experimental animals and for humans, 223
Local toxicity, 233
Log P, physicochemical properties of drug and, 262
Long periodicity phase, stratum corneum and, 9, 9
Loop probe, 134, 135
Loricrin, 7, 368, 380
Lower limit of quantification, 249
LPP. See Long periodicity phase
LTR formation, representative images of, in skin samples, 54
LTRs. See Localized transport regions
LTS, 289
LTS Lohmann Therapie-Systeme AG, 347
Luteinizing-hormone-releasing hormone, iontophoretic delivery of, 78
Lymph vessels, in dermis, role of, 10
Lysine acetylsalicylate, iontophoresis and delivery of, 70
MAA. See Marketing Authorisation Application
Macromolecules, electroporation and delivery of, 57
Macroscopic appearance and odor, formulation characterization and, 281
Magnetic fields, musculoskeletal injuries and use of, 57
Magnetic technologies, 57–58
Magnusson and Kligman maximization test, 310
Mannitol, electroporation and delivery of, 55
Marketing Authorisation Application, 213
Market opportunity identifying, with product to fit, 349–350
understanding, new product development and, 345–355
Marzulli-Maibach modification, 323, 325
Massage, transdermal delivery and, 49
Mast cell chymase, 380
Mast cells, 381
in dermis, 10
thymic stromal lymphopoetin and, 379
Mathematical models
drug candidate selection and, 256
various aspects of skin absorption and, 197
Maurer optimization test, 310
MCC. See Mast cell chymase
MD. See Microdialysis
MDTS. See Metered-Dose Transdermal System
Mechanical irritation, transdermal products and, 296
Medicine, current practices in vs. future of, 368
Melanin, function of, 6
Melanocytes, 5, 6
aging skin and, 11
in dermis, 10
Melting point, 25, 258
MEM. See Minimal essential medium
Membrane
for liquid/gel reservoir transdermal patch, 288
for solid matrix transdermal patch, 288
Menostar (3M), 289
Merkel cells, 5, 6
MEST, 312r
evaluation, 320
induction phase and challenge phase, 319
preliminary work done on, 318–319
Metabolism, detecting, in vitro diffusion studies and, 101
Metal-working fluids, 333
Metered-Dose Transdermal System, 30
Methotrexate, electroporation and delivery of, 55
Methotrexate iontophoresis, psoriasis and, 72–73
Methylcellulose, dry-coated microneedles and, 47
Methylphenidate
indication, U.S. approval, and EU marketing of, 358r
pharmacokinetic and physicochemical properties of, 359r
Methylprednisolone, indication/action for, 363r
Metoclopramide iontophoresis, 78
Metronidazole, indication/action for, 363t
Mexoryl SX, in vitro and in vivo absorption values for, 173t
Mice
sensitization tests in, 312r, 318–321
LLNA, 312t, 320–321
MEST, 312t, 318–320
VAET, 312t, 321
Miconazole, indication/action for, 363t
Microbial limit test, formulation characterization and, 282–283
Microbial quality, formulation characterization and, 282–283
Microchannel depths, thermal ablation and, 52
Microdermabraded skin, in vivo delivery through, 50
Microdermabrasion, biochemical and immunohistochemical responses to, 51
Microdialysis, 131–148
advantages and challenges, 146–148
analytical aspects, 146
BE of topically administered drugs, 144–145
bioavailability, 142
calibration, 139–242
no-net-flux method, 140
retrodialysis, 140–141
stop-flow/flow-rate method, 140
experimental procedure and considerations, 133–139
application site, 137
insertion of probes, 137
measuring probe depth by ultrasound scan, 138
perfusate, 137
probe, 133–137
pump, 139
tissue trauma, 138–139
history behind, 132
introduction, 131
microdialysis methodology, 132–133
monitoring changes in BA by DMD, 142–144
blood circulation, 143–144
damaged skin barrier, 142–143
effect of iontophoresis, 143
Microdialysis (cont’d)
pharmacokinetics, 141–142
regulatory authorities, 148
sampling by linear probe, 132
skin reaction and, 138

Micro-nanoprojection array area, coated and uncoated projections prior to insertion into skin, 46
Microneedle delivery vaccines, rationale for, 45
Microneedles
dissolving, 47
dry-coated, 47
with dry-formulated vaccine, 47
hollow, 45
MicronJet, scanning electron micrographs of, 45
for vaccine delivery, 44–48
MicronJet microneedles, scanning electron micrographs of, 45
Microscopic appearance and odor, formulation characterization and, 281
Microwave dielectric analysis, water examined in vivo within stratum corneum, 159
MIF. See Migration inhibition factor
Migraine
iontophoresis and treatment of, 76–77
Zelrix for, 362
Migration inhibition factor, 327
Minimal essential medium, 89, 103
Minipigs, laboratory use of, 247
Minipig skin
normal, 247
rat skin vs., 248
Minoxidil, indication/action for, 363
Miscibility of solvents, cosolvents selected on basis of, 268
Mites, skin barrier breakdown and, 377
MLT. See Microbial limit test
MMT. See Dimethyltriazoldiphenyl tetrazolium-formazan (MTT) cell viability assay
Modified Draize human sensitization test, 312
induction phase and challenge phase, 326
Moisturization, in healthy and diseased skin states, 10
Molar solubility of drug in cosolvent, defined, 27
Molar solubility of drug in water, defined, 26
Molds, PAR2 activation and, 377
Molecular size, skin permeation and, 17, 258
Molecular weight permeant and, 25
physicochemical properties of drug and, 262
Mometasone ointment, comparing BE of, as determined by in vivo VC assay and in vitro excised skin model, 179
Mometosone, indication/action for, 363
Money, ideas and, 203–204
Morphine iontophoresis, 73
Mouse ear model, 312, 331
Mouse skin, acceptance values for T2O permeability coefficient and electrical resistance, using standard diffusion cells for, 193
MP. See Melting point
MPM. See Multiphoton microscopy
MPM-FLIM. See Multiphoton microscopy and fluorescence lifetime imaging
Multiphoton femtosecond laser imaging systems, 160
Multiphoton microscopy, 58, 59
Multiphoton microscopy and fluorescence lifetime imaging, 58
Mupirocin, indication/action for, 363
Musculoskeletal injuries, magnetic fields and, 57
Mutual recognition, for product approval in EU, 212
MW. See Molecular weight
MWFs. See Metal-working fluids
Mylan, 214
Mylan Fentanyl Transdermal System, 291, 300
Mylan Laboratories, 360
Mylan Technologies, 290, 358
Naltrexone, dermaportation and, 58
Nanoparticles, pressure wave-mediated delivery and, 54
Nanopatches, dissolving, 47
Nanotechnology, 365
Napkin dermatitis, environmental factors and, 385
National Academy of Sciences (NAS), 331
National procedure for product approval in EU, 212
Natural moisturizing factor, 4, 368, 387
skin quality and low levels of, 374
stratum corneum and, 9, 10
NCE development programs, more
traditional drug delivery modes and, 347
NCEs. See New chemical entities
NDAs. See New Drug Applications
Nd:YAG solid-state laser. See Neodymium-doped yttrium aluminum garnet solid-state laser
Near infrared, water profiles in atopy and, 158–159
Needlesticks, fear around, 69
Neodymium-doped yttrium aluminum garnet (Nd:YAG) solid-state laser, 162
Netherton syndrome, 375, 379
Neupro, 289, 347, 360
Neuralgia, 228
Neurodegenerative diseases, iontophoretic drug delivery and, 77–78
Neurodegenerative products, mandatory centralized procedure for, 213
New chemical entities, 233, 234, 345
allergic skin sensitization and, 241–242
carcinogenicity and, 238–239
dermal applications and standard testing program for, 252–253
general toxicology and, 234–235, 237
genotoxicity and, 237–238
line extension and, 245
local skin irritation and, 240–241
photosafety and, 242–244
reproductive toxicity and, 239
safety pharmacology and, 239–240
suboptimal drug delivery and, reasons for, 346
New Drug Applications, 347, 358
filing, 209, 211
New product development, qualitative/quantitative market research and investment in, 348–349
Nickel, AD and contact sensitization to, 384
Nicoderm (Alza), 289
Nicoderm CQ, flux, therapeutic dose range, and patch size, 292t
Nicotinamide, in vitro and in vivo absorption values for, 173t
Nicotinates, indication/action for, 363t
Nicotine
flux, therapeutic dose range, and patch size, 292t
indication, U.S. approval, and EU marketing of, 358t
pharmacokinetic and physicochemical properties of, 359t
Nicotine patches, generic versions of, 290
Nicotine transdermal product, manufacturer, transdermal flux, therapeutic dose, and patch size
Nicotinic acid
IVIV correlation, urinary collection times and, 168–169
total absorption of, from IVIV study conducted under harmonized protocol, 169t
in vitro and in vivo absorption values for, 173t
NIR. See Near infrared
Nito-Dur (Key Pharmaceutical), 289
Nitrobenzene, in vitro and in vivo absorption values for, 173t
Nitroglycerin
flux, therapeutic dose range, and patch size, 292t
indication, U.S. approval, and EU marketing of, 358t
pharmacokinetic and physicochemical properties of, 359t
transdermal delivery and use of, 33t
Nitroglycerin patches, generic versions of, 290
Nitroglycerin transdermal product, manufacturer, transdermal flux, therapeutic dose, and patch size
NMF. See Natural moisturizing factor
NMR. See Nuclear magnetic resonance
Nonanionic surfactants, 266
Nonclinical safety guidelines, 234
Nonclinical studies for pharmaceutical products, purpose of, 251
No-net-flux method, 140
Nonlinear methods, predictions of skin absorption and, 260–261
Nonocclusive passive transdermal formulations, 361
Nonocclusive transdermal systems, examples of additional Phase I type studies required by regulatory authorities for, 207t
Nonsteroidal anti-inflammatory agents, iontophoresis and delivery of, 70–71
Norelgestromin pharmacokinetic and physicochemical properties of, 359t
transdermal delivery and use of, 337
Norethindrone acetate, pharmacokinetic and physicochemical properties of, 359t
Norspan, 361
North America, pesticide regulation in, 187
Norwood Abbey Ltd., 53
Novartis, 352
Noven, 214, 289, 358, 360
NSAID for topical application development of formulation for: case study 3 aims, 275
development work, 275
technical challenges, 275
NSAIDs. See Nonsteroidal anti-inflammatory agents
NTS, flux, therapeutic dose range, and patch size, 292t
Nuclear magnetic resonance, 156, 160–161
Numerical methods, drug candidate selection and, 256
NuPathe Inc., 362
Nuvo Research, Inc., 365
Nystatin, indication/action for, 363t
OBJ Ltd., 58
Occlusive dressings, hydration and, 18
Occlusive transdermal systems, examples of additional Phase I type studies required by regulatory authorities for, 207t
Occlusivity, transdermal systems and, 298
Occupational exposure, to pesticides, 186
Octadecanoic acids, 157
OECD. See Organisation for Economic Cooperation and Development
OECD Secretariat, 184
OET. See Open epicutaneous test
Office of Pesticides Programs, 185
OFM. See Open flow microperfusion
Oil/water emulsions, 265
Ointments, 270
size of dosing area and, 251
topical dosage forms for, 263
Oleic acid, 157
fluorescence lifetime, anisotropy and, 160
skin barrier and biological effects of, 387, 391
in terbinafine formulation, drug uptake into SC and, 120
Olive oil, skin barrier and biological effects of, 387, 391
One-chambered static (vertical) diffusion cell design, 86, 88, 89
Open-coil probe, 136
Open epicutaneous test, 310, 312t
challenge phase and evaluation, 314
induction phase, 313
test material application, 313
Open flow microperfusion, 136
o-phenylphenol, in vitro and in vivo absorption values for, 173t
Opioids, iontophoresis, fast-acting pain relief and, 73–74, 76
OPPS. See Office of Pesticides Programs
Optimization test, 312t
classification scheme, 316t
evaluation, 316
induction phase, evaluation, and challenge phase, 315
Opto-thermal transient emission radiometry, 161
Oral dose forms, specified doses for, 220
Organisation for Economic Cooperation and Development, 184, 251, 278, 309
Test Guideline 427
complex formulations and, 191
dermal absorption studies for pesticides and, 186
Test Guideline 428, 85, 98, 100, 184
complex formulations and, 191
dermal absorption studies for pesticides and, 186
methods for assessing skin integrity in, 192
RF, solubility of test chemical and, 193–195
test guidelines, development of, 184–185
Orphan diseases, mandatory centralized procedure for, 213
Ortho Evra, 289, 361
Orthorhombic lattice lipid packing, stratum corneum and, 9
OT. See Optimization test
OTTER. See Opto-thermal transient emission radiometry
Oxidation reactions, product “in use” and, 267
Oxidative degradation, of drugs in aqueous solutions, 265–266
Oxybutynin 
indication, U.S. approval, and EU marketing of, 358t
pharmacokinetic and physicochemical properties of, 359t
transdermal delivery and use of, 33t
Oxytrol, 289, 360
Packing lattices, stratum corneum and, 9
Paediatric Investigation Plan, 213
Pain management, iontophoresis and, 70–71
Parabens, 244
Parafilm, 159
Paragraph IV filing, product protection from, 352–353
Parathyroid hormones, iontophoretic delivery of, 78
Parkinson’s disease 
iontophoretic drug delivery of
R-apomorphine and, 77–78
Neupro and, 360
transdermal drug delivery and, 347
Partition, permeant and, 24
Partition coefficient, skin permeation and, 17
PAR2 
expression of, from lesional skin of AD patients, 374
LB secretion and activation of, 372
molds and activation of, 377
thymic stromal lymphopoetin and, 379
Passive absorption of drugs through skin, pathways for, 23
Passive skin permeation enhancement, 23–38, 38
chemical permeation enhancers, 32–37
miscellaneous strategies, 37
skin and percutaneous absorption, 23–26
strategies to influence thermodynamic activity, 26–32
Passive topical local drug delivery, 362, 364
Passive transdermal systemic drug delivery, 357–362
history behind, 357–362
product launching in U.S. and Europe, 358t
PassPort system, 52
Patch adhesion, sample diary page for, 225
Patches 
examples of additional Phase I type studies required by regulatory authorities for, 207t
LidoSite lidocaine delivery system, 69
self-adhesive, 287
Patch formulations., assessment of adhesion properties, 224
Patch size, dosage strength and, 220
Patch test, for contact allergy, first, 310
Patent life of blockbuster drugs, expiring, global pharmaceutical industry and, 345
Patents 
obtaining, 205
Paragraph IV certification and, 353
Paticchei, 296
Patient-controlled anesthesia, morphine iontophoresis and, 73
Patient global assessment, 76
Patient information leaflets, 213
PCA. See Patient-controlled anesthesia
PDMS. See Polydimethylsiloxane
Pediatric populations, transdermal formulations and, 225–226
PEG. See Polyethylene glycol
Penetration enhancement 
aims of, 43–44
strategies for, 44
Peptides 
electroporation and delivery of, 57
iontophoresis and, 78–79
Percutaneous absorption
age and, 92–94, 93t
early studies in field of, 86
factors affecting drug permeation:
permeant properties, 24–25
ionization, 25
molecular size, 25
partition, 24
solubility/melting point, 25
factors related to, 311t
processes for, 24
race and, 94, 95t
safety evaluation of pesticides within EU and, 186–187
skin and, 23–26
Percutaneous absorption prediction, Flynn data set and development of, 258
Perfusate
calibration and, 139–140
DMD and, 137
Perfusate collection, MD system and, 133
Periodic Update Reports, 207, 214
Permeability barrier function, defined, 371
Permeation. See Skin permeation
Permeation enhancement
mechanisms of: case studies, 35–37
isopropyl myristate, 36, 36–37
propylene glycol, 35–36, 36
Permeation enhancers, 299–300
drug delivery and, 302
excipient compatibility and, 303
irritation/sensitization and, 306
performance parameters and, 301t
stability and, 305
wear properties and, 304
Permeation experiment, 96–98
application of test material, 96–97
duration of experiment, 97
membrane integrity, 96
number of replicates, 98
sample interval, 97–98
temperature, 98
Permeation profile, for highly volatile compound permeating through human skin in vitro, 97
Pentamethrin, indication/action for, 363t
Pesticides
assessent guidelines, subdivision F of, 310
elimination profile and, 198
within EU, risk assessment relating to, 186–187
human skin as gold standard for assessing dermal absorption of, 191
OECD test guidelines and studies on dermal absorption of, 185
PET. See Preservative efficacy test
PET films, 298
Pfizer, 351
PG. See Propylene glycol
PGA. See Patient global assessment pH
as antimicrobial barrier, 371–372
formulation characterization and, 281–282
skin barrier structure modulated by, 371
skin surface, atopic dermatitis and, 374
skin surface, skin barrier structure/function and, 389t
Pharmaceutical industry, global, challenges faced by, 345–346
Pharmaceutical product development, funding, 204
Pharmaceutics, 219–220
Pharmacokinetic evaluation, of dermal dosage forms, 220–221
Pharmacokinetics
innovative technologies to improve existing drugs and, 346
microdialysis and, 141–142
Pharmacology, excised human skin model in field of, areas related to, 177
Pharmacovigilance, 209
Pharmatrix, 289
Phase 0 clinical trials, 206
Phase I clinical trials, 206–208, 217
Phase II clinical trials, 208, 217
Phase III clinical trials, 208, 217
Phase IV clinical trials, 209
Phenol, in vitro and in vivo absorption values for, 173t
Phenols, 266
Phenoxyethanol, 266
Phenoxyisopropanol, indication/action for, 363t
Phentermine, 349
Phonophoresis, transdermal, 54
Phoresor II, 72
Index 435

Phospholipids, 265
Photoacoustic FTIR spectroscopy, depth profiling and, 159
Photoallergy, 224, 243–244
Photocytotoxicity, 243
Photogenotoxicity, 243, 244
Photoirritation potential, examining, 224
Photolabile drugs, 266
Photosafety, 224, 242–244
Phototoxicity, 243
Physicochemical properties of drug, 262
Pigmented films, 299
Pig skin, acceptance values for $T_2O$ permeability coefficient and electrical resistance, using standard diffusion cells for, 193
Pilocarpine iontophoresis, diagnosis of cystic fibrosis and, 73
PILs. See Patient information leaflets
Pimecrolimus, atopic dermatitis and, 383
Piroxicam indication/action for, 363 iontophoresis and delivery of, 71
Pirprofen, iontophoresis and delivery of, 70
$pKa$, physicochemical properties of drug and, 262
PK profiles, idealized, 293
Plasticizers, adhesive modifiers and, 300
Polyacrylates, 271
Polydimethylsiloxane, silanol end-blocked, advantages/disadvantages, 297
Polyethylene glycol, 194 drug solubility and, 265 solubilization effect and, 26
Polymers, stabilization of supersaturated systems and, 31
Polyols, drug solubility and, 265
Poly saccharides, 266
Polyurethane backing films, 298
Porcine skin, human skin and, 247
Potassium, specific gradients of, across epidermis, 371
Potts and Guy two-parameter model, prediction of dermal absorption and, 258, 259t, 260
p-phenylenediamine, in vitro and in vivo absorption values for, 173t
PpIX, iontophoretic delivery and, 72
Pre-clinical disease, 368
Pre-clinical phase, drug development and, 217
Pre-formulation stage, defined, 261
Pre-IND, 211
Pre-Investigational New Drug (IND) meeting, 217
Pre-New Drug Application (NDA) meeting, 217
Preservative content, formulation characterization and, 281
Preservative efficacy test, formulation characterization and, 282–283
Preservatives, commonly used, 266
Preventative medicine, 368
Primary pharmacodynamics, 233
Pro active inflammatory treatment, for atopic dermatitis, 383–384
Proactive medicine, 368
Probes, 133 categories of, 134, 135, 136 “cuff-off value” of, 136 DMD study and, 133–137 insertion of, 135, 137 manufacturing, 136t MD system and, 132, 133 measuring depth of, by ultrasound scanning, 138 placement in dermis, 134 uses for, 136 wire inside, 135
Prodrugs, transdermal delivery and, 101
Product concept, science or research and, 204
Product development, 203–215. See also
Transdermal product formulation development
chemistry, manufacturing, and controls, 209–210
clinical trials, 206–209
drug discovery, formulation, and toxicology testing, 205–206
ideas and money, 203–204
product launch and beyond, 214–215
protecting investments, 204–205
regulatory affairs, 210–214
for transdermal drug delivery, 345–355
ensuring the product is right, 350–351
identifying market opportunity with product to fit, 349–350
incremental vs. revolutionary change, 349
IP and product protection, 352–354
line extension for “Big Pharma,” 351–354
technology and, 354–351
Product launch, 214–215
Profilaggrin, 375
Profitability, global pharmaceutical industry and, 345
Proinflammatory cytokines, skin barrier disruption and, 378–379
Proline-rich proteins, 368
Propoxur, in vitro and in vivo absorption values for, 173
Propylene glycol, 159
drug solubility and, 265
mechanism of action for, 36
permeation enhancement and, 35–36
precipitation of ibuprofen within SC and, 118
solubilization effect and, 26
in vitro rate of absorption profiles of ketoconazole cream, with varying levels of, 178
Prostep (Elan), 289
ProStrakan, 350, 360
Protease inhibitors, atopic dermatitis and reduced expression of, 375
Protein envelope, stratum corneum, 7
Protein expression, assessment of human skin barrier structure/function and, 390
Proteins, iontophoresis and, 78–79
Proteolytic allergens, skin barrier breakdown and, 377
Pruritus
atopic dermatitis and, 380, 383
improving, with emollient use, 386
reducing, skin barrier repair therapies and, 388
Psoriasis, 228
barrier function and, 13–14
developing topical formulation for: case study 2
aim, 274
development approach, 274–275
technical challenges, 274
emollients and, 265
methotrexate iontophoresis and, 72–73
occlusive formulations for, 270
overexpression of SCCE and, 6
role of skin barrier in, 367
topical products for, special considerations, 226
Psoriatic skin, IR spectra from, pre- and post-treatment with UV radiation, 158
PSURs. See Periodic Update Reports
PII value, Draize rabbit model and interpretation of, 329, 329
Puckering, transdermal products and, 295
Pumps
in MD system, 133
microdialysis, 139
Pyrrolidones, 265
QC. See Quality control
Qnexa, 349
QSAR database, 241–242
QSPRs, 258–261
Quality control, formulation development and, 269–270
Quantitative structure-property activity relationships. See QSPR
Q values, experimental and predicted, DPK protocol and, 115, 116
Rabbit skin, acceptance values for T<sub>2</sub>O
permeability coefficient and electrical resistance, using standard diffusion cells for, 193
Race, percutaneous absorption and, 94, 95
Radiofrequency (RF) microelectrodes, 52
Radio waves, skin probing and, 156
Raman spectroscopy
confocal, 60
spectral profiles and, 159
R-apomorphine, iontophoretic drug delivery
of, 77–78
Rate and extent of drug delivery, 293
Rat skin
acceptance values for T2O permeability coefficient and electrical resistance, using standard diffusion cells for, 193
minipig skin vs., 248
normal, 248
RC. See Retardation coefficient
Reactive inflammatory treatment, for atopic dermatitis, 381–383
Rebound flare, atopic dermatitis, TCS and, 382–383
Receptor fluid, 103, 190, 193–195
Receptor solutions, in vitro skin permeation and, 89
Reconstructed human epidermis, 335
“Red burning skin syndrome,” 383
Reference chemicals
dermal absorption, good practice across industry sectors and, 195
interlaboratory comparison of, using human epidermal membranes, 196
Reference listed drug, 177, 354
Registry of Toxic Effects of Chemical Substances, 241
Regressional analysis, QSRRs and, disadvantages with, 260–261
Regulatory affairs, product development and, 210–214
Regulatory bodies
lack of worldwide harmonization across, 184
maintaining good relationships with, 213
microdialysis and, 148
Regulatory exclusivity periods, protecting investments and, 205
Regulatory process, drug development and, overview, 217–218
Relative humidity, stability testing and, 276
Relative recovery
calibration and, 139, 140
factors related to, 133
Release liners
for adhesive matrix, 299
drug delivery and, 301–302
excipient compatibility and, 303
irritation/sensitization and, 306
for liquid/gel reservoir transdermal patch, 288
performance parameters and, 301
for solid matrix transdermal patch, 288
stability and, 305
wear properties and, 304
Repeat-dose toxicity, 233
Repeat-dose toxicology, 234
Repeat irritation test, guinea pig, 330
Reproductive toxicity, 233, 239
Research, product concept and, 204
Retardation coefficient, 260
Retrodialysis
by calibrator, 140, 141
defined, 140–141
by drug, 140
Revenue growth, global pharmaceutical industry and, 345
RF. See Receptor fluid
RHE. See Reconstructed human epidermis
Rheology, formulation characterization and, 282
RIPT, 312
Draize human sensitzation test, 323, 324
Marzulli-Maibach modification, 323, 325
Shelanski-Shelanski test, 323, 324
variations of, 323
Voss-Griffin test, 323, 324–325
Risk assessment, 183–198
development of OECD test guidelines for dermal absorption, 184–185
good practice across all industry sectors, 190–198
complex formulations, 190–191
data interpretation, 195–198
reference chemicals, 195
RF and solubility of test chemical, 193–195
skin integrity measurement, 191–193
historical perspective, 183–184
introduction, 183
relative to pesticides within EU, 186–189
RIT. See Repeat irritation test
Ritalin, 349
Rivastigmine
  indication, U.S. approval, and EU marketing of, 358f
  pharmacokinetic and physicochemical properties of, 359f
  transdermal patch, 360
RLD. See Reference listed drug
RNAse 7, 5
Robinson-Wilschut model, prediction of dermal absorption and, 258, 259f
Rodent species, in safety studies, 247
Rosacea
  aqueous gel formulations and, 270
  developing topical gel formulation for: case study 1
    aim, 271
    developmental approach, 272–274
    technical challenges, 272
  role of skin barrier in, 367
  serine protease-PAR2 axis and, 372
Rotigotine
  indication, U.S. approval, and EU marketing of, 358f
  pharmacokinetic and physicochemical properties of, 359f
  Rotigotine patch, 360
Route of administration
  general toxicology and, 237
  reproductive toxicity and, 239
RR. See Relative recovery
RTECS. See Registry of Toxic Effects of Chemical Substances
Rubber adhesives, advantages and disadvantages with, 297
Safety monitoring and reporting, 214
Safety pharmacology, 233, 239–240
Safety studies, 233
  allergic sensitization, 241–242
  animal models, 246
  carcinogenicity, 238–239
  excipients, 244–245
  exposure, 249–250
  general toxicology, 234–235, 237
  genotoxicity, 237–238
  life cycle management, 245–246
  local skin irritation, 240–241
  photosafety, 242–244
  practical considerations, 250–252
  reproductive toxicity, 239
  safety pharmacology, 239–240
  species selection, 246–249
  standard testing for NCEs or excipients, 252–253
Safety surveillance (Phase IV trials), 209
Salicylic acid
  DMD, tape stripping and penetration of disrupted skin barrier, 143
  indication/action for, 363f
  in vitro and in vivo absorption values for, 173f
Sancuso, 289, 349–350, 360
Sano/Elan, 290
SAT. See Split adjuvant test
SAXD. See Small angle X-ray diffraction
SC. See Stratum corneum
Scabbing, 296
Scabies mites, filaggrin ingestion by, 377
SCC. See Squamous cell carcinomas
SCCE. See Stratum corneum chymotryptic enzyme
SC cohesion, human skin barrier structure/function and, 389f
SC compounds, molecular imaging of, skin barrier structure/function and, 389f
Schwartz-Peck test (and modifications), 312f
  description of, 322–323
  induction phase, usage period, and challenge phase, 323
Schwarz Pharma, 347, 360
Science, product concept and, 204
Scopolamine
  indication, U.S. approval, and EU marketing of, 358f
  pharmacokinetic and physicochemical properties of, 359f
SCTE. See Stratum corneum tryptic enzyme
Sebaceous glands, 4, 10–11
Sebum, function of, 11
Secondary pharmacodynamics, 233
Selegiline
  indication, U.S. approval, and EU marketing of, 358f
  pharmacokinetic and physicochemical properties of, 359f
Self-adhesive patches, 287
Semisolid formulation development program, key events of, 257
Semisolids
development of, 270–271
skin surface cleaning, formulation application and, 123
topical dosage forms, 263
transdermal products, 287
types of, 270
Sensitivity and irritation testing, 309–336
dermatopharmacokinetics, 310–311
factors affecting percutaneous absorption, 311
guinea pig sensitization tests, 311–318
historical perspective on, 309–310
human sensitization assays, 321–327
in mice, 318–321
for predicting sensitization potential, 312
skin irritation and corrosion, 327–336
Sensitization. See also Irritation/sensitization
testing, 206
transdermal products and, 296
Serendipity, product development and, examples, 291
Serine leukoprotease inhibitor, 369
Serine protease activity, barrier disruption and, 371
Serine protease-PAR2 axis
genetic/environmental factor interaction in, 378
skin barrier repair and, 372, 373
Shareholders, 204
Shear builders/filters, adhesive modifiers and, 299
Shelanski-Shelanski test (S-S test), 323, 324
Shire, 360
Side-by-side cell, 87
Side-by-side probe, 134, 135
Side effects
innovative technologies to improve existing drugs and, 346
transdermal drug delivery and reduction of, 347
Silberberg, Inge, 310
Silicone adhesives, 299
Silicone-coated release liners, 303
Silicon polymer adhesives, 296, 297
Single-application patch testing, 312t, 331–332
Single-layer networks, 261
Skin
allergic sensitization, 241–242
antimicrobial properties of, 372
complex structure of, 155
cross-section of, 4
fluorescent properties of, 160
IR spectrum of, 156
as largest organ of the body, 3
local irritancy of, 240–241
primary function of, 3, 23
psoriatic, IR spectra from, pre- and post-treatment with UV radiation, 158
structure and function of, 3–11
dermis and appendages, 10–11
epidermis, 4–10
subcutaneous tissue, 11
Skin, description of, 335
Skin abrasion
obstacles to commercial application of, 51
transdermal delivery and, 49–51
Skin and penetrant imaging, 59–60
Skin barrier, 367, 368–372
assessing structure and function of, 387–388, 390
defective, genetic susceptibility to, 374–376
homeostasis, 371–372
noninvasive assessment of structure and function in vivo, 389t–390t
physiological factors with influence on, 11–14
age, 11–12
anatomical site, 12
ethnicity, 12–13
gender, 13
skin disorders, 13–14
repair of, 386–387
structure of, 368–370
Skin barrier repair
clinical significance of, 388
preventing relapses of AD and, 385
Skin blood flow, aging, percutaneous absorption and, 94
Skin disorders, skin barrier and, 13–14
Skin exposure to agrochemical products, safety issues and, 187
Skin flexing, 48
Skin integrity measurement, dermal absorption, good practice across industry sectors and, 191–193
Skin irritation corrosion and, 327–328
in vitro assays of, 312t, 334–336
Skin membrane
design of in vitro skin permeation experiments and donor age effects, 92–94, 93t
intra- and intersubject variation, 92
membrane preparation, 95–96
racial differences, 94, 95t
storage conditions, 95
Skin irritation
corrosion and, 327–328
in vitro assays of, 312t, 334–336
Skin metabolism
in vitro skin perfusion methodology and, 100–103
detection of metabolism, 101
factors affecting enzymic activity, 102–103
modeling, 103
nature of enzymes, 100–101
prodrugs, 101
site of metabolism, 101–102
Skin permeation, 14
permanent physicochemical characteristics and, 16–18
hydration, 18
molecular size, 17
partition coefficient, 17
solubility, 18
Skin permeation assessment, methods for, 111
Skin permeation pathways, 14–16
permeation via appendages, 14–15
permeation via stratum corneum intercellular route, 16
transcellular route, 15–16
Skin reaction, microdialysis and, 138t
Skin stretching, 48–49
Skin surface cleaning, formulation application and, 122–123, 123
Skintex, 335
SLNs. See single-layer networks
SLPI. See Serine leukoprotease inhibitor
SLS. See Sodium lauryl sulfate
Small angle X-ray diffraction, 37
Soaps, atopic dermatitis and, 385 = 386
Sodium lauryl sulfate
atopic dermatitis and, 385
contact dermatitis, barrier reduction and, 13
Sodium pyrrolidone carboxylic acid, in corneocytes, 368
Solid matrix patches, 287
advantages and disadvantages with, 288
schematic, 288
Solids, topical dosage forms for, 263
Solubility of drug
in binary cosolvent system, 27
formulation development and, 267–268
permeant and, 25
physicochemical properties of drug and, 262
skin permeation and, 18
Solubilization, mixed cosolvent systems and, 26–27
Solute penetration in skin
massage and, 49
skin abrasion and, 49–51
skin flexing and, 48
skin stretching and, 48–49
tape stripping and, 48
Solvent-borne adhesives, 296
Solvents
loss of, supersaturated states and, 30
pre-formulation study and selection of, 268
Somerset Pharmaceuticals, 360
Sonophoresis, transdermal, 54
SonoPrep, 365
Sound waves, skin probing and, 156
SPA. See Special Protocol Assessment
SPC. See Summary of Product Characteristics
Special Protocol Assessment, 211
Species selection, for in vivo dermal testing, 246–249
Spectrophotometric method, tape stripping, quantifying removal of SC and, 124–125
Spectroscopic methods of skin permeation, 155–163
conclusions and future of, 163
electromagnetic spectrum, 156
electronic, 160–161
NMR, 160–161
UV and fluorescence, 160
electron spin resonance, 161
impedance, 162
laser-induced breakdown spectroscopy, 162
opto-thermal transient emission radiometry, 161
skin structure, 155
vibrational, 156–159
Sphingolipids, ceramides in stratum corneum and, 8
SPINK5 gene, 369, 379
Split adjuvant test, 310, 312
challenge phase and evaluation, 317
induction phase, 316–317
Sprays, transdermal, 287
Squamous cell carcinomas, iontophoretic delivery of cisplatin and, 72
SR oral drug delivery, 351
Stability of adhesive modifiers, 305
of adhesives, 305
of backing film, 305
of drug product, 304–305
ICH, 283
of permeation enhancers, 305
of release liners, 305
transdermal products and, 295
Stability testing, topical product formulation and, 276
Staphylococcus aureus, 377, 385
Statistical analysis (linear vs. nonlinear) methods, QSPRs and, 260–261
Sterility, formulation characterization and, 283
Stop-flow/flow-rate method, 140
Storage, enzymic activity, skin permeation and, 102–103
Strakan, 289
Stratum basale, 5, 5–6, 7
Stratum corneum, 3, 4, 4, 5, 7–10, 43
growing and, 11–12, 93
biophysics of, 8–9
chemical permeation enhancers and, 265
complex formulations and, 190
composition of, 109
cumulative thickness removed, 127
description of, 7
DPK approach and drug distribution profiles across, 113–118, 114
clearance phase, 112, 117–118
uptake phase, 112, 114–117
drug partitioning into, 24
hydration of, 18
molecular structure of ceramides in, 8
NMR and studying hydration of, 160
occlusivity, transdermal systems and, 298
permeation via intercellular route, 16
via transcellular route, 15–16
permeation pathways, 15
as primary skin barrier, 368
skin permeation and, 17
structure of, 155
tape stripping and quantifying removal of, 124–125
thickness of, at different body sites, 370, 370
total thickness of, determining, 125–126
transdermal drug delivery and, 347
two-chamber cell and, 86–87
water examined in vivo within, with
microwave dielectric analysis, 159
water in, 9–10
Stratum corneum chymotryptic enzyme, 6, 369
Stratum corneum lipids, lateral packing and molecular arrangement of, 9
Stratum corneum thiol protease, 369
Stratum corneum trypsin enzyme, 369
Stratum granulosum, 6, 7
Stratum lucidum, 6
Stratum spinosum, 5, 6, 7
Subclinical skin barrier defect, genetic/environmental factor interaction in, 377–378
Subcutaneous tissues, 3, 11
Subepidermal capillary, 4
Sulforhodamine B
LTR formation in full-thickness human cadaver skin with, 54
LTR formation in pig skin with, 54
Sumatriptan iontophoresis, for migraine, 76–77, 362
Summary of Product Characteristics, 213
Sunflower oil, skin barrier and biological effects of, 387, 391
Supersaturated systems
production of, 26–27, 30
loss of solvent, 30
mixed cosolvent systems, 26–27, 30
stabilization of, and effect of additives, 31–32
Supersaturation studies, for transdermal drug delivery, 28–29;
Surface adsorption theory, 31
Surfactants, 265
Sweat ducts, 4
Sweat glands, 4, 4, 10, 11
Sweat pores, 4
Synera, 365
Synergy, product development and, 291
Synthetic dermal assay systems, 335
Tackifiers, adhesive modifiers and, 300
Tacrine, iontophoretic drug delivery of, 77
Tacrolimus, atopic dermatitis and, 383
Tape stripping, 48, 109–127. See also
   Dermatopharmacokinetic approach
   acute barrier damage by, 371
   applications of, 110–121
dermatopharmacokinetic approach and, 110–122
   FDA draft guidance, 111
   improving, 113–118
   perspective and limitation with, 121–122
two-time approach, 119–120
   experimental procedure and validation, 122–127
data processing, 126–127
determination of total SC thickness, 125–126
   formulation application, 122
   quantification of drug in tape strips, 125
   quantification of SC removed, 124–125
   skin surface cleaning, 122–123
   tape stripping procedure, 123–124
   overview of, 109–110
   procedure for, 123–124, 124
   schematic representation of, 110
Tape strips, quantification of drug in, 125
Tazarotene, indication/action for, 363
TCL. See Topical calcineurin inhibitors
TCS
   atopic dermatitis and potency of, 381–383
   reducing flares in AD and, 384
Tea catechins, electroporation and delivery of, 55
Technology, applications best fit for, questions related to, 347–348
Teflon, diffusion cell design and, 88, 89
Tegaderm dressing, with EMLA cream, 18
Teikoku, 289
TER. See Transcutaneous electrical resistance
Terbinafine
   ATR-FTIR and quantification of, 125
   drug uptake into SC with oleic acid added to, 120
   indication/action for, 363
Terbutiline sulfate penetration, magnetic fields and, 57
Terpenes, 36
Terpentine oil, indication/action for, 363
Testim, 361
   Paragraph IV filing and, 353, 354
Test Method B6, of the European Community, 310
Testoderm (Alza), 289
Testosterone products, 361–362
   age-related differences in percutaneous absorption of, 93
   indication, U.S. approval, and EU marketing of, 358
   interlaboratory comparison of, using human epidermal membranes, 196
   in OECD guidance, 195
   pharmacokinetic and physicochemical properties of, 359
   rate of absorption of estradiol and, from excised skin and in human subjects, 177
   total absorption from IVIV studies conducted under harmonized protocol, 170
   transdermal delivery and use of, 33, 176, 228
   transdermal products, black box warnings and, 207
in vitro and in vivo absorption values for, 173–174
Tetracaine, electroporation and delivery of, 55
TEWL. See Transepidermal water loss
TGA. See Therapeutic Goods Association
Tg.AC mouse model, carcinogenicity studies and, 238–239
Th2 cytokines, 381
subclinical inflammation and, 379, 380
Therapeutic Goods Association (Australia), 218
Theratech/Watson, 289
Thermal ablation, 52–53
Thermodynamic activity
production of supersaturated systems, 26–30
loss of solvent, 30
mixed cosolvent systems, 26–27, 30
other techniques, 30
Thermometers, infrared, for measuring skin surface temperature, 98
Thiourea
IVIV correlation, urinary collection times and, 168
total absorption of, from IVIV study conducted under harmonized protocol, 169
in vitro and in vivo absorption values for, 174
3M, 289
3T3 neutral red uptake (NUR) assay, 243
Th2 polarization, 379
Thymic stromal lymphopoetin, subclinical inflammation and, 379
Timolol, electroporation and delivery of, 55
Tissue trauma, microdialysis and, 138–139
Tocopherols, 266
Tolnaftate, indication/action for, 363
Topical calcineurin inhibitors, 383
anti-pruritic action of, 383
reducing flares in AD and, 384
Topical dermatological corticosteroids, special considerations for, 226–227
Topical dosage forms, typical, 264
Topical drug delivery, 362–365
active topical local drug delivery, 364–365
passive topical local drug delivery, 362, 364
skin disorders and, 13–14
Topical drugs, examples, and indications for human use, 363
Topical efficacy, drug concentration and, 262–263
Topical product formulation development, 255–283
analytical method, 267
compatibility, 268–269
decision tree, based on drug physicochemical properties, 273
decision tree, based on formulation type, 272
dosage forms, 263
drug candidate selection, 256
ethos of, 256
formulation characterization, 281–283
drug content and uniformity, 281
macroscopic/microscopic appearance and odor, 281
microbial quality or MLT and PET, 282–283
pH, 281–282
preservative content, 281
rheology and viscosity, 282
sterility, 283
formulation optimization, 279–280
formulation selection, 280
ICH stability, 283
initial considerations of drug, 262–263
drug pharmacology and topical efficacy, 262–263
drug physicochemical properties, 262
key events in, 257
philosophy of, 255–256
pre-formulation studies, overview, 261–262
QSPRs, 258–261
statistical analysis methods, 260–261
summary of, for prediction of dermal absorption, 259
selection of excipients, 263–267
product “in use” considerations, 267
regulatory perspective, 263–265
role of excipients, 265–266
solubility, 267–268
stability testing, 276
Topical product formulation development (cont’d)

- target profiles, 269–275
- development approach case studies, 271–272, 274–275
- semisolid topical formulations, 270–271
- *in vitro* drug release studies, 276–277
- *in vitro* skin permeation studies, 278–279

Topical products

- BA/BE of: dermatopharmacokinetic approach, 110–120
- drug distribution across the SC, 113–118
- FDA draft guidance, 111–113
- “two-time” approach, 119–120
- excipients and, 118

Topical semisolids, solvent selection for, 268

Topiramate, 349

Total flux, of permeant through skin, 25

Toxicity

- genotoxicity, 237–238
- linking to exposure, 249–250
- reproductive, 239

Toxicology

- excised human skin model in field of, 177
- areas related to, 234–235, 237

Toxicology testing, drug discovery, formulation and, 205–206

Transappendageal route, 23

Transcellular drug diffusion, 23

Transcellular route, permeation via stratum corneum, 15–16

Transcutaneous electrical resistance, skin corrosion studies and, 336

Transcutol, 157

Transdermal, defined, 287

Transdermal drug delivery, 357–362

- active transdermal systemic drug delivery, 362
- advantages with, 346–347
- focus on existing molecules, 347
- IP and product protection, 352–354
- limitations with, 347
- line extension for “Big Pharma,” 351–354
- mechanical methods, 48–51
- massage, 49
- skin abrasion, 49–51
- skin flexing, 48
- skin stretching, 48–49
- tape stripping, 48
- new product development for, 348–355
- passive transdermal systemic drug delivery, 357–362
- pharmacokinetic and physicochemical properties, commercially available for human use, 359
- side effects and, 347
- skin disorders and, 13–14
- supersaturation studies for, 28–29
- technology: push or pull?, 345–351
- ensuring the product is right, 350–351
- identifying market opportunity with product to fit, 349–350
- incremental vs. revolutionary change, 349
- typical enhancers used in, 33

*in vitro-in vivo* correlation, 176

Transdermal formulations, pediatric populations and, 225–226

Transdermal iontophoresis

- antiemetics, 78
- clinical applications of, 67–80
- “how” and “why” of iontophoresis, 67–68
- topical application: increasing local bioavailability, 68–73
- peptides and proteins, 78–79
- systemic applications: antimigraine drugs, 76–77
- opioids, 73–76
- treatment of neurodegenerative diseases, 77–78

Transdermally administered products, examples of additional Phase I type studies required by regulatory authorities for, 207

Transdermal patches

- annual manufacture of, 43
- branded, FDA-approved, 290
- generic versions of, 290
- hydration and, 18
- solid matrix, 288
- types of, 287
Transdermal product formulation development, 287–306
design considerations, 291–300
drug delivery, 292
  efficiency, 293
  rate and extent, 293
excipient compatibility and acceptability, 294
excipients, 296–300
  adhesive modifiers, 299–300
  adhesives, 296–297
  backing films, 297–299
  permeation enhancers, 300
  release liners, 299
history behind, 289–290
interaction and examples, 300–306
delivery vs. and example, 300–302
excipient compatibility, 302–304
irritation/sensitization vs., 305–306
between performance parameters and system components, 301
stability vs., 304–305
wear vs., 304
irritation and sensitization, 295–296
overview, 287–289
performance criteria, 292–300
philosophy of product development, 290–291
  constrained optimization, 291
  function over form/time = money/research vs. development, 291–292
  serendipity and synergy, examples, 291
stability, 295
transdermal product examples, 292
wear, 294–295
Transdermal products
bioavailability and bioequivalence of, 221–222
examples of, 292
interference from other applied products and, 223
labeling aspects of, 224
specified doses for, 220
types of, 287
Transderm Nitro, 289
Transderm Scop, 176, 289
Transepidermal route, 23
Transepidermal water loss, 237
aging skin and, 12
atopic dermatitis and increase in, 373, 374
damaged skin barrier and, 142
gender and, 13
impedance and, 162
preventing, skin barrier and, 368
skin integrity measurement and, 191–192
subclinical skin barrier defect in AD and, 376
tape stripping, total thickness of SC and, 126
tape stripping and, 48, 113, 114, 123–124
Transference studies, 221, 222–223, 229
TransPharma, 52
Transtec, 361
Traub-Tusing-Spoon method, 322
Tretinoin, indication/action for, 363
tretinoin gels, in vitro comparison of primary end points for test and reference for, 179
Triacetin, 265
Triamcinolone, indication/action for, 363
Triclopyr BEE, in vitro and in vivo absorption values for, 174
Trilosan, indication/action for, 363
TSLP. See Thymic stromal lymphopoetin
Tumor necrosis factor-alpha
  normal skin barrier repair and, 372
  skin barrier disruption and, 378
Two-chambered diffusion cell design, 86
“Two-time” approach, 119–120, 127 benefits with, 119–120
  key features of, 119
UCB, 360
Ultrasound
  enhanced transdermal delivery and, 54–55
  probe depth measured with, 138
Ultraviolet, skin probing and, 156
Ultraviolet (UV) radiation, 3
United States
  clinical trials in, 219
  product approval system in, 210–212
Universal receptor approach, advantages of, 194
Upsher-Smith Laboratories, Inc., 353, 354
Uptake phase, dermatopharmacokinetic approach, drug distribution across SC and, 112, 114–115, 117
Urea
in corneocytes, 368
indication/action for, 363t
moisturizers with, 387
in vitro and in vivo absorption values for, 174t
Urocanic acid, in corneocytes, 368
UVA/UVB filters, tape stripping, DPK approach and, 122
UVA/UVB rays, photosafety evaluation and, 243, 244

Vaccine delivery
electroporation and, 57
microneedles for, 44–48
ultrasound and, 55
VAET, 312r, 321
Vasodilatation, assessment of human skin barrier structure/function and, 389t
VE, hydrophobic drugs and drug absorption, 24
Vegetable oils, skin barrier and biological effects of, 387
Vehicle, investigating potential toxic effects of, 235
V8 protease, 377
Viable epidermis, 4
ViaDerm system, 52, 53
Vials, in MD system, 133
Vibrational spectroscopic methods, 156–159
Vidarabine monophosphate, iontophoresis and delivery of, 71–72
Vinblastine solution, iontophoretic delivery of, 73
Viscosity, formulation characterization and, 282
Vital systems, safety pharmacology and, 239
Vitamin C
electroporation and delivery of, 55
skin abrasion and delivery of, 50
Vitronectin, in dermis, 10
Vivelle-DOT, 347
flux, therapeutic dose range, and patch size, 292t
Vivus, 349
Volar forearm, hydration profiles of, after 90 minutes occlusion and hydration, 159
Voss-Griffith test, 323, 324–325
Vyteris, Inc., 69
Washing studies, dermal products, interference from other applied products and, 223, 229
Washing the skin, atomic dermatitis and, 385–386
Water
as natural skin penetration enhancer, 18
skin irritation and dryness related to, 386 in stratum corneum, 9–10
Water solubility, in vitro absorption studies and, 91
Watery liquids, size of dosing area and, 251
Watson Pharmaceuticals, 290, 360
Watson/Theratech, 289
WAXD. See Wide angle X-ray diffraction
Wear properties
adhesive modifiers and, 304
adhesives and, 304
backing film and, 304
drug and, 304
permeation enhancers and, 304
release liners and, 304
for transdermal products, 294
Webril, 333
Webril/Blenderm patches, 325
WHI. See Women’s Health Initiative
Wide angle X-ray diffraction, 37
Women’s Health Initiative, 361
Xenobiotic metabolizing enzymes, nature of, 100–101
Xerosis, 374, 380
X-rays, skin probing and, 156
Zars Pharma, 365
Zelrix, 362
Zero-net-flux method, 140