а

analysis of variance (ANOVA) 88, 90-92, aberrant and atypical result. See continued method performance verification absolute evaluation of intercept 158-159 acceptable deviation, evaluation of calibration models 159-160 acceptance criteria 27, 30, 79 - analytical procedures transfer 353, 355 accuracy 132–135 detector testing for 31 - for equivalence testing 358-363 - precision 95-107 procedure performance acceptance criteria (PPAC) 51, 59-64, 69 acceptance limit 6, 30, 78-79, 83, 84, 125, 288, 291, 319, 320, 367 - for accuracy 121, 128 - for observed bias 125 - joint evaluation of accuracy and precision 136 - precision 158, 165, 175, 369 - specification 82, 97, 101, 105, 119, 166, 309, 310 accuracy 63-64, 177-178, 335 - and range 119-121, 137 – acceptance criteria (ATP requirements) 132 - 135– – drug product 126–127 - - drug substance 122-126 – integration mode accuracy 130–131 - - and precision joint evaluation 136 - - response factors 131-132 – spiked impurities recovery 129–130 quantitative tests 70 relationship with precision 64–65 actuation profile experiments 330-331 additivity of variances principle 84-85

98-99, 101, 117, 264, 277 - lack-of-fit test 157 analytical instrument and system qualification (AISO). See under analytical instrument qualification (AIQ) analytical instrument qualification (AIQ) 12, 14.18 - analytical instrument and system qualification (AISQ) risk-based approaches 20, 23-25 - data quality and integrity in good manufacturing practice (GMP) 11-12 - definition 14 - efficient and economic HPLC performance qualification 36-37 - - AIQ importance 25-27 - - continuous PQ general procedures 34 - 36- - control charts 33-34 – modular parameters transfer into holistic approach 29-32 – OQ/PQ data in comparison with SST data 32 - 33 – revised OQ/PQ parameter list development 27-29 - importance of 25 - roles and responsibilities 17-18 - terminology clarification 19 - United States Pharmacopeia (USP) General Chapter <1058> 12, 14-20 analytical procedures transfer 348-349 - comparative testing 355-371 - coordination 350, 352 - experimental studies design and acceptance criteria 353, 355 - familiarization and training 353

Method Validation in Pharmaceutical Analysis: A Guide to Best Practice, Second Edition. Edited by Joachim Ermer and Phil Nethercote. © 2015 Wiley-VCH Verlag GmbH & Co. KGaA. Published 2015 by Wiley-VCH Verlag GmbH & Co. KGaA.

411

```
412 Index
```

analytical procedures transfer (contd.) regulatory and international guidance 349 - 350 result evaluation and transfer report 355 h - strategy 352-353 analytical quality by design (AQbD) 217-220, 223-224, 240-241 - control strategy 239-240 C design of experiments (DOE) 225–227 failure mode effect analysis (FMEA) 227 - 230 – illustrative case study 231–234 method validation requirements 220–221 robustness 221–223 - statistical analysis for robustness example 234 - 237analytical significance 84 analytical target profile (ATP) 4-8, 41,326 - 334 bias and uncertainty in procedure 50–51 decision rules 42–43 - - compliance 43-45 – – guard bands 48–49 - derivation 343-345 – example 56–57 - feasibility testing 345-346 - finalizing 346 - fitness definition 42 key performance indicators 51 measurement uncertainty 51 – – estimation 53–55 – – meaning 51–52 – random variability sources 55 - - reporting 52-53 target measurement uncertainty – analysis cost 49–50 – – calculation 45–47 analytical transfer team (ATT) 350, 352 analytical validation analytical life cycle 8–9 analytical target profile (ATP) 5–8 – concepts and process development 1–4 - three-stage approach to analytical life-cycle validation 4-5 assay 62 - accuracy 63-65 – linearity 67 - precision 62-65 range 67–68 specificity 65–67 automated delivered dose uniformity procedure 333-334

autosampler 29 - temperature accuracy 29

bias 119, 178 - and uncertainty 50-51

calibration 19, 180-182 - format optimization 97-99 – of impurity determinations 99–101 – model 121, 162 – – requirements 146 - multiple point 146, 159 - multi-variate 163 - single-point 88, 119, 121, 151, 152, 158, 161-163, 308, 315 - universal 122 chromatographic and functional assays 359-363 chromatographic system suitability parameters 288 - 290- injection precision 291-293 signal-to-noise ratio 290–291 - system precision for impurities 293 - test for required detectability 291 chromatography data system (CDS) 35 coefficient of correlation 153-154 coefficient of variation (CV) 62-63, 85-86, 97 - 98combined uncertainty 53 - calculation 55 comparative testing direct comparison 367–369 - - accuracy 370-371 -- precision 369-370 - equivalence-based methodology 355-356 – acceptance criteria for equivalence testing 358 - 363 – decision procedure 365–367 – inter-laboratory study 357–358 - - principle 356-357 - - real example 367 – statistical analysis 363–364 – transfer end-points 358 compendial/pharmacopeia test procedures implementation 348 - background 337 - challenges and need for verification 338 - 339- current approach to verification of procedures 339-340 - current verification process and lifecycle approach integration 340

- generation and publishing of methods 336 - 337- implementation using lifecycle approach 341 - 346- performance gualification 346-347 use of procedures in laboratory for first time 339 confidence intervals (CIs) 81-84, 150-151, 364 continued method performance verification 377 aberrant data investigation – atypical and aberrant results classification 393-399 – laboratory failure investigation 391-393, 405 - - statistical outlier tests for out-of expectation results 399-405 - continual improvement 406 - - control of change 406-409 - routine monitoring 377-380 – control chart application examples to analytical procedures 382-383 – control chart establishment 380–382 – periodic review 383–385 – root cause determination using CuSum analysis 385-390 continuous knowledge feedback loop 342 continuous performance qualification (cPO) 8 - general procedures 34-36 control charts 33-34, 378-388 control strategy 342-343 critical analytical method variables (CAMVs) 218, 224 critical method attributes (CMAs) 218, 223-226,231 critical method variables (CMVs) 218, 224, 231, 239 CuSum analysis 385-390

d

data quality
components 14
triangle 14
– enhanced 22
decision rules. See under analytical target profile (ATP)
design of experiments (DOE) 209, 212–213, 215, 218, 224–227, 231–234, 239, 245, 258, 286
design qualification (DQ) 14, 26
detection limit. See under quantitation limit detector drift 32

detector noise 31 differential scanning calorimetry (DSC) 122 diode array detection 142–143 diode array detector (DAD)-UV 199, 200 Dixon's Q-test 401–403 DryLab 245–256, 258, 270

е

empirical procedure 55 equivalence data analysis methods 363–364 equivalence tests 124–125, 132, 156 – for intercept 158 EURACHEM approach 174, 266 expanded uncertainty 53 – calculation 55 extrapolation 158–159 extreme studentized deviate (ESD). *See* Grubb's test

f

failure mode effect analysis (FMEA) 227–230, 331–333 fish-bone diagram 55, 74, 223, 231, 327, 329, 366 fit, robustness study 271–276 flow rate accuracy 29–30 Food and Drug Administration (FDA) 1, 3, 4 four Qs model 14–15

function of mutual information (FUMI) 84

g

good manufacturing practice (GMP) data quality and integrity 11
quality data criteria 11–12
regulatory rationale for qualified analytical instruments 12
Graybill–Wang Modified Large Sample (MLS) method 364
Grubb's test 399, 402

GUM 46-47

h

Hampel test 403-405
heteroscedasticity 160
high performance liquid chromatography (HPLC) 36-37, 195
AIQ importance 25-27
calculation method 396
calculation table 398
continuous PQ general procedures 34-36
control charts 33-34, 378-388
Dixon's test on example data 403
Hampel's method on example data 405
injection sequence 396

high performance liquid chromatography (HPLC) (contd.) method gualification for identity, assay, and degradation products case study 308 - 310- - accuracy 318-320 – experimental 310 - - linearity 314-318 – – precision 320–321 - - qualification summary 310, 313-314 - - quantitation limit 321, 323 – – range 323–324 – specificity 314 - modular parameters transfer into holistic approach 29-32 - OQ/PQ data in comparison with SST data 32 - 33peak area data 397 - revised OQ/PQ parameter list development 27 - 29- risk assessment of change in column manufacturer 408 – sampling diagram 394 standard bracketing scheme 395 homoscedasticity 148 HorRat value 69, 93 Horwitz curve 93 Horwitz equation 68-69, 93 application to concentration values 69 - 70

i

injection precision. See system precision injection volume

accuracy 27
linearity 29

installation qualification (IQ) 14, 26
intermediate precision 62–63, 115–116, 179, 203–205, 321
International Conference on the Harmonisation (ICH) 1–2, 8, 41, 60, 242
International Society of Pharmaceutical Engineering (ISPE) 349–352
Ishikawa diagram. See fish-bone diagram

j

JMP Pro Statistical software (SAS, version 10.0) 234

I

lack-of-fit tests. *See* statistical linearity tests Lambert–Beer law 147 law of propagation of errors 97 LC-MS 143-145 LC-Simulator ACD labs software 203 least-squares regression. See unweighted linear regression leverage 150 limit of detection (LOD) 29 limit of quantitation (LOQ) 209 limit tests 69 - limit of detection (LOD) 69-70 - precision 70 specificity 70 linearity 145-147, 180, 335 - assay procedure 67 - calibration models 162 - DL/QL determination 167-174 - of injection volume and detector response 29 - nonlinear and regression techniques 162 - 163- unweighted linear regression 147-151 - - graphical evaluation 151-153 – intercept evaluation (systematic errors absence) 158-160 – numerical regression parameters 153 - 155 – statistical linearity tests 155–158 - weighted linear regression 160-161

m

Maldener test 85 Manhattan plot 389-391 measurement requirement establishment 59 - 60- assay procedure 62 -- accuracy 63-65 - - linearity 67 -- precision 62-65 -- range 67-68 -- specificity 65-67 - identification 60-62 - impurities 68-69 - limit tests 69 – limit of detection (LOD) 69–70 - - precision 70 – – specificity 70 – purpose 60 - quantitative tests - - accuracy 70 -- precision 71 – specificity and range 71 measurement uncertainty 51, 182 - estimation 53-55 - meaning 51-52

- random variability sources 55 - reporting 52-53 method capability index 78 method design and understanding 191–192 - analytical quality by design (AQbD) 217-220, 223-241 - - control strategy 239-240 - - design of experiments (DOE) 225-227 – failure mode effect analysis (FMEA) 227 - 230- - illustrative case study 231-234 – method validation requirements 220-221 – – robustness 221–223 – statistical analysis for robustness example 234 case study robustness investigations 241 - 243- - basic and intrinsic parameters 243-245 - - computer-assisted robustness studies examples 245-287 - development 194-205 - optimization 203, 206-217 - selection 192-194 system suitability tests (SSTs) 287–288 – chromatographic parameters 288–293 – – design 294 – non-chromatographic system parameters 293 - 294method operable design region (MODR) 209, 212-215, 219, 237 method performance characteristics 73-74 - accuracy and range 119-121, 137 – acceptance criteria (ATP requirements) 132 - 135- - accuracy and precision joint evaluation 136 – – drug product 126–127 - - drug substance 122-126 – integration mode accuracy 130–131 – – response factors 131–132 – spiked impurities recovery 129–130 - detection and quantitation limit – approached based on blank 167 – comparison of approaches 175–176 - - DL/QL determination from linearity 167 - 174 – pharmaceutical impurity determination requirements 164-167 – precision-based approaches 174–175 - linearity 145-147, 163-164 - - calibration models 162 – nonlinear and regression techniques 162 - 163

 – unweighted linear regression 147–160 - - weighted linear regression 160-161 - precision 74 - - acceptance criteria 95-107 – – benchmarks 107–116 – concentration dependency 93–95 --levels 84-89 – normal distribution and parameters 74 - 84- - sources 116-118 – – and variance calculation 89–93 - specificity 137-140, 145 - - chromatographic resolution 140-141 - - demonstration by accuracy 140 - - peak purity (co-elution) 141-145 method performance qualification 303-305 - analytical procedures transfer 348-349 - - comparative testing 355-371 - - coordination 350, 352 – experimental studies design and acceptance criteria 353, 355 - - familiarization and training 353 – regulatory and international guidance 349 - 350- - result evaluation and transfer report 355 - - strategy 352-353 - compendial/pharmacopeia test procedures implementation 348 - - background 337 - - challenges and need for verification 338-339 – current approach to verification of procedures 339-340 – current verification process and lifecycle approach integration 340 - - generation and publishing of methods 336 - 337 – implementation using lifecycle approach 341 - 346 – performance qualification 346–347 – use of procedures in laboratory for first time 339 - HPLC method qualification for identity, assay, and degradation products case study 308-310 -- accuracy 318-320 - - experimental 310 -- linearity 314-318 - - precision 320-321 – qualification summary 310, 313–314 - - quantitation limit 321, 323 -- range 323-324 - - specificity 314

- precision study example 305-307

method performance gualification (contd.) pressurized metered dose inhaler delivered dose uniformity procedure design and gualification – analytical control strategy summary 336-337 – analytical procedures 324–325 - - design to meet ATP 326-334 – human and environmental factors 325 – performance characteristics 334–335 - - qualification 335-336 – testing for inhalation products 325–326 method qualification 9 mixture-related factors, in robustness studies 266 - 267mobile phase proportioning 30 MODDE software package 267, 270, 271, 275, 280, 281, 286, 287 model independent tests 157-158 multiple linear regression (MLR) 262

n

noise and drift measurement 30–32 non-chromatographic system parameters 293 normal distribution curve 45

0

observed bias 133
omeprazole 61
one-factor-a-time (OFAT) approach 245
operationally defined procedure. *See* empirical procedure
operational qualification (OQ) 15, 26
– comparison with SST data 32–33
– revised parameter list development 27–29
out-of expectation (OOE) 385, 394, 399–405
out-of-specification (OOS) 386, 391, 393, 405

р

percentage recovery calculation 127–128
performance-based approach 61
performance qualification (PQ) 15, 26–27
comparison with SST data 32–33
general procedures 34–36
revised list for HPLC instrument qualification 28
Plackett-Burman design 226–228, 260, 267–270, 279, 286
precision 62–63, 119, 178, 335
acceptance criteria
acceptable precision for assay 101–105
acceptable precision for impurities and minor components 105–107 - - calibration format optimization 97-101 - benchmarks 107-108 – intermediate precision and reproducibility 115 - 116- - repeatability 108, 112-115 – system precision 108 - concentration dependency 93-95 intermediate precision and reproducibility 86,88-89 - levels 84-89 limit tests 70 - normal distribution and parameters 74-84 - quantitative tests 71 - relationship with accuracy 64-65 - repeatability 86 - reportable result 95-97 – sources 116–117 – stability studies 117–118 - system and instrument precision 85-86 - variance calculation 89-93 - - from linear regression 92-93 prediction interval 150-151 prediction profiler 235-236 pressurized metered dose inhaler delivered dose uniformity procedure design and qualification - analytical control strategy summary 336-337 analytical procedures 324–325 design to meet ATP 326-334 human and environmental factors 325 performance characteristics 334–335 - qualification 335-336 - testing for inhalation products 325-326 probability approach 64, 102-105 procedure acceptance criteria 61 procedure performance acceptance criteria (PPAC) 51, 59-64, 69 procedure performance measures (PPMs) 51, 59-61, 63, 65, 68 proportional model 158 pure error 271, 274

9

qualification 19, 25
design (DQ) 14
installation (IQ) 14, 26
method 9
operational (OQ) 15, 26
performance (PQ) 15, 26–28, 32–36
qualified equipment 8
qualitative factors, in robustness studies 266
quality analytical profile (QAP) 223

quality by design (ObD) 2-3, 9, 41-42, 194, 197,214 - method terminology 220 quality risk management (QRM) 11 quality target method profile (QTMP) 223 Ouality Target Product Profile 5-6 quantitation limit 164, 176-177, 181, 321, 323 - approached based on blank 167 comparison of approaches 175–176 - DL/QL determination from linearity 167 - 169 – approach based on German Standard DIN 172 - 173 – regression line 95% prediction interval 171 - 174 – relative uncertainty 173–174 - - standard deviation of response 169 - 171- pharmaceutical impurity determination requirements 164-165 – general quantitation limit 166–167 – intermediate quantitation limit 166 - precision-based approaches 174-175 quantitative factors, in robustness studies 265 - 266quantitative tests - accuracy 70 - precision 71 - specificity and range 71 r

range 180, 323–324. See also under accuracy - assay procedure 67-68 - quantitative tests 71 rechromatography 141-142 recording limit 172 recovery 120, 122, 135, 319-320, 324 – dose 333 - function 128 - impurities 129-130 - percent 120, 126-128 regression – linear 92–93 - multiple (MLR) 262 - unweighted 147-160 - weighted 148, 160-161 relative standard deviation (RSD) 7, 32-33, 65, 68-69, 75, 89-90, 94, 108, 135, 291, 292, 356, 363. See also precision repeatability 62, 86, 108, 112-115, 179, 292, 321 repeated median estimator 163

reportable result 6-8, 41-44, 95-97, 179-180, 228, 293, 303-305, 308, 324, 345 - 347reproducibility 63, 115-116, 179, 207-275 residuals 151-152 residual standard deviation 154-155, 170 response factor 153 reversed phase chromatography 137–138, 196, 199 reversed-phase high-performance liquid chromatography (RP-HPLC) 198, 201 risk assessment model 23 risk priority number (RPN) 229-230 robust parameter 84 robustness investigations case study 242 - 243- basic and intrinsic parameters 243-245 computer-assisted robustness studies examples 245 – testing based on chromatography modeling software 246-258 – testing based on experimental design 258, 261-287

root mean square error (RMSE) 234

s

sensitivities 152-153 shaking profile experiments 329-330 signal-to-noise ratio 290-291 – measurement 29 significance tests 84, 122-124, 156 solvent delivery system 29-30 specification - limit 46, 82, 97, 101, 105, 119, 166, 309, 310 - out-of 385, 391, 393, 405 - performance-based 59 - zone 42, 47-48 specificity 60, 65, 137-140, 145, 181, 334 assay procedure 65–67 - chromatographic procedures 65-66 chromatographic resolution 140–141 - demonstration by accuracy 140 – limit tests 70 non-chromatographic procedures 66–67 - peak purity (co-elution) 141-145 - quantitative tests 71 spiking 126 standard addition 128-129, 162 standard deviation 102 - calculation 89 – confidence intervals 82 - distribution 77 - of intercept 170-171 - normally distributed datasets 78-80

standard deviation (contd.) - reporting 80-81 - uncertainty 80,83 standard error 81, 82 - of prediction 129 statistical evaluations 158 statistical outlier tests, for out-of expectation results 399-405 studentized residuals 151 student-t-factor 82, 102 supercritical fluid chromatography (SFC) 196 system precision 80, 83, 85-87, 93, 108, 179, 291-293, 320-321 - for impurities 293 system repeatability 292 system suitability tests (SSTs) 26 - 27, 83,108, 117, 182, 214, 304, 380 chromatographic system suitability parameters 288-290 – injection precision 291 – signal-to-noise ratio 290–291 – system precision for impurities 293 – test for required detectability 291 - comparison with operational and performance qualification data 32-33 - design 294-295 non-chromatographic system parameters 293 - 294t target measurement uncertainty

target measurement uncertainty – analysis cost 49–50 – calculation 45–47 target standard deviation (TSD) 107 thermostating precision 29 tolerance/prediction interval approach 102 top-down approach precision 74

и

United States Pharmacopeia (USP) General Chapter <1058> 12, 14

– AIQ

- - roles and responsibilities 17-18

- - terminology clarification 19 - analytical apparatus, instruments, and systems 19-20 analytical instrument gualification life cycle 14 - 15 data quality triangle 14 - enhanced data quality triangle 20 - increased granularity 18-19 - instrument groups mapping to GAMP software categories 20 - risk-based classification of apparatus, instruments, and systems 15-17 software validation 18 unweighted linear regression 147-160 user requirement specifications (URS) 26 v validation 19, 25, 59 analytical. See analytical validation - characteristics 2, 138 - definition 59 - during drug development 60-61, 126, 129 – life-cycle 5, 8 – of linearity 147 - method 4, 220-221

- pharmacopoeial methods 338

30

148

Ζ

w

z-scores 399-400

- process 13, 378

software 18, 310

wavelength accuracy

weighted regression

variance of injection 86

– protocol 140 – simultaneous 137

- study 121