Table of contents

Preface i
Acknowledgments iii
List of abbreviations and acronyms v
Introduction ix
Chapter 1 – ISO compliance
1.1 Introduction 1
1.2 Total quality management philosophy 2
1.3 Good Laboratory Practices and Good Management Practices 3
1.4 ISO 15189 4
1.4.1 Principles 4
1.4.2 Selection of examination procedure 6
1.4.3 Verification of examination procedure 6
1.4.4 Validation of examination procedure 8
1.4.5 Measurement uncertainty of measured quantity values 8
1.4.6 Internal quality control 9
1.4.7 External quality assessment/proficiency testing 10
1.5 ISO 9001 10
1.5.1 Principles 10
1.5.2 Technical requirements and ISO 9001 12
1.5.3 ISO 9001 requirements crossed with medical laboratory technical specifications 12
1.5.4 ISO 9001 added-value to the medical laboratory 13
1.6 Discussion / Conclusion 13
References 18
Chapter 2 – Significant causes of error in qualitative tests
2.1 Introduction 23
2.2 Analytical uncertainty components 24
2.2.1 Effect on the trueness of binary results 24
2.2.2 Lack of the equilibrium of immunoassay reaction 27
2.2.3 Carry-over 28
2.2.4 Reagent and calibrator lot effects 28
2.2.5 Biased results caused by interfering factors 29
2.2.6 Quality policy to reduce the impact of analytical uncertainty to weak positive results using the "gray zone" and trinary classification 32

2.2.7 Analytical sensitivity and analytical specificity in molecular diagnostic methods for infectious diseases 32
2.3 Biological uncertainty components 33
2.3.1 Bias by the seroconversion window period 33
2.3.2 Bias by erroneous diagnostic in the samples for estimating the diagnostic accuracy 33
2.3.3 Biased results by mutation of agents 34
2.3.4 Other types of biological bias 34
2.4 Discussion/Conclusion 35
References 37
Chapter 3 – Measurement uncertainty and analytical total error in qualitative tests
3.1 Introduction 41
3.2 The dilemmas of measurement uncertainty and total analytical error 41
3.3 Metrological traceability of the results 47
3.4 Evaluation by the "Uncertainty Approach" 48
3.4.1 Principles 48
3.4.2 Empirical approach: Single-laboratory validation 51
3.4.3 Empirical approach: Interlaboratory comparisons 52
3.4.4 Empirical approach: External quality assessment/proficiency testing 52
3.4.5 Calculus of expanded uncertainty *U* 53
3.4.6 Report measurement uncertainty 53
3.4.7 Compliance assessment 54
3.4.8 Case study 1: Screening immunoassay (short-term data) 55
3.4.9 Case study 2: Screening immunoassay (long-term data) 57
3.4.10 Case study 3: Screening immunoassay (EQA/PT data) 57
3.4.11 Case study 4: Nucleic acid test 58
3.5 Evaluation by the "Error Approach" 59
3.5.1 Principles 59
3.5.2 Empirical approach: Single-laboratory validation 60
3.5.3 Empirical approach: Interlaboratory comparisons 61
3.5.4 Empirical approach: External quality assessment/proficiency testing 61
3.5.5 Calculus of total analytical error 61
3.5.6 Compliance assessment 61
3.5.7 Case study 5: Screening immunoassay (short-term data) 62
3.5.8 Case study 6: Screening immunoassay (long-term data) 62
3.5.9 Case study 7: Screening immunoassay (EQA/PT data) 63

3.5.10 Case study 8: Nucleic acid test 63
3.6 Evaluation of analyte concentrations near the cutoff by the C_5-C_{95} interval 64
3.6.1 Principles 64
3.6.2 Samples 66
3.6.3 Technique model 66
3.6.4 Compliance assessment 66
3.6.5 Case study 9: immunoassay 68
3.7 Discussion / Conclusion 70
References 72
Chapter 4 – Performance of binary classification tests
4.1 Introduction 79
4.2 Principles 80
4.3 Samples 80
4.3.1 Samples of individuals with the true condition 80
4.3.2 Samples of individuals without the true condition 81
4.4 Condition accuracy 81
4.4.1 The approach 81
4.4.2 Condition sensitivity 82
4.4.3 Condition specificity 84
4.4.4 Paired comparison of condition sensitivity and specificity of the two tests 86
4.4.5 Complementary measurements 88
4.4.6 Condition uncertainty 90
4.4.7 Case study 10: Screening immunoassay evaluation 91
4.4.8 Case study 11: Comparison of a pair of screening immunoassays 93
4.4.9 Case study 12: ABO blood test evaluation 95
4.4.10 Case study 13: HLA typing 96
4.4.11 Case study 14: Chromosome analysis evaluation 98
4.5 Condition accuracy by analyzing numerical data 99
4.5.1 The approach 99
4.5.2 Equations 99
4.5.3 Compliance assessment 100
4.5.4 Case study 15: Two qualitative tests 100
4.6 Seronegative window period 102
4.6.1 Principles 102
4.6.2 Equation 103
4.6.3 Compliance assessment 103
4.6.4 Case study 16: Screening immunoassay 104

4.7 Discussion / Conclusion 105
References 107
Chapter 5 – Agreement of binary classification tests
5.1 Introduction 111
5.2 Principles 111
5.3 Samples 112
5.3.1 Positive samples 112
5.3.2 Negative samples 112
5.4 Agreement 112
5.4.1 The approach 112
5.4.2 Overall agreement 113
5.4.3 Positive agreement 113
5.4.4 Negative agreement 114
5.4.5 Compliance assessment 115
5.4.6 Agreement uncertainty 115
5.5 Case study 17: Screening immunoassay 115
5.6 Discussion / Conclusion 117
References 119
Chapter 6 – Computation of the cutoff for "in-house" and modified tests
6.1 Introduction 121
6.2 Receiver operating characteristic curve 121
6.2.1 Principles 121
6.2.2 ROC curve 122
6.2.3 Area under the curve 124
6.2.4 Hypothetical values to identify the cutoff 127
6.2.5 The importance of sensitivity-specificity tradeoffs 128
6.2.6 The importance of the efficiency and the Youden's index 128
6.2.7 Samples 129
6.2.8 Case study 18: Efficiency of 100% 130
6.2.9 Case study 19: Efficiency less than 100% 132
6.3 Discussion / Conclusion 136
References 137
Chapter 7 – Internal quality control and external quality assessment
7.1 Introduction 139
7.2 Understanding the causes of variation 140
7.3 Quality control material 141
7.3.1 Principles 141

7.3.2 Vial to vial variability 142
7.3.3 Level of the concentration of the measurand 142
7.3.4 Assayed versus unassayed controls 145
7.3.5 Pretreatment steps 145
7.3.6 Matrix 145
7.4 Quality control principles 146
7.5 Establishing IQC frequency 148
7.6 Internal quality control, approach I: qualitative results classified on an ordinal scale 148
7.6.1 The approach 148
7.6.2 Analytical run 149
7.6.3 Probability of error detection and the probability of false rejection 149
7.6.4 Control rules 150
7.6.5 Single-rule and multirule quality control 153
7.6.6 Actions for when a rule is violated 154
7.6.7 Multistage quality control strategy 155
7.6.8 Power function graph 155
7.6.9 Critical systematic error 158
7.6.10 Sigma metrics 159
7.6.11 Case study 20: Ordinal test and DPMO-derived sigma metric 163
7.6.12 Case study 21: Ordinal test and SE_{crit}-derived sigma metric 164
7.7 Internal quality control, approach II: "pure" qualitative results not quantifiable 165
7.7.1 The approach 165
7.7.2 Control rules 166
7.7.3 Case study 22: Nominal test and DPMO-derived sigma metric 166
7.8 External quality assessment/proficiency testing 167
7.8.1 The approach 167
7.8.2 Types of EQA/PT schemes 169
7.8.3 *z*-score 170
7.8.4 Compliance assessment 170
7.9 Discussion / Conclusion 171
References 174
Index of terms **179**