THERMAL VALIDATION IN MOIST HEAT STERILIZATION



Jeanne Moldenhauer Editor

CONTENTS

Introduction

I	Thermal Validation and Why it is Important Jeanne Moldenhauer	I
	Introduction	I
	Physical Validation of Sterilization Processes	2
	Uses of Temperature Distribution and Heat Penetration Studies	5
	Installation and commissioning of equipment	5
	Installation Qualification (IQ)	6
	Engineering evaluations	7
	Operational Qualification (OQ)	7
	Empty chamber temperature distribution	7
	Mapping studies	9
	Heat penetration studies	11
	Performance Qualification (PQ)	11
	Temperature distribution studies	11
	Heat penetration studies	12
	Maintenance of validation status	13
	Troubleshooting aberrant cycles	13
	Maintenance support	14
	Conclusion	14

iii

References About the Author

2 Steam Sterilization Process Validation

James Agalloco

Introduction Validation Supportive Activities Equipment Qualification (EQ) Installation Qualification (IQ) Operational Qualification (OQ) Validation maintenance Sterilization process development Performance Qualification (PQ) Introduction to sterilization Component mapping Determination of sterilization process objective Empty chamber studies Load definition Temperature penetration/biological indicator studies Validation using the overkill method Validation using the BB/BI and bioburden methods Additional perspectives on terminal sterilization Sterilization-in-place (SIP) Equivalence in Validation Sterilizer equivalence Load equivalence Container equivalence Formulation equivalence Product equivalence Multiple equivalence Time equivalence Equivalence for sterilization processes Establishing equivalence **Biological Indicators** Validation Maintenance/Change Control/Re-validation Conclusion Appendix 1: Steam Sterilization Overkill Acceptance Criteria References

About the Author

iv

	Contents	v
3	Regulatory Expectations for Thermal	
	Validation — USA	51
	Jeanne Moldenhauer	
	Introduction	51
	United States Regulatory Expectations	51
	Calibration	53
	Sterilizers using steam or air-steam mixtures	54
	Sterilizers using superheated water	54
	Minimum sterilization processing	55 55
	Testing of sterilization processes	55 55
	Heat distribution studies	55
	Heat penetration studies	
	Sterilization process design	56 57
	Sterilization process controls	57 59
	Expectations of U.S. Regulators During Inspections Sterilization Validation Document to be Submitted in Support	37
	of Product Applications	63
	Heat distribution (also called temperature distribution) and	63
	heat penetration studies	63
	Thermal monitors	63
	The effects of loading on thermal input	64
	Information to be included in the batch record	65
	Sterilization in Support of Aseptic Processing Applications	65
	The qualification of sterilizers	65
	Requirements for thermal validation studies	66
	Sterilization of equpment, containers and closures	67
	Equipment controls and instrument calibration	68
	Routine operation	69
	Conclusion	69
	Acknowledgements	69
	References	69
	About the Author	70
4	European Expectations For Thermal Validation	71
	Roland Marie Frédéric Guinet	
	Introduction	71
	Validation	73
	Risk Assessment	77
	European Pharmacopoeia (EP) and European Medicines	
	Agency (EMA)	79
	EU GMP Annex 1	82
	General principles for all sterilisation processes	82

General principles for heat sterilisation processes	83
Moist heat specific points	84
Annex I §94	84
Annex I §95	84
Annex I §96	95
Dry heat specific points	95
Performance Qualification of Sterilisation Processes	95
General recommendations for moist heat, dry heat and SIP	95
Definition of loads to be sterilised or depyrogenised	86
Physical qualification	87
Biological qualification	90
Review and Approval of Validation	
Ongoing Control	
Routine monitoring and/or release	92
System suitability	93
Change control	93
Periodic regualification/revalidation	94
Conclusion	95
References	
About the Author	

5 The EMEA's Decision Tree for Selection of Sterilisation Methods

Jeanne Moldenhauer Introduction Background Flow Chart Explaining the Sterilization Choices for Aqueous Products Conclusion References About the Author

6 Importance of Accurate Measurements in Thermal Validation Studies

Göran Bringert Introduction Industry Trends Regulations, Standards and Guidance for Validation Quality Management Systems European Community Risk Assessment and Risk Management

vi

Contents

Corrective Action Preventive Action (CAPA) Application Specific Regulations **Environmental Testing** Summary of Standards and Regulations Process measurement uncertainty requirements Overall validation system Test Uncertainty Ratio (TUR) Regulatory Requirements for Calibration Calibration Calibration Uncertainty and Calibration Ratios **Calibration Procedure** Pre-study calibration Post-study calibration Post-study verification **Calibration Basics** Transfer standard Temperature reference Transfer Calibration Error **Reducing Stem Conduction Errors** Pressure Measurement Thermal Process Validation FDA definition of process validation What Is Critical? **Risk** assessment Validation Concept Definitions Validation Validation plan Validation protocol Validation report Validation procedure Lethality Calculation **Process Temperature Uniformity Overall Validation System Uncertainty Error Sources** Sensor Design **Response Time** Thermocouple Specifics **Temperature Sensors** Insulation Simplified Thermoelectric Theory Nonhomogeneous Regions Resistance Thermometers (RTDs) Validation Studies Temperature distribution studies

Thermal mapping Heat penetration studies Measuring System Errors About the Author

7 Performance of Thermal Validation Studies

Kevin Trupp Introduction Details for Moist Heat Sterilization Applications Saturated steam sterilizers Steam Air Mixture (SAM) sterilizers Superheated water sterilizers Commodity processors Steam In Place (SIP) Details for Dry Heat Sterilization Applications Details for Gaseous and Sterilization/Decontamination **Applications** Ethylene Oxide Vaporized Hydrogen Peroxide (VHP) Details for Controlled Environmental Applications Common Issues Related to Thermal Validation Summary and Conclusions About the Author

8 Practical Aspects of Thermal Validation for Moist Heat Sterilization

Angela S. Coon and Michael J. Sadowski Introduction Moist Heat Sterilization Process Applications Distribution Temperature and Heat Penetration Temperature Types of Thermal Probes and Datalogging Systems used to Monitor Temperature Distribution and Heat Penetration Temperature in the Development and Validation of Moist Heat Sterilization Processes Wired Temperature Datalogging Systems Wirless Temperature Datalogging System Sterilization Science: Principles of Microorganism Inactivation Sterile Sterility Sterilization Probability of a Non-Sterile Unit (PNSU)

viii

Contents

Biological indicator D_T -value z-value F-value **F**_{PHY} Spore Log Reduction (SLR) Development of Moist Heat Sterilization Processes Characterization of Process Load Selection of the Moist Heat Sterilization Process Type Saturated Steam Processes Saturated Steam Gravity Displacement Cycles Air Overpressure Processes Steam-air Mixture (SAM) Process Superheated Water Process Steam Characteristics **Temperature Distribution Studies** Considerations in the Development of Efficient Loading Patterns Heat Penetration Studies **Probing Techniques** Cold Spot Studies Porous/Hard Goods Master Site/Master Solution Determination Studies Determination of Sterilization Cycle Parameters Key and Critical Parameters Heat up conditions Exposure (dwell) temperature Exposure (dwell) pressure Exposure (dwell) time Physical Lethality Requirements from Regulatory Standards Physical Lethality Requirements Based on the Overkill Design Approach Physical Lethality Requirements Based on the Product Specific Design Approach Determination of Exposure Time Required to Deliver Minimum Lethality Requirements Post Exposure Conditions Limitations of Temperature Probes in the Prediction of Microbiological Inactivation During Qualification of Moist Heat Sterilization Processes Performance Qualification (PQ) Predecessors to Performance Qualification Physical Qualification Microbiological Qualification

PNSU Calculations Requalification Optimization of the Moist Heat Sterilization Processes Summary References About the Authors

9 Analysis of Heating and Cooling Data

Dr. Irving Pflug Brief Background to Conduction-Heat Transfer Heating and Cooling Objects or Products in Containers Conduction-Heat Transfer Solution to a Problem of Unsteady-State, Conduction-Heat Transfer Using the Sphere as the Example Geometrical Shape Solution to the Problem of Unsteady-State-Conduction-Heat Trasfer in an Infinite Cylinder Convection-Heat Transfer Heating Products in Containers Analysis of Natural Convection–Heat Transfer Using a Newtonian-Heating Approach Unsteady-State Heat Transfer Graphically, Conduction and Convection Example Heating and Cooling Graphs Plotting and Analyzing Heating and Cooling Data The Semilogarithmic-Graph Paper The Temperature Scale The Heating-Medium Temperature Plotting the Data Points Drawing a Straight Line Through the Data Points A Discussion of Autoclave or Retort Come-Up Time, the Corrected-Zero Time, and the Use of the Corrected-Zero Time in Calculating the F_{h} -Value Autoclave Temperature Validation Literature Cited About the Author

Glossary

Index

х