Global Regulatory Frameworks

Produced by the Animal Health Institute

Quality System & *Description*	**PIC/S** (PE 009-12, Parts 1 & 2; Jan 2017 version)	**9 CFR**	**MHRA Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017** "Orange Guide"	**WHO Annex 2- Good Manufacturing Practices for Biological Products**
Site Master Plan *The firm has developed a site master plan providing a high level overview of the facility, products and systems. The site master plan is periodically reviewed.*	No specific section on site master plan; however Part 1 and 2 (and Annex 1 sections as well) imply a plan is required. Chapter 4 PE 009-13 (Part 2) 01JAN17 pg 8 "*Buildings and Facilities* ". Also implies in Chapter 4 PE 009-13 (Part 1) 01JAN17 pg 25 (4.29) "*Documentation* ".	9 CFR 102.3, 102.4, 102.5(c)(3), (VSM 800.50) 104.5, (VSM 800.101), 113.6, 113.50, (VSM 800.51) 114.7(a), 108.1 - 108.7 (VSM 800.78)	Part III: GMP Related Documents, Section 1-9 Explanatory Notes on the Preparation of a Site Master File	Section 4 "Principles and general considerations", pages 104 - 105
Quality Manual *The firm has developed a Quality Manual defining the oversight functions of the Quality Unit.*	Part 1, Ch 1 (*Introduction*), Pg 1: *Pharmaceutical Quality System* and Part 2, Pg 4, Sec 2: *Quality Management*	VSM 800.53; VSM 800.59; VSM 800.63; 9 CFR 102.4(b)(2); 9 CFR 116	Chapter 2 "EU Guidance on Good Manufacturing Practice", section 1.7	Section 5 " Pharmaceutical quality system and quality risk management", page 106. Main reference: Pharmaceutical Quality System as defined in A*nnex 2 WHO Good Manufacturing Practices for Pharmaceutical Products* : main principles pages 85 - 88.
Stability for Expiration Dating of Serials *The firm has a program to define initial product stability.*	Part 1, Ch 6 (*Quality Control*), Pg 37: *On-going Stability Programme* and Part 2, Ch 11 (*Laboratory Controls*), Pg. 28, Sec. 11.5: *Stability Monitoring of APIs*	9 CFR 114.13	Chapter 11 "Laboratory Controls" section 11.50 to 11.56.	Section 16 "Quality Control Samples" 16.2 and 16.5 pages 121 - 122
Extension of Expiration dating of serials *The firm has a process for evaluate and seek approval for serial specific data extensions.*	Part 2, Ch 11 (*Laboratory Controls*), Pg 28, Sec. 11.6: *Expiry and Retest Dating* Note: Not specific to product serials	9 CFR 114.14	Chapter 11 "Laboratory Controls" section 11.60 to 11.63	Section 16 "Quality Control Samples", 16.6 page 122 Note: not specifically discussed.
On-going Stability Testing *The firm has an ongoing stability program that includes annually placing serials on stabilty testing during the dating of the product.*	Part 1, Ch 6 (*Quality Control*), Pg 37, Sec 6.26-36: *On-going Stability Programme* and Part 2, Ch 11 (*Laboratory Controls*), Pg 28, Sec 11.5: *Stability Monitoring of APIs*	VSM 800.77; 9 CFR 114.12; 9 CFR 114.13	Chapter 6 "Quality Control", section 6.28 to 6.36 "On-going stablity programme" Chapter 11 "Laboratory Controls" section 11.50 to 11.56.	Section 16 "Quality Control", 16.6, page 122
Validation Master Plan *The firm has completed a master plan outlining validation approaches.*	Part 2, Ch 12 (*Validation*), Pg 29 and Annex 15: *Qualification Validation*	9 CFR 109.2 & 116; ICSOP0013.03, Section 8.6; VSM 800.91	Annex 15 "Qualification and Validation", section 1.5	Section 4 "Principles and general consideration" Paragraph 3 page 122, and Section 9 "Premises and Equipment" 9.2 page 111 ; 9.4 (cleaning validation) page 112; Section 15 "Validation" 15.1 page 119 (process validation)
Cleaning Validation *The firm has validated the effectiveness of defined cleaning and sanitization procedures.*	Part 1, Ch 5 (*Production*), Pg 28, Sec 5.21-24: *Validation* and Part 2, Ch 12 (*Validation*), Pg 32, Sec 12.7: *Cleaning Validation* and Annex 15: *Qualification Validation*	9 CFR 108.5(b)(1)	Annex 15 "Qualification and Validation", section 10	Section 9 "Premises and Equipment" 9.2 page 111 ; 9.4 (cleaning validation) page 112;

Process Validation *The firm has defined through process validation key parameters of the manufacturing procedure and monitors these parameters on a continual basis.*	Part 1, Ch 5 (*Production*), Pg 28, Sec 5.21-24: *Validation* and Part 2, Ch 12 (*Validation*), Pg 30, Sec 12.4: (*Approaches to Process Validation*) & Pg 31, Sec. 12.5: *Process Validation Program*	9 CFR 102.3(b)(2)(ii), 104.5(a)(5), & 114.8(d); VSM 800.50 & 800.101	Part 1 Basic Requirements for Medicinal Products Chapter 5 Production Section Validation 5.23 through 5.26; Annex 15 Qualification and Validation* and 2017 Chapter 12 Validation 12.1 through 12.8	Section 15 "Validation" 15.3 and 15.4 page 120 (process validation and critical process monitoring)
Analytical Method Validation *The firm has validated the reporducibilty and accuracy of testing methods, including codified assays.*	Part 2, Ch 12 (*Validation*), Pg 33, Sec 12.8: *Validation of Analytical Methods* and Annex 15: *Qualification Validation*	VSM 800.50 & 800.112; 9 CFR 113.8, 113.5(e), 113.7(b), & 113.9; assorted Supplemental Assay Methods	Part 2 Basic Requirements for Active Substances Used as Starting Materials Chapter 12 Validation 12.8 and Annex 15 Qualification and Validation*	Section 16 "Quality Control" 16.7 page 122 (process validation)
Computer System Validation *The firm has oversite and validation of computer systems, databases and spreadsheets used in preparing or testing product.*	Part 2, Ch 5 (*Process Equipment*), Pg 13, Sec 5.4: *Computerized Systems*	9 CFR 116.1; VSM 800.122	Part 2 Basic Requirements for Active Substances Used as Starting Materials Chapter 12 Validation 12.1 and Annex II Annex II Potential Applications for Quality Risk Management - reference II.4 and Annex 11 Computised Systems (Project Phase 4 Validation)	Not addressed in document
Media Fills *The firm conducts media fill checks on a defined basis and after major changes.*	Part 1, Ch 6 (*Quality Control*), Pg 36-37, Sec 6.19, 6.21, & 6.23	VSM 800.53, 800.59, & 800.63; 9 CFR 116 & 102.4(b)(2); ICSOP0013.03, Section 3.4	Part 2 Basic Requirements for Active Substances Used as Starting Materials Chapter 12 Validation and Annex 15 Qualification and Validation*	No specific mention of Media Fills. However, in Section 11 "Clean Rooms" references WHO Environmental monitoring of clean rooms in vaccine manufacturing facilities. If one looks into this WHO document another document is referenced which specifically discusses Sterile Media Files *WHO Technical Report Series, No. 961, 2011 Annex 6 WHO good manufacturing practices for sterile pharmaceutical products.*
Preventive Maintenance Program *The firm has a program that defines when preventative maintenance is performed on key equipment on a defined frequency.*	Part 2, Ch 5 (*Process Equipment*), Pg 11, Sec 5.2: *Equipment Maintenance and Cleaning*	VSM 800.91	Annex II Potential Applications for Quality Risk Management - reference II.4	PM program is not specifically mentioned in the Annex 2 however, embedded in the document are sections referencing regularly checking the performance of HEPAs (Section 10.6 page 114). Also reference The PM program should be discussed in the Quality Risk Management (QRM) document for Production.
Calibration *The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.*	Part 2, Ch 5 (*Process Equipment*), Pg 12, Sec 5.3: *Calibration*	9 CFR 109.2; VSM 800.91; ICSOP0013.03 Section 8.6	Part 1 Basic Requirements for Medicinal Products Chapter 5 Production Section 5.3	Section 15 "Validation" page 119 implies that a QRM approach should be used to determine the scope and extent of validation, which also implies a PM program is needed as well as calibration of equipment.
Document Control *The firm has a program to control the issuance of manufacturing documents, testing methods and SOP's.*	Part 1, Ch 4, Pg 17-25: *Documentation* and Part 2, Ch 6, Pg 14-18: *Documentation and Records*	9 CFR 116.1 - 116.8	Part 1 Basic Requirements for Medicinal Products Chapter 4 Documentation	Section 17 "Documentation (batch processing records)" page 122

Label Control *Establishment and maintenance of procedures to control labeling activities including the integrity, quality inspection and storage of the label. The procedures should also include the labeling operations for packaging of a product.*	Part 1, Ch 5 (*Production*), Pg 30, Sec 5.40-43: *Packaging Materials* & Sec 5.44-57: *Packaging Operations* and Part 2, Ch 9, Pg 23-25 (*Packaging and Identification Labelling of APIs and Intermediates*)	VSM 800.54 & 800.208; 9 CFR 112.1 - 112.10 & 116.3	Part 1 Basic Requirements for Medicinal Products Chapter 4 Documentation and Chapter 5 Packaging Materials, Packaging Operations 5.45 through 5.70; Part 2 Basic Requirements for Active Substances Used as Starting Materials Chapter 6 Section 6.3 and Chapter 9 Packaging and Identification Labelling of APIs and Intermediates	Section 14 "Labeling" page 119
Specification Management *The firm has written testing specifications for each material (solutions to final product) produced at the site.*	Part 1, Ch 4, Pg 17-25 *Documentation* and Part 2, Ch 6, Pg 14-18: *Documentation and Records*	VSM 800.51 & 800.206; 9 CFR 114.8, 113.50, & 113.53	Part 1 Basic Requirements for Medicinal Products Chapter 6	Section 7 "Starting Materials" page 107 and Section 17 "Documentation (batch processing records)" 17.3-17.4 page 123
Training Program *The firm has a defined employee training and qualification program for proceedures and processes, including periodic retraining.*	Part 1, Ch 2 (*Personnel*), Pg 11, Sec 2.10-2.14: *Training* and Part 2, Ch 3 (*Personnel*), Sec 3.1: *Personnel Qualifications*	VSM 800.63; 9 CFR 114.7	Part I, Chapter 2, Sections 2.10 through 2.14; Part I, Annex 1, Point 36; Part I Annex 5, Points 1 and 2; Part II, Chapter 3, Sections 3.10 through 3.12	Section 6 "Personnel" 6.1, and 6.3 pages 106-107
Deviation/Investigation/ CAPA Program *The firm has a define process for conducting and documenting investigations, including root cause analysis and CAPA implementation.*	Part 1, Ch 1 (*Pharmaceutical Quality System*), Pg 7, Sec 1.12-13: *Quality Risk Managment* a nd Annex 20: *Quality Risk Management*	VSM 800.210; 9 CFR 116.5(b)	Part I, Chapter 8; Sections 8.16 through 8.19; Part I, Annex 16 Chapter 3; Part III, Quality Risk Management Section	Section 4 "Principles and general considerations" page 104 and Section 5 "Pharmaceutical quality system an quality risk management" page 106
Change Control / Change Management *The firm has a program to evalaute, track, and control changes in a systematic approach. The change control program includes input from a cross functional group.*	Part 2, Ch 13, Pg 33-34: *Change Control* and Part 2, Ch 2, Pg 4-5: *Quality Risk Management* and Annex 20: *Quality Risk Management*	OoP; 9 CFR 114.9(a) & 114.8	Part 1, Annex 15, Sections 11.1 through 11.7; Part II, Chapter 13	Section 4 "Principles and general considerations" page 104 and Section 5 "Pharmaceutical quality system and quality risk management" page 106
Inventory Management *The firm has an electronic system (ex. SAP) for inventory and release management.*	Part 1, Ch 5, Pg 26-32: *Production* and Part 2, Ch 10, Pg 25: *Storage and Distribution*	VSM 800.108; 9 CFR 116.2	Part I, Chapter 4, Sections 4.27 through 4.28; Part I, Chapter 5, Sections 5.63 through 5.70; Part I, Annex 16, Chapter 4, Sections 4.1 through 4.3; Part II, Chapter 10	Section 7 " Starting Materials" 7.1 page 107 references "*...finished product should be clearly defined and controlled according to the principles set out in Annex 2 WHO Good Manufacturing Practices for Pharmaceutical Products. Section 8 'Seed lots and cell banks' 8.11 page 111"*
Market Action/Recall Management *The firm has defined processes for conducting market action.*	Part 1, Ch 8, Pg 43-44: *Complaints and Product Recall* and Part 2, Ch 15, Pg 36: *Complaints and Recalls*	VSM 800.57 & 800.60; 9 CFR 115.2(b) & 105.3(b-c)	Part I, Chapter 8, Sections 8.20 through 8.31; Part II, Chapter 15	Section 12 "Production", 12.8 and 12.10 page 117-118
Vendor Qualification Program *The firm has identified key materials, supplies or service providers and has established an audit program and oversight.*	Part 2, Ch 7, Pg 18-20: *Materials Management*	VSM 800.115; 9 CFR 114.16, 113.50	Part I, Chapter 5, Sections 5.27 through 5.29 and the "Active Substances" section; Part I, Chapter 7; Part II, Chapter 7, Sections 7.10 through 7.14; Part II, Chapter 16	Section 7 "Starting Materials", 7.3 and 7.4 page 108

Annual Product Reviews *The firm has a program for Annual Product reviews which check: Critical in process controls and final product results, review all failed specificatoins, review all changes, review all quality related returns, review of stability results, review of relevant equipment and utilities.*	Part 1, Ch 1, Pg 6-7: *Product Quality Review*	9 CFR 114.8(d.)	Part I, Chapter 1, Section 1.10; Part II, Section 2.6; Part II, Section 12.6	Section 15 "Validation", 15.7 page 120
Internal Audit Schedule *The firm has established a self inspection following a pre-established schedule.*	Part 1, Ch 9, Pg 45: *Self Inspection*	VSM 800.91 -- there is a statement for "guide for self-inspection"	Part I, Chapter 9; Part II, Section 2.5, Part III, Site Master File, Chapter 9	*S*tatement: "The effectivenss of the control strategy in monitoring, reducing and managing such risks should be regularly reviewed and the systems updated as required taking into account scientific and technical progress." in Section 5, "Pharmaceutical quality system and quality risk management" page 106. No direct statement towards requirement for a self inspection or internal audit requirement. This could be placed in PQR too. Section 6 "Personnel" 6.4 page 107 mentions auditors in regards to the presence of personnel not routinely involved in production operations.
Complaint Investigation *The firm has a program to receive, investigate and trend adverse events and complaints received from customers.*	Part 1, Ch 8, Pg 43-44: *Complaints and Product Recall* and Part 2, Ch 15, Pg 36: *Complaints and Recalls*	9 CFR 116.5(b) & 116.9 and VSM 800.125	Part I, Chapter 8; Part II, Chapter 15	Section 7 "Starting Materials: 7.2 page 108 refers to adverse events and document retention periods