Global Regulatory Frameworks

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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"
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
Quality Manual	The firm has develop 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
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.
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
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.
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 Additional VSM updates underway as of 4/4/19	Annex 15 "Qualification and Validation", section 1.5
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

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Process Validation	The firm has defined through process validation key parameters of the manufacturing proceedure 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
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*
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)
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*
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, Part IV, Bullet D- *Equipment*	Annex II Potential Applications for Quality Risk Management - reference II.4
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, Section D. Equipment; ICSOP0013.03 Section 8.6	Part 1 Basic Requirements for Medicinal Products Chapter 5 Production Section 5.3

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Quality System	Description	PIC/S	9 CFR	MHRA Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017
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
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
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
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
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* and 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
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

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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
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
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
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 relavent 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
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
Complaint Investigation	The firm has a program to receive, investigate and trend adserve 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	Part I, Chapter 8; Part II, Chapter 15

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