Health Canada Santé Canada

Mutual Recognition Agreement Evaluation Guide of Good Manufacturing Practices Compliance Programs

Appendix 5.1 - Summary of the MRA Evaluation Guide			
Component	**Sub-component**	**Importance**	**Evaluation method**
1 - Legislative and Regulatory Requirements and Scope	1A - Empowering legislation	Critical	Documentation review
	1B - Conflict of interest	Very important	Documentation review On-site evaluation at Inspectorate
2 - Regulatory directives and policies	2A - Procedures for designating inspectors	Very important	Documentation review
	2B - Enforcement Policies	-	Evaluated as part of sub-component 7B
	2C - Code of conduct/ Code of ethics	Very important	Documentation review
	2D - Training certification policies/guidelines	-	Evaluated as part of sub-component 4C
	2E - Alert/crisis management policies/procedures/guidelines	-	Evaluated as part of sub-component 8A
	2F - Organizational structure	-	Evaluated as part of sub-component 11A
3 - GMP Standards	3A - Details/ scope of GMP	Critical	Documentation review
	3B - Process validation	-	Evaluated as part of sub-component 3A
4 - Inspection resources	4A - Staffing: Initial qualification	Very important	Documentation review On-site evaluation at Inspectorate
	4B - Number of inspectors	Very important	Documentation review On-site evaluation at Inspectorate
	4C - Training programme	Very important	Documentation review On-site evaluation at Inspectorate
	4D - QA mechanism to assure effectiveness of training program	-	Evaluated as part of sub-component 4C
5 - Inspection procedures	5A - Inspection strategy	Very important	Documentation review On-site evaluation at Inspectorate
	5B - Pre-inspection preparation	Very important	Documentation review On-site evaluation at Inspectorate Observed inspections
	5C - Format and content of inspection reports	Very important	Documentation review Observed inspections
	5D - Inspection methodology	-	Evaluated as part of sub-components 5E
	5E - SOP for conducting inspections	Critical	Documentation review Observed inspections
	5F - Inspection procedures - Post-inspection activities	Very important	Documentation review On-site evaluation at Inspectorate Observed inspections
	5G - Inspection procedures – Storage of inspection data	Important	Documentation review Observed inspections
6 - Inspection performance standard	6A - Performance standards	Very important	Evaluated as part of sub-components 11A
7 - Enforcement powers and procedures	7A - Provision for written notice of violations	-	Evaluated as part of sub-component 7B
	7B - Non-compliance management	Critical	Documentation review On-site evaluation at Inspectorate
	7C - Appeal mechanism	Important	Documentation review On-site evaluation at Inspectorate
	7D - Other measures	-	Evaluated as part of sub-components 7B
8 - Alert and crisis systems	8A - Alert mechanisms	Critical	Documentation review On-site evaluation at Inspectorate
	8B - Crisis management mechanisms	-	Evaluated as part of sub-component 8A
	8C - Alert performance standards	Important	Documentation review
9 - Analytical capability	9A - Access to laboratories	Critical	Documentation review On-site evaluation at Laboratory On-site evaluation at Inspectorate
	9B - SOPs for analytical support	Very important	Documentation review On-site evaluation at Laboratory
	9C - Validation of analytical methods	Very important	Documentation review On-site evaluation at Laboratory
10 - Surveillance programme	10A - Sampling and audit procedure	Very important	Documentation review On-site evaluation at Laboratory On-site evaluation at Inspectorate
	10B - Recall monitoring	-	Evaluated as part of sub-component 7B
	10C - Consumer complaint system	Critical	Documentation review On-site evaluation at Inspectorate
	10D - Adverse reaction reporting system/ procedures	-	Not evaluated - not considered within the scope of a GMP regulatory compliance programme. *
	10E – Medicinal product defect reporting system/ procedures	-	Evaluated as part of sub-component 10C
11 - Quality management system	11A - Quality management system	Critical	Documentation review On-site evaluation at Inspectorate On-site evaluation at Laboratory

* Pharmacovigilance is outside the scope of the GMP compliance programme with exception of indicator 11. Adverse reactions related to GMP should be scrutinized under subcomponent 11.

Glossary
• Articles = Any item such as products (active pharmaceutical ingredient, finished medicinal products, investigational medicinal products, or any intermediates), containers, packages, labels, documentation, etc. • Component/Sub-Component = Elements of a GMP regulatory compliance programme. For additional information on the level of importance and the evaluation methods, refer to the table "*Summary of the MRA Evaluation Guide*" provided at the beginning of this document. • Dosage form = Pharmaceutical form • Equivalent = Not necessarily identical, but leading to the same result. • GMP regulatory compliance programme = Includes components such as the supporting infrastructure of legislative and regulatory requirements, GMP standards, inspection/enforcement resources and procedures, performance standards, alert and crisis system, analytical capability, surveillance programme and quality management systems. • Key performance indicators (KPI) = Performance indicators established for planning and reporting on the components/sub-components of a GMP regulatory compliance programme. • Marketing Authorization Holder (MAH) = holder of the medicinal product authorization. • Manufacture = Fabricate as defined in relevant GMP guidelines. • Medicinal products = Drug products • Official Medicines Control Laboratories (OMCL) = Laboratories used for the purpose of official testing. • Pharmacovigilance = Surveillance of adverse reactions reporting. • Product = Active pharmaceutical ingredient, finished medicinal product, investigational medicinal products, or any intermediate. • Product defect = Quality defect related to a product such as Out-of-Specifications (OOS), etc.
General Notes
• The entire checklist must be used for the assessment/evaluation of GMP regulatory compliance programme as regards active pharmaceutical ingredients and medicinal products. • This checklist is used as a high level document. It is meant to detail the "WHAT" and not the "HOW". The "HOW" is expected to be covered in a lower level document such as a guidance document or a procedure.

Appendix 5.2 - MRA EVALUATION GUIDE					
Indicator Number	**Indicators**	**Method of Evaluation** **DR: Documentation Review** **OSEI: On-site Evaluation at Inspectorate** **OSEL: On-site Evaluation at Laboratory** **OI: Observed Inspection**			
		DR	**OSEI**	**OSEL**	**OI**
Sub-component 1A Legislative and regulatory requirements and scope - Empowering legislation (Critical)					
1	The legislation identifies key delegations/and functions in the organization(s)/ regulatory authority(ies) assigned for overall responsibility for the GMP regulatory compliance programme.	X			
2	The authority to designate inspectors is vested in legislation.	X			
3	The identity of designated inspectors and scope of jurisdiction of legislation are available to companies being inspected.	X			
4	There is legal authority for an inspector to enter at any reasonable time in any place where active pharmaceutical ingredients and/or medicinal products are fabricated, packaged, stored, tested, imported and exported.	X			
5	There is legal authority for taking samples and submitting them to designated laboratories.	X			
6	There is legal authority for obtaining evidence such as documents, photographs/videos of premises and equipment.	X			
7	There is legal authority to open and examine any article subject to legislation.	X			
8	There is the legal authority to seize or detain any article believed to be in violation.	X			
9	The legislation allows entry to a private dwelling.	X			
10	Legislation requires that the person who has the responsibility of the site where active pharmaceutical ingredients and medicinal products are manufactured, imported and exported, to cooperate and not obstruct an inspector.	X			

Appendix 5.2 - MRA EVALUATION GUIDE					
Indicator Number	**Indicators**	**Method of Evaluation** **DR: Documentation Review** **OSEI: On-site Evaluation at Inspectorate** **OSEL: On-site Evaluation at Laboratory** **OI: Observed Inspection**			
		DR	**OSEI**	**OSEL**	**OI**
11	Legislation requires a marketing authorization holder and/or a manufacturer of medicinal product to report to the regulatory authority any serious adverse medicinal product reactions.	X			
12	Legislation requires the marketing authorization holder and a manufacturer of active pharmaceutical ingredients or medicinal product to assess, investigate and document any product defect impacting quality.	X			
13	Legislation requires the marketing authorization holder and/or the manufacturer to notify a competent regulatory authority before or upon commencement of a recall of medicinal product and to submit pertinent information.	X			
14	All companies that fabricate, package/label, import, export, distribute and test medicinal products or active pharmaceutical ingredients, are required to hold a manufacturing authorization or be a registered company for active pharmaceutical ingredients.	X			
15	The holder of the manufacturing authorization is required to notify the regulatory authority of significant changes or of conditions, which may affect the quality, safety or efficacy of a medicinal product.	X			
16	Legislation requires that the manufacturing authorization include: the address of each site, the manufacturing activities, the category of medicinal products, and dosage forms.	X			
17	Legislation prohibits the processing and sale of active pharmaceutical ingredients or medicinal products under unsanitary conditions or leading to adulteration.	X			
18	Good Manufacturing Practices are legal requirements.	X			
19	The legislation specifies that a manufacturer and / or a person is liable for a defective medicinal product and provides for prosecution and/or penalties upon conviction.	X			
20	There is legislative authority to suspend, revoke or amend a manufacturing authorization.				

Appendix 5.2 - MRA EVALUATION GUIDE					
Indicator Number	**Indicators**	**Method of Evaluation** **DR: Documentation Review** **OSEI: On-site Evaluation at Inspectorate** **OSEL: On-site Evaluation at Laboratory** **OI: Observed Inspection**			
		DR	**OSEI**	**OSEL**	**OI**
		X			
21	Active pharmaceutical ingredients and medicinal products intended for exportation only are covered by the same or equivalent legislation as the products intended for the domestic market.	X			
Sub-component 1B Legislative and regulatory requirements and scope - Conflict of interest (Very important)					
22	A policy/guideline exists that details the situations regarded as conflict of interest.	X			
23	Employees are required to declare their compliance with the conflict of interest policy.	x	X	X	
Sub-component 2A Regulatory directives and policies - Procedures for designating inspectors (Very important)					
24	A process for designation of inspectors exists.	X			
Sub-component 2B Regulatory directives and policies - Enforcement Policies					
Included under sub-component 7B. Enforcement powers and procedures - Non-compliance management.					
Sub-component 2C Regulatory directives and policies - Code of conduct/ Code of ethics (Very important)					
25	A policy/guideline exists that details situations regarded as Code Of Conduct.	X			
Sub-component 2D Regulatory directives and policies - Training certification policies/guidelines					
Included under sub-component 4C. Inspection resources - Training programme.					
Sub-component 2E Regulatory directives and policies - Alert/crisis management policies/procedures/guidelines					
Included under sub-component 8A. Alert and crisis systems - Alert mechanisms.					
Sub-component 2F Regulatory directives and policies - Organizational structure					
Included under sub-component 11A. Quality management system					

Appendix 5.2 - MRA EVALUATION GUIDE					
Indicator Number	**Indicators**	**Method of Evaluation** **DR: Documentation Review** **OSEI: On-site Evaluation at Inspectorate** **OSEL: On-site Evaluation at Laboratory** **OI: Observed Inspection**			
		DR	**OSEI**	**OSEL**	**OI**
Sub-component 3A GMP Standards - Details/ scope of GMP (Critical)					
26	GMPs are covered within a regulatory framework (this indicator has been combined with indicator 27)	X			
27	The GMP regulatory framework covers all GMP requirements including but not limited to: Quality management, premises, equipment, personnel, sanitation, raw material testing, manufacturing control, quality control department, complaints, product recalls, packaging material testing, finished product testing, records, samples, stability and sterile products.	X			
Sub-component 3B GMP Standards - Process validation					
Included under sub-component 3A GMP Standards - Details/ scope of GMP.					
Sub-component 4A Inspection resources - Staffing: Initial qualification (Very important)					
28	The minimum qualifications for GMP inspection staff are defined.	X			
29	Duties of staff involved in the GMP regulatory compliance program are defined.	X	X		
30	Evidence exists that the GMP inspectors meet the minimum qualifications.		X		
Sub-component 4B Inspection resources - Number of inspectors (Very important)					
31	The number of inspectors dedicated to the GMP inspection programme is sufficient to meet the prescribed inspection frequency/inspection programme.	X	X		
Sub-component 4C Inspection resources - Training programme (Very important)					
32	A training program for inspectors is established and records are maintained.	X	X		
33	A mechanism to evaluate the effectiveness of training exists.	X	X		
Sub-component 4D Inspection resources - QA mechanism to assure effectiveness of training programme					

Appendix 5.2 - MRA EVALUATION GUIDE					
Indicator Number	**Indicators**	**Method of Evaluation** **DR: Documentation Review** **OSEI: On-site Evaluation at Inspectorate** **OSEL: On-site Evaluation at Laboratory** **OI: Observed Inspection**			
		DR	**OSEI**	**OSEL**	**OI**
Included under sub-component 4C Inspection resources - Training programme.					
Sub-component 5A Inspection procedures - Inspection strategy (Very important)					
34	Documents that describe the work expected, anticipated results and resources applied to fulfil the functions of GMP inspections are available.	X	X		
35	A scheduling system identifies companies due for inspections within a set time frame.	X	X		
Sub-component 5B Inspection procedures - Pre-inspection preparation (Very important)					
36	A procedure details the requirements for pre-inspection activities, and is followed.	X	X		X
37	The inspection plan is based on the company's GMP compliance history, critical activities and type(s) of dosage forms or products manufactured.		X		X
Sub-component 5C Inspection procedures - Format and content of inspection reports (Very important)					
38	A procedure for the format and content of inspection reports is available.	X			
39	Observations are factual and are based on proper interpretation of applicable legislation.				X
40	Observations are classified/ categorized according to risk.	X			X
41	Assessment of the company's overall compliance status is in line with the inspection findings.				X
42	Inspection reports are completed in the required reporting format and timeframe.				X
Sub-component 5D Inspection procedures - Inspection methodology					
Included under sub-components 5E. Inspection procedures - SOP for conducting inspections					
Sub-component 5E Inspection procedures - SOP for conducting inspections (Critical)					

Appendix 5.2 - MRA EVALUATION GUIDE					
Indicator Number	**Indicators**	**Method of Evaluation** **DR: Documentation Review** **OSEI: On-site Evaluation at Inspectorate** **OSEL: On-site Evaluation at Laboratory** **OI: Observed Inspection**			
		DR	**OSEI**	**OSEL**	**OI**
43	A procedure details the requirements for conducting inspections, and is followed.	X			X
44	Critical stages and parameters of manufacturing processes are assessed.				X
45	Qualification and validation are assessed.				X
46	The inspection plan is adjusted, where warranted, based on the findings of the inspection.				X
47	The depth of the inspection is appropriate and based on the findings of the inspection.				X
Sub-component 5F Inspection procedures - Post-inspection activities (Very important)					
48	A procedure details the requirements for post-inspection activities, and is followed.	X	X		X
49	Inspection findings and conclusions are subject to an internal review.	X	X		X
Sub-component 5G Inspection procedures - Storage of inspection data (Important)					
50	A policy/procedure is available for the storage of inspection data.	X			
51	An inspection report database (or archive) is maintained in a secure and controlled manner.		X		
Sub-component 6A Inspection performance standard - Performance standards (Very important)					
Included under sub-component 11A Quality management system - Quality management system.					
Sub-component 7A Enforcement powers and procedures - Provision for written notice of violations					
Included under sub-component 7B Enforcement powers and procedures - Non-compliance management					
Sub-component 7B Enforcement powers and procedures - Non-compliance management (Critical)					
52	There is provision for written notice of violations to be sent to the company.	X	X		

Appendix 5.2 - MRA EVALUATION GUIDE					
Indicator Number	**Indicators**	**Method of Evaluation** **DR: Documentation Review** **OSEI: On-site Evaluation at Inspectorate** **OSEL: On-site Evaluation at Laboratory** **OI: Observed Inspection**			
		DR	**OSEI**	**OSEL**	**OI**
53	Recall procedures/mechanisms and records are available.	X	X		
54	GMP certificates, manufacturing authorization suspension/withdrawal procedures/mechanisms are available and a list of suspended/withdrawn authorizations/GMP certificates is maintained.	X	X		
55	Seizure procedures/mechanisms and records are available.	X	X		
56	Prosecution procedures/mechanisms and records are available.	X	X		
Sub-component 7C Enforcement powers and procedures - Appeal mechanism (Important)					
57	Appeal procedures/mechanisms and records are available.	X	X		
Sub-component 7D Enforcement powers and procedures - Other measures					
Included under sub-components 7B Enforcement powers and procedures - Non-compliance management					
Sub-component 8A Alert and crisis systems - Alert mechanisms (Critical)					
58	Two-way alert procedures/mechanisms and records are available.	X	X		
Sub-component 8B Alert and crisis systems - Crisis management mechanisms					
Included under sub-component 8A Alert and Crisis systems - Alert mechanisms					
Sub-component 8C Alert and crisis systems - Alert performance standards (Important)					
59	Performance standards for the transmission of two-way alert are established and are followed.	X	X		
Sub-component 9A Analytical capability - Access to laboratories (Critical)					
60	The regulatory authority has access to laboratories capable of conducting necessary analyses for the purpose of official testing.	X		X	

Appendix 5.2 - MRA EVALUATION GUIDE					
Indicator Number	**Indicators**	**Method of Evaluation** **DR: Documentation Review** **OSEI: On-site Evaluation at Inspectorate** **OSEL: On-site Evaluation at Laboratory** **OI: Observed Inspection**			
		DR	**OSEI**	**OSEL**	**OI**
61	Regulatory Authority's or contract laboratories are qualified according to a recognized standard.	X		X	
62	All reported product defects obtained in the laboratory are documented and investigated.	X	X	X	
Sub-component 9B Analytical capability - SOPs for analytical support (Very important)					
63	Documents are available that detail the work expected, anticipated results and resources applied to fulfil the functions of the laboratories.	X		X	
64	Procedures covering all elements of laboratory operations are available and are followed.	X		X	
Sub-component 9C Analytical capability - Validation of analytical methods (Very important)					
65	The test method validation guideline is equivalent to the ICH standard and records are available.	X		X	
Sub-component 10A Surveillance programme - Sampling and audit procedure (Very important)					
66	The market surveillance programme for active pharmaceutical ingredients and medicinal products is developed involving at least the inspection and laboratory departments using risk management principles and covers dosage forms of different medicinal product types.	X	X	X	
67	The market surveillance programme performance is reviewed annually and records of review are available.		X	X	
Sub-component 10B Surveillance programme - Recall monitoring					
Included under sub-component 7B Enforcement powers and procedures - Non-compliance management					
Sub-component 10C Surveillance programme - Consumer complaint system (Critical)					
68	A consumer complaint system/procedure and records are available.	X	X		

Appendix 5.2 - MRA EVALUATION GUIDE					
Indicator Number	**Indicators**	**Method of Evaluation** **DR: Documentation Review** **OSEI: On-site Evaluation at Inspectorate** **OSEL: On-site Evaluation at Laboratory** **OI: Observed Inspection**			
		DR	**OSEI**	**OSEL**	**OI**
69	Issues of high risk are investigated immediately.		x	x	
70	Compliance staff and/or inspection staff can access complaint information.		x		
71	All product defects reported (e.g. through the complaint and two-way alert systems) are documented and investigated.		x		
Sub-component 10D Surveillance programme - Adverse reaction reporting system/ procedures					
Not evaluated - not considered within the scope of a GMP regulatory compliance programme.					
Sub-component 10E Surveillance programme - Drug product defect reporting system/ procedures					
Included under sub-component 10C Surveillance programme - Consumer complaint system					
Sub-component 11A Quality management system - Quality management system (Critical)					
72	The quality management system is based on a recognized international standard.	x			
73	The quality manual covers all elements of GMP regulatory compliance programme.	x			
74	Key performance indicators (KPI) for the overall GMP regulatory compliance programme are established and available.	x	x	x	
75	The quality management system has been implemented and is followed.		x	x	
76	A documentation control system is in place.		x	x	
77	Quality audit plans and records are available.		x	x	
78	Management reviews the performance of the quality management system on an annual basis.		x	x	