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Compliance and Inspection

EVALUATION GUIDE FOR GMP REGULATORY COMPLIANCE PROGRAMME

Audit Checklist

(Revision 2 including API and common with Canada and PIC/S)



Summary of the Audit Checklist			
	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 - Organisational 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 programme	-	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-component 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

Component	Sub-component	Importance	Evaluation method
11 - Quality management system	11A - Quality management system	Critical	Documentation review On-site evaluation at Inspectorate On-site evaluation at Laboratory

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 Audit Checklist*” 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.
- 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.

Indicator Number	Indicators	Method of Evaluation			
		DR	OSEI	OSEL	OI
		DR: Documentation Review OSEI: On-Site Evaluation at Inspectorate OSEL: On-Site Evaluation at Laboratory OI: Observed Inspection			
Sub-component 1A Legislative and regulatory requirements and scope - Empowering legislation (Critical)					
1	The legislation identifies key delegations/functions in the organisation/regulatory authority assigned for overall responsibility of 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 medicinal products are manufactured, 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 subjected to legislation.	X			
8	There is the legal authority to seize or detain articles 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	X			

Indicator Number	Indicators	Method of Evaluation			
		DR	OSEI	OSEL	OI
	ingredients and medicinal products are manufactured, imported and exported, to cooperate and not obstruct an inspector.				
11	Legislation requires a marketing authorisation holder and a manufacturer of medicinal product to report to the regulatory authority any serious adverse medicinal product reactions.	X			
12	Legislation requires a marketing authorisation holder and a manufacturer of active pharmaceutical ingredients or of medicinal product to document any product defect impacting its quality.	X			
13	Legislation requires the marketing authorisation holder and the manufacturer to notify a competent regulatory authority upon commencement of a recall of medicinal product and to submit pertinent information.	X			
14	All companies that manufacture, import, export medicinal products are required to hold a manufacturing authorisation or be identified as holder of a manufacturing authorisation or as a registered company for active pharmaceutical ingredients.	X			
15	The holder of the manufacturing authorisation 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 authorisation include: the address of each site, the manufacturing activities, the category of medicinal products and the dosage form.	X			
17	Legislation prohibits the sale and processing of active pharmaceutical ingredients and medicinal products under unsanitary conditions or leading to adulteration.	X			
18	GMPs are legal requirements.	X			
19	The legislation specifies that a manufacturer and/or a person is liable for a defective medicinal	X			

Indicator Number	Indicators	Method of Evaluation			
		DR	OSEI	OSEL	OI
	product and provides for prosecution and/or penalties upon conviction				
20	There is legislative authority to suspend, revoke or amend a manufacturing authorisation.	X			
21	Active pharmaceutical ingredients and medicinal products intended for exportation only are covered in the 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 exist that details situations regarded as Code Of Conduct/Code Of Ethics.	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 - Organisational structure					

Indicator Number	Indicators	Method of Evaluation			
		DR	OSEI	OSEL	OI
	Included under sub-component 11A. Quality management system				
Sub-component 3A GMP Standards - Details/ scope of GMP (Critical)					
26	GMPs are covered within a regulatory framework.	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, 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 inspectors are defined	X			
29	Duties of staff involved in the GMP regulatory compliance programme 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 programme for inspectors is established and records are maintained.	X	X		

Indicator Number	Indicators	Method of Evaluation			
		DR	OSEI	OSEL	OI
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					
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/categorised according to risk.	X			X
41	Assessment of the company's overall compliance rating 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					

Indicator Number	Indicators	Method of Evaluation			
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Included under sub-components 5E. Inspection procedures - SOP for conducting inspections					
Sub-component 5E Inspection procedures - SOP for conducting inspections (Critical)					
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 in line with the inspection findings.				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					

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DR: Documentation Review					
OSEI: On-Site Evaluation at Inspectorate					
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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		
53	Recall procedures/mechanisms and records are available.	X	X		
54	GMP certificates, manufacturing authorisation suspension/withdrawal procedures/mechanisms are available and a list of suspended/withdrawn authorisations/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 and management of crisis system are established and are followed.	X	X		

Indicator Number	Indicators	Method of Evaluation			
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DR: Documentation Review OSEI: On-Site Evaluation at Inspectorate OSEL: On-Site Evaluation at Laboratory OI: Observed Inspection					
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	
61	Regulatory Authority's or contract laboratories are qualified according to a recognised standard.	X		X	
62	All reported products defects are documented and investigated.	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					

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DR: Documentation Review					
OSEI: On-Site Evaluation at Inspectorate					
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Sub-component 10C Surveillance programme - Consumer complaint system (Critical)					
68	A consumer complaint system/procedure and records are available.	X	X		
69	Issues of high risk are investigated immediately.		X	X	
70	Compliance staff and or inspection staff can access complaint information.		X		
71	All reported products defects 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 - Medicinal 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 defined based on a recognised 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	

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
78	Management reviews ensure the performance of the quality management system on an annual basis.		X	X	

**ANNEX EVALUATION GUIDE FOR GMP REGULATORY
COMPLIANCE PROGRAMME– AUDIT CHECKLIST
IMPLEMENTATION OF EC LEGISLATION AND GUIDANCE RELATED TO GMP
HUMAN AND VETERINARY – ALL RELEVANT ARTICLES TO BE CHECKED**

EC requirement		
Article (Human)	Subject	Article (Veterinary)
1. Directive 2001/83/EC, as amended by Directive 2004/27/EC – Human Medicinal Products		
2. Directive 2001/82/EC, as amended by Directive 2004/28/EC – Veterinary Medicinal Products		
40(1) (2)	Authorisation for manufacture	44(1) (2)
40(3)	Authorisation for import	44(3)
41	Requirements for applicant in order to obtain manufacturing authorisation	45
42	Granting of authorisation	46
43-45	Time limits for the handling of the application	47-49
46	Obligations of holder of manufacturing authorisation	50
	(a) Services of the adequate staff	
	(b) Comply with national legislation of the Member State concerned	
	(c) Give prior notice of changes	
	(d) Allow inspections	
	(e) Enable qualified person to carry out its duties	
	(f) Comply with GMP rules	
47	Implementation through Directive and Guidelines	51
	Guidelines including annexes as published under EUDRALEX Volume 4 - Medicinal Products for Human and Veterinary Use : Good Manufacturing Practice (http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm)	
	Principles of GMP for active substances used as starting materials	
48	Requirement of qualified person	52
49	Conditions of qualification of qualified person and professional background	53
51	Responsibilities of qualified person	55
56	Enforcement of qualified person's obligations	56
53	Application to homeopathic medicinal products	57
111	Detailed Provisions for inspections at premises of manufacturers (please list in detail each aspect of implementation of this article)	80

EC requirement		
Article (Human)	Subject	Article (Veterinary)
113	MS to ensure that holder of a manufacturing authorisation furnishes proof of the control tests to be carried out in compliance with marketing authorisation (Administrative batch protocol review)	81
114	Official Control Batch Release Testing (May-Provision)	82

Article	Subject
2. Directive 2003/94/EC (Human) – and Directive 91/412/EEC (Veterinary) –GMP	
1	Scope of application of GMP rules
2	Repeated inspections by MS
3	Comparable standards to Compilation of Community Procedures (http://www.emea.eu.int/Inspections/GMPCompproc.html)
	<ul style="list-style-type: none"> Quality Systems framework
	<ul style="list-style-type: none"> Procedures related to Rapid Alerts
	<ul style="list-style-type: none"> Procedures related to GMP Inspections
	<ul style="list-style-type: none"> Forms used by Regulators (GMP inspection report format, manufacturers authorisation)
	<ul style="list-style-type: none"> Procedures related to Centralised Procedures
4	Responsibility of manufacturer and importer
	Compliance of medicinal products and investigational medicinal products manufacturing (in EC or whether imported) with GMP
5	Obligations of the manufacturer:
	<ul style="list-style-type: none"> Manufacturing operations in accordance with information in application
	<ul style="list-style-type: none"> Adaptation to scientific and technical progress
6	Quality assurance system
7	Qualified personnel at the manufacturing site, job descriptions of qualified personnel, training
	Hygiene programme
8	Premises and equipment
9	Documentation
	<ul style="list-style-type: none"> Manufacturing procedures
	<ul style="list-style-type: none"> Traceability of batches
	<ul style="list-style-type: none"> Protection of data processing systems
10	Production
	<ul style="list-style-type: none"> Pre-established procedures, resources
	<ul style="list-style-type: none"> Validation

11	Quality control
	<ul style="list-style-type: none"> • Quality control department
	<ul style="list-style-type: none"> • Quality control laboratories
	<ul style="list-style-type: none"> • Final control of finished products
12	Work contracted out
	<ul style="list-style-type: none"> • Written contract
	<ul style="list-style-type: none"> • Clearly defined responsibilities
	<ul style="list-style-type: none"> • No sub-contracting
	<ul style="list-style-type: none"> • Respect of GPM and allow inspections
13	Implementation of a system for recording and reviewing complaints
	Implementation of a system for product recall
14	Self inspection

Article	Subject
3. Directive 2001/20/EC Good Clinical Practice	
13 (1)	Authorisation for total and partial manufacturing of investigational medicinal products
13 (2)	Qualified person for investigational medicinal products
13 (3)	GMP for manufacturing and testing of investigational medicinal products

Article	Subject
4. Directive 2005/28/EC Good Clinical Practice	
9	General conditions for a manufacturing and import authorisation
10	Applicant's requirements to obtain an authorisation
11-12	Obligations of competent authority
13	Obligations of holder of an authorisation
21	Requirements related to inspectors
22	Teams of Inspectors
23	Inspection Procedures (here: only in relation to GMP verification)