Promoting the
QUALITY OF MEDICINES Plus

Guide for Conducting Risk-Based Inspections Using the PQM+ Risk-Based Inspection Tool

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USAID
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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a six-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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Acronyms and Abbreviations

CAPA	corrective and preventive action
FMEA	failure mode and effects analysis
FMECA	failure mode, effects, and criticality analysis
GDP	good distribution practices
GMP	good manufacturing practices
GSP	good storage practices
GSDP	good storage and distribution practices
GxP	regulated good practices
HIV/AIDS	human immunodeficiency virus/acquired immunodeficiency syndrome
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LMICs	low- and middle-income countries
NRA	national regulatory authority
OCS	overall compliance score
PIC/S	Pharmaceutical Inspection Co-operation/Scheme
PQM+	Promoting the Quality of Medicines Plus
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QMS	quality management system
QRM	quality risk management
RBI	risk-based inspection
RPN	risk profile or risk priority number
RR	risk rating
SOP	standard operating procedure
TRS	technical report series
USAID	U.S. Agency For International Development
USP	United States Pharmacopeial Convention
WHO	World Health Organization

Definitions

Compliance: The adherence to GxP and regulatory requirements.

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage, or transport.

Critical: Having the potential to significantly impact product quality or performance.

Critical observation: An observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user. It includes situations that may produce a product with immediate or latent health risks, or that involves fraud, misrepresentation, or falsification of processes, products or data.

Elements: A distinct objective statement of a system used to determine the outcome of compliance with the requirements of GMP or GSDP.

Failure mode: Ways that a process or subprocess can fail to provide the anticipated result.

Failure mode and effects analysis (FMEA): A systematic method of identifying and preventing product and process problems.

Good manufacturing practice (GMP): An aspect of quality assurance which ensures that products are consistently produced and controlled according to the quality standards appropriate for their intended use and as required by the marketing authorization.

Good distribution practices (GDP): An aspect of quality assurance that ensures that the quality of a medical product is maintained throughout the supply chain.

Good storage practices (GSP): An aspect of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout their storage.

Harm: Damage to health, including the damage that can occur from loss of product quality or availability.

Hazard: Any circumstance in the production, control, and distribution of a pharmaceutical that can cause harm.

Inspection: An on-site evaluation of a facility by a regulatory authority to determine whether a manufacturing facility is operating in compliance with regulatory requirements and/or commitments made as part of the approval to market a product.

Knowledge management: A systematic approach to acquiring, analyzing, storing and disseminating information related to products, manufacturing processes, and components.

Major observations: A deficiency that is not critical but consists of several other related deficiencies that indicate a departure from GxP and manufacturing authorization requirements.

Other observation: An observation that cannot be classified as either critical or major but indicates a departure from GxP requirements.

Product lifecycle: All phases in the life of the product from the initial development through marketing until the product's discontinuation.

Quality: The degree to which a set of inherent properties of a product, system, or process fulfills requirements.

Quality risk management (QRM): A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Quality system: The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Regulated good practices (GxP): The group of good guides governing regulated practices. Although GxP refers to all good practices, in this document it refers only to GMP and GSDP.

Requirements: The explicit or implicit needs or expectations of the patients or their surrogates (e.g., health care professionals, regulators and legislators).

Risk: The combination of the probability of occurrence of harm and the severity of that harm.

Risk assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk-based decision-making: An approach to, or a process of, making decisions that considers knowledge about risks relevant to a decision and whether risks are at an acceptable level.

Risk control: Part of the risk management process that includes decision-making to reduce, mitigate, and/or accept risk and the sharing of information about risk, and risk management between the decision-maker and other stakeholders.

Risk management: The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk.

Score: The calculated numerical value that represents the extent of compliance against assessment criteria.

Severity: A measure of the possible consequences of a hazard.

Stakeholder: Any individual, group, or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision-makers might also be stakeholders. For this guide, the primary stakeholders are the patient, health care professional, regulatory authority, and industry.

System: A regulated pattern of interacting activities and techniques that unite to form an organized whole.

Executive Summary

National regulatory authorities (NRAs) are responsible for inspecting pharmaceutical manufacturers and storage and distribution facilities to ensure compliance with regulated good practices (GxP); these inspections are crucial for ensuring pharmaceutical product quality and patient safety. However, especially in low-and-middle-income countries (LMICs), NRAs often face significant challenges in performing inspections effectively and efficiently due to limited resources, a shortage of skilled inspectors, and a large number of facilities to be inspected. If regulators adopt a risk-based approach to inspection, they can make evidence-based decisions to safeguard quality and patient safety while efficiently and effectively utilizing scant resources. To this end, the Promoting the Quality of Medicines Plus (PQM+) program, funded by the United States Agency for International Development (USAID) and implemented by USP and its consortium of partners, developed a software-based Risk-Based Inspection (RBI) Tool that facilitates effective and efficient regulatory inspection processes.

The RBI Tool is designed to modernize traditional inspection processes, fostering sustainable and risk-based decisions in quality assurance of pharmaceutical manufacturing, supply, and distribution. Based on risk-based thinking and grounded on quality risk management (QRM) principles and international best practices as applied to RBI, the RBI Tool is comprised of two modules: good manufacturing practices (GMP) and good storage and distribution practices (GSDP). Each module is comprised of predefined set of *systems* and *elements* (and associated *risk ratings*) (see References and Appendix 1 and 2). To ensure that the RBI Tool is adapted to the national context, NRAs should review and objectively adopt the appropriate and relevant *systems* and *elements* prior to applying the RBI Tool for inspection. The RBI Tool harmonizes and streamlines the regulatory inspection process through a structured process encompassing coordinated pre-inspection preparation, scheduling and planning for inspection, conducting assessment, reporting, and follow-up with corrective and preventive actions (CAPAs).

The risk-based inspection approach described in this guide is a paradigm shift from the traditional paper-based inspection approaches that are resource intensive, inefficient, and prone to subjectivity and bias. This guide introduces risk-based thinking and the RBI approach with the associated QRM and GxP concepts. The document is primarily intended for NRAs in resource-constrained environments but is applicable to any organization seeking to use or develop similar software-based RBI tools.

Introduction

One of the primary responsibilities of NRAs is to perform inspections of pharmaceutical manufacturers and storage and distribution facilities, processes, and operations to ensure quality and compliance with national laws, regulations, as well as national and international standards collectively referred to as the good practices (GxP). Specifically, GMP - applicable to pharmaceutical manufacturers, and GSDP - applicable to storage and distribution facilities, form a fundamental part of the quality assurance system in the pharmaceutical industry. Any departure of the manufacturing process or storage/distribution conditions from established GxP requirements presents a *potential source of risk* that may result in failure of product quality; in turn, this may lead to failure in patient treatment and health.

Using a risk-based approach, NRAs are required to build systems to ensure compliance with regulations throughout the product lifecycle starting from the upstream manufacturing process through the downstream distribution chains, until the final finished product reaches the patients in need. NRAs (or the responsible agencies) conduct GMP inspections of manufacturing facilities first as part of the licensing process, followed by routine periodic inspections at predetermined intervals and when warranted for cause or investigative purposes. Traditionally, GMP inspections are conducted both for domestic and foreign manufacturing facilities and involve an inspector team's visit to the manufacturing facility to assess its compliance. GSDP inspections, on the other hand, are often limited to pre-licensing activities and occasional *ad hoc* inspections of the storage and distribution facilities. Consequently, many such facilities may not get (re)inspected for extended periods of time. Moreover, the large number of these facilities ranging from importers, wholesalers, and retail and healthcare establishments also makes GSDP inspections a daunting undertaking for NRAs.

In resource-limited settings, such as in LMICs, the lack of sufficient and/or skilled human resources and the costs associated with travel to auditee sites present real challenges to inspectorates. GSDP inspections are especially taxing due to the large quantities of storage and distribution facilities and the complex matrix of products being stored or distributed. Taken together, these constraints hinder NRAs from conducting full-scale inspections and corrective action follow-ups across every step of manufacturing operations and supply chain distribution outlets as required. Therefore, it is useful to introduce alternative, risk-based approaches, as required by their regulations, to facilitate NRAs in fulfilling their regulatory responsibilities.

Risk-based thinking is based on risk management principles that allow NRAs to adopt RBI approaches to categorize facilities by risk, identify GxP systems that may not be adequately implemented, and determine a reinspection cadence in line with national laws, among several others. In pharmaceutical manufacturing and regulation, QRM is an integral part of the quality management systems (QMS) to control risk by building quality into the entire system through enforcement of GxP. Risks from product quality failures and impacts on patient safety are of primary importance to NRAs, pharmaceutical manufacturers, and storage and distribution facilities. Effective QRM facilitates better and informed risk-based decision-making processes to address product quality failures and ensure patient safety.

Adoption of RBI approaches require a thorough understanding of QRM, and the risk-based decision-making methods used. To assist NRAs in LMICs in the adoption and implementation of RBI approaches using internationally accepted practices, the USAID-funded PQM+ program developed the RBI Tool, a software-based tool that semi-automates the inspection process and the generation of inspection records and reports. The RBI Tool is designed to facilitate regulatory inspections by NRAs in LMICs, considering the need for proper use of scarce

resources and efficient planning, with prior understanding of risk level and risk assessment approaches. This contrasts with the current practice of conducting inspection of *all* facilities and processes and reporting manually. The RBI Tool allows NRAs to improve their inspection processes and compliance assessments of pharmaceutical establishments in line with national regulations and recognized GxP requirements. Other benefits of using the RBI Tool include, but are not limited to, facilitating the adoption of RBI practices in general, bringing efficiency to inspectorate activities, developing knowledge management and evidence-based decision-making processes, establishing GxP-compliant pharmaceutical organization databases, and being able to quantitatively measure compliance level and monitor progress.

The RBI Tool, which includes modules for both GMP and GSDP, was piloted in several countries with an active PQM+ project that expressed interest in participating in the orientation, training, and piloting of the tool. PQM+ collaborated with the Bangladesh Directorate General of Drug Administration and the Kenya Pharmacy and Poisons Board for the pilot testing of the GMP module, and with the Ghana Food and Drugs Authority, the South African Health Products Regulatory Authority, and the Medicines Agency of Madagascar (Medicament de Madagascar) for the GSDP module. Pilot testing with each NRA team included an orientation and training workshops to introduce the principles of the RBI approach, the RBI Tool interface, and the GMP/GSDP modules, and provided participants with an overview of the risk-based GMP and GSDP inspection best practices with an emphasis on international standards. Participants' feedback was largely positive, highlighting the tool's usability and value in facilitating and organizing the work of inspectors to prioritize and conduct consistent inspections, efficiency in organizing, and generating inspection reports, thus allowing for better allocation of limited resources. NRAs noted that the RBI Tool will facilitate the adoption of international standards and guidelines, such as the WHO or PIC/S, leading to harmonization and uniformity in the pharmaceutical sector. Limitations the pilot users noted related to high-speed internet connectivity constraints and areas of improvement in the user interface functionality.

The RBI Tool described in this guide is one example of a tool that NRAs can choose to adopt to facilitate the institutionalization of the RBI concept to modernize the traditional inspection process. The authors recommend that NRAs review the principles and operational manuals of the existing RBI process to ensure that it addresses and aligns with applicable regulatory requirements to ensure product quality in both manufacturing sites and storage and distribution environments. The authors also recommend that NRAs conduct field testing to ensure the tools are functional and meet their needs and expectations prior to adoption.

The RBI concepts discussed in this guide that form the basis of the RBI Tool draw from international guidance and practices, including (but not limited to):

- ICH Q9 Quality risk management. 2023
- ICH Q10 Pharmaceutical quality system. 2008
- WHO TRS 981, Annex 2. WHO guides on quality risk management. 2013
- WHO TRS 986 Annex 2. WHO Good manufacturing practices for pharmaceutical products: Main principles. 2014
- WHO TRS 996, Annex 4. Guide on good manufacturing practices: inspection report. 2016
- WHO TRS 1025 Annex 7. Good storage and distribution practices for medical products. 2020
- WHO TRS 961 Annex 9. Model guidance for the storage and transport of time and temperature sensitive pharmaceutical products. 2011
- PI040-01 PIC/S Guidance on classification of GMP deficiencies. 2019

This guide reviews the principles of QRM and RBI and describes how these principles are applied in the design of the RBI Tool developed by PQM+. This guide also describes how to use the RBI Tool to plan, schedule, execute, and generate risk-based GxP reports.

Purpose & Audience

The purpose of this document is to provide a detailed understanding of risk-based decision making and RBI principles and the practical application of these concepts in conducting regulatory inspections using the RBI Tool. The RBI Tool is software developed by the PQM+ program to assist NRAs in LMICs to conduct RBIs. The risk-based approaches described herein are applicable to GMP and GSDP assessments of pharmaceutical manufacturers, storage, supply, and distribution facilities.

While the primary audience for this guide is NRAs in resource-constrained environments, the information and guidance provided in this document can be applied by any organization or entity that seeks to use or adopt other software-based RBI Tools to facilitate the execution of GMP and GSDP inspections.

Inspection Challenges and Benefits of the RBI Tool

Many NRAs in LMICs operate under resource-constrained environments, which limit their ability to conduct routine inspections of all GMP and GSDP facilities under their jurisdictions. The RBI approach, if implemented correctly with thorough understanding of the principles involved, can be useful to overcome these challenges. When RBI is applied appropriately in inspections of manufacturing and supply chain distribution facilities, it increases both efficiency and effectiveness. Ultimately, QRM leads to more efficient resource utilization by allowing lower risk issues to be mitigated less formally with fewer resources. As a result, limited resources are freed up and can be allocated toward managing higher risk issues.

Common Inspection Challenges

To understand the value and benefits of the RBI approach and the RBI Tool, it is important to note the common challenges that many inspectorates in LMICs face. These include, but are not limited to:

- Lack of adequate financial and qualified human resources to establish risk-based processes to conduct GxP inspections.
- Lack of system-based approaches to establish organizational-level QRM to build quality into systems.
- Lack of appropriate and practical guidance and tools to facilitate the planning, scheduling, and execution of inspections.
- Lack of a risk-based approach in decision-making due to poor knowledge management.
- Inconsistency in the understanding and interpretation of GxP requirements during the inspection process.
- Subjectivity in decision-making using traditional observation reporting that is prone to bias.
- Presence of large numbers of pharmaceutical facilities subject to inspections.

Benefits of the RBI Tool

The value of the risk-based approach to GxP inspections (versus inspection of *all* facilities and processes) and that of using a tool to implement RBI (versus performing inspections manually, which can be challenging) is that it allows for efficient and effective utilization of scarce resources without jeopardizing any quality standards and regulatory requirements. The RBI Tool guides this process by:

- Facilitating LMIC NRAs' progress toward adoption of international standards for RBI.
- Streamlining inspection processes by facilitating inspection scheduling, planning, conducting, reporting, and follow-up with CAPAs.
- Harmonizing assessment questions across facilities of the same type, thus minimizing inspection bias between inspectors.
- Facilitating and/or enhancing the establishment of practical, evidence-based risk-based decision-making processes.
- Measuring a pharmaceutical organization's compliance level quantitatively, which in turn helps to establish a phased approach to attaining compliance.
- Applying risk level and compliance scores to measure the extent to which a facility has implemented the applicable WHO TRS elements and its level of compliance.
- Allowing the creation of a database of potential GMP- /GSDP-compliant suppliers that could serve as a source for interested procurement agencies.
- Maintaining repositories of inspections and monitoring inspection processes by creating a facility database, inspector pool, inspection history, CAPA progress monitoring, and inspections status dashboard.
- Allowing the development of inspection-related knowledge management processes.
- Generating comparative analyses of inspection data among facilities of the same type, including the level of compliance and comparisons.

Understanding Quality Risk Management (QRM) and Risk Based Inspection

The concept of risk-based thinking and the RBI approach described in this guide is based on QRM principles. QRM is a fundamental element of an effective pharmaceutical quality system (PQS). The expectation from effective QRM is to provide a proactive methodology for identifying, assessing, and controlling potential risks to quality throughout the product lifecycle.

All processes associated with the manufacturing and supply of pharmaceuticals have inherent failure risks that may lead to varying levels of harm to patients. Hence, regulatory decisions to "accept" or "reject" an organization or facility following regulatory compliance assessments (i.e., inspections) may have critical consequences to patient health. For example, accidentally accepting a noncompliant manufacturing or distribution facility may result in patient exposure to harmful and/or substandard products. Ideally, an organization's departure from regulatory requirements would result in noncompliance and be cited as a violation requiring corrective and preventive actions. However, inspection processes can be erratic due to a combination of poor procedures, lack of inspector knowledge/experience, subjectivity and bias, and other factors, thus unintentionally overlooking situations of noncompliance.

The decision-making process to "accept" or "reject" an organization or facility often comes with complexities, uncertainties, and vulnerabilities involving science, expertise, laws, art, and other

external factors. The ability to assess facilities properly and more objectively is maximized by QRM thinking, which weighs the potential harm arising from noncompliance against benefit to patients.

Any tools used to implement QRM need to be evaluated for their appropriateness in commensurate to the risk level and complexity of the process. Effective tools create opportunities for both NRAs and pharmaceutical manufacturers. For NRAs, a systematic and structured process to undertake regulatory inspection increases coordination among inspectors leading to effective risk-based decision-making. By employing QRM, the NRA is in a position to accept *residual* risks that arise from rejecting or accepting a given facility. For pharmaceutical manufacturing, storage, and distribution organizations, QRM employed as an integral element of the PQS minimizes the risks of wrongly accepting unacceptable products or rejecting acceptable products.

One of the challenges in establishing an effective QRM is subjectivity and bias about the degree of potential harm. Subjectivity in conventional GMP/GSDP inspections influences the effectiveness of risk management and complicates decision-making. Therefore, it is important to manage and minimize subjectivity. To minimize subjectivity and bias during RBI, it is important to establish defined assessment criteria *prior* to an assessment. A prerequisite of the RBI approach is that all *systems* and *elements* evaluated during inspection are identified in advance and assigned a numeric risk rating commensurate with the severity of noncompliance. Severity is a measure of the potential consequences of the harm; thus, a preassigned risk rating mitigates subjectivity and bias during an inspection.

The Concepts: Hazard, Harm, Risk

The concepts of **hazard** and **hazardous situations** that may lead to **harm** are helpful to understand RBI. Many regulatory requirements are written with the aim to ensure quality by enforcing GxP principles, but they may not appropriately address the concepts of hazard identification and failure mode analysis to establish a proactive QRM system. In the revised ICHQ9(R1) Quality Risk Management guidance, the term “risk identification” has been replaced with “hazard identification,” emphasizing that hazard is different from risk.

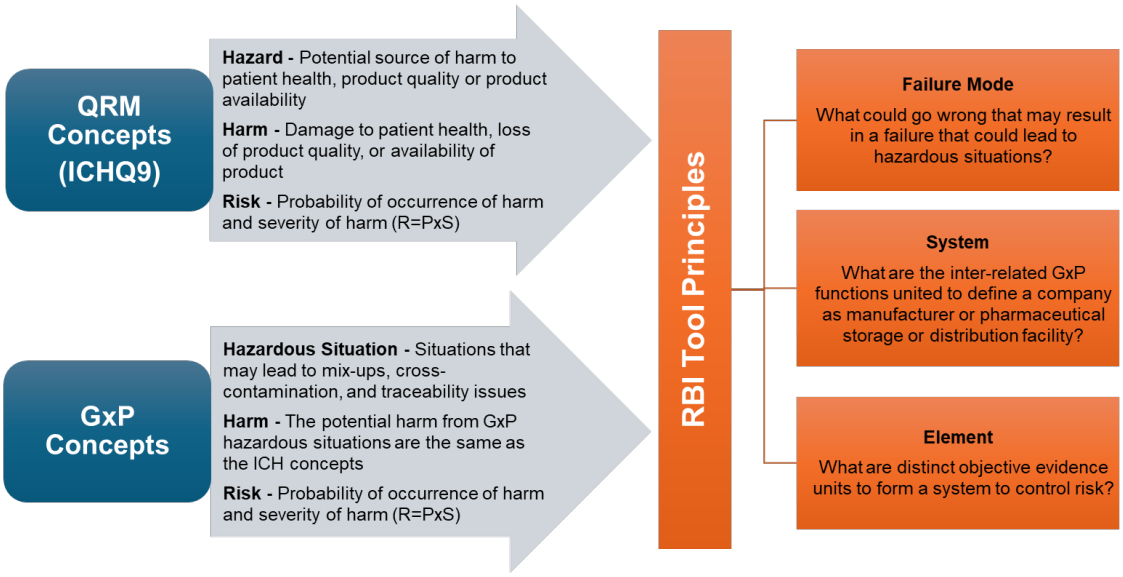
Risk is the combination of the probability of occurrence of harm and the severity of that harm, expressed as:

Risk = Probability (P) x Severity (S)

Understanding the sources of hazard that may cause harm, the choice of methodology for risk analysis, and the dimensions of risk assessments are at the foundation of QRM. Manufacturing environments that operate without the concept of QRM are likely to lead to hazardous situations that may result in potential harm. The hazards (i.e., potential causes) that could cause harm in QRM applicable to pharmaceuticals are defined as those that can negatively impact patient health, product quality, or product availability. Good practices aim to prevent common hazards and hazardous situations that could cause harm, such as mix-ups, cross-contamination, and lack of traceability.

The QRM and GxP concepts of hazard, harm, and risk form the basis of the RBI principles and the RBI Tool (Figure 1). The RBI Tool algorithm applies these concepts in the context of inspections by establishing failure modes of predefined GxP systems and elements and RBI principles to objectively measure risk. The following sections explain the RBI principles and their practical implementation via the RBI Tool.

Figure 1. Relationship between QRM and GxP concepts and the RBI Tool principles



Failure Modes and Effects Analysis

In the QRM process, identification of the potential sources of hazard is the first step of risk assessment. At this stage, the probability of occurrence of harm or the severity of harm need not be a consideration, as the focus should be on hazard identification.

There are several examples of QRM tools that can be employed to facilitate risk assessment processes in pharmaceutical manufacturing, such as process mapping, cause and effect analysis, and failure mode and effects analysis (FMEA). While these tools can be used individually or in combination to conduct from basic to advanced risk analysis and risk assessments, the FMEA is the most widely used tool for summarizing the *failure modes* and the consequences of failure. In addition, its derivative, failure modes, effects, and criticality analysis (FMECA) may also be employed. FMECA includes a criticality analysis component of the risk analysis factors employed in the next step of risk assessment.

FMEA is a helpful tool to understand the steps of the risk assessment process and risk scoring (Table 1). FMEA is based on *forward* risk assessment planning and relies on a thorough understanding of the product and process, to methodically break down a complex process into smaller, more manageable sub-processes to identify the specific failure modes associated with the individual components of the process. FMEA helps to identify hazards and hazardous situations through the evaluation of potential failure modes for processes, outcomes, and/or product performance. Once individual failure modes are established, control strategies (i.e., risk reduction strategies) can be designed to contain, reduce, control, or eliminate the potential failures. The FMEA is a powerful tool for summarizing the important failure modes, the factors causing failures and the likely effects of these failures both *before* and *after* risk mitigation actions. In applying FMEA, failure modes help in identifying hazards (the first step of risk assessment), while failure effects help to understand the harm and the consequences of the harm during the risk assessment process.

The next step of risk assessment involves the investigation of the degree of severity (S) of the consequences of failure, the probability of occurrence (O), and the detectability (D) of the failure.

Table 1. Example Failure Mode and Effects Analysis Template

Before Risk Mitigation										After Risk Mitigation				
Process steps	Failure modes	Failure causes	Failure effects	Existing control	[S]	[O]	[D]	RPN	Recommended actions	Actions taken to reduce [O] of failure	[S]	[O]	[D]	RPN (after action)

The FMECA tool component with forward risk assessment and control strategy

RPN = Risk Priority Number

RBI Tool Failure Mode Approach

The RBI Tool is an example of the **practical application of the QMS and QRM principles** to facilitate the RBI process using a software-aided tool. As described above, in *forward* risk-based thinking, FMEA is used to facilitate risk assessment to demonstrate the effectiveness of the QRM process to identify, analyze, and undertake action to control risks.

The incorporation of FMEA into risk assessments enables actions beyond risk control and presents improvement opportunities. Improvement opportunities are identified differently from failure modes, by working backwards from the objective evidence of inspection findings (*reverse* FMEA). Since the objective evidence does not exist before the assessment, *reverse* FMEA is projected based on the creation of assessment elements in failure mode. The RBI Tool applies *reverse* FMEA by thinking defining system and elements of GxP inspection based on existing regulatory GxP requirements. Hence, the major process step in *reverse* FMEA is the description of the elements that make up the systems, followed by the assignment of a risk rating for each element. S*ystems*, *elements*, and *risk rating,* defined in the RBI Tool in advance of any assessment, and the *GxP point* and *element score,* respectively determined during and after an inspection, are components of the RBI Tool FMEA model (Table 2). The Introduction to the RBI Tool section discusses each component in detail.

Appendices 1 and 2, respectively, list all the GMP and GSDP systems and elements included in the RBI Tool and provide a template based on the RBI Tool FMEA model to help NRAs review and select the specific systems, elements, and risk ratings appropriate to establish their own RBI processes.

Table 2. Components of the RBI Tool reverse FMEA model

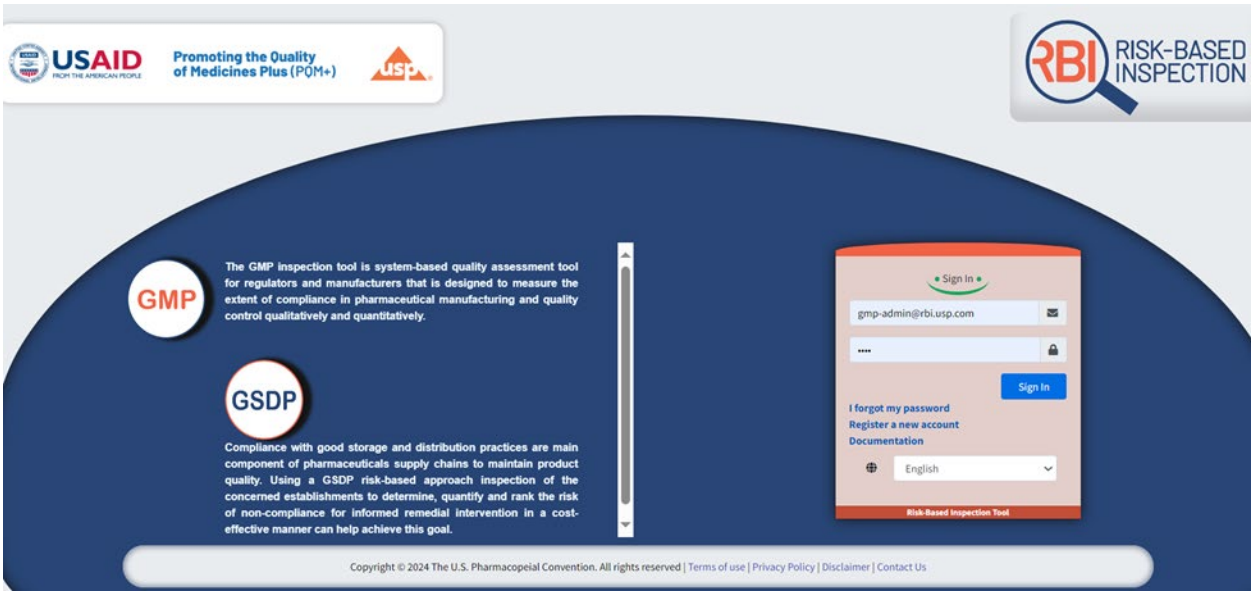
Systems	Elements	Risk Rating	GxP Point	**Element Score** [Risk Rating x GxP Point]
Defined interrelated regulatory requirements selected based on enforced GxP principles. These form the backbone of the RBI Tool.	Distinct *objective statements* that collectively define and determine the specific *system.* These form the backbone of the RBI Tool.	The numerical rating determined by the NRA during inspection planning to measure the possible consequences of a hazard if the *element (i.e., the objective statement)* fails to meet the requirement.	The numerical rating determined by the inspector during the inspection.	Product of Risk Rating and GxP point calculated by the tool after the inspection.

Introduction to the RBI Tool

The RBI Tool is a software application designed and developed by PQM+ according to the QRM and RBI principles outlined in the WHO, ICH, and PIC/S guidelines referenced in the Introduction to assist NRA inspectorates in LMICs to execute GMP and GSDP inspections per industry best practices (Figure 2). The RBI Tool applies basic risk management principles per ICH Q9 addressing risk identification, analysis, and mitigation and serves as a quality improvement tool to facilitate regulatory inspection processes and performance.

The primary purpose of the tool is to streamline the inspection process in LMICs from planning to the qualitative and quantitative reporting of observations, thus bringing efficiency to inspectorate's activities. The use of the tool provides the evidence necessary to facilitate the adoption of RBI practices (as opposed to the inspection of all facilities and processes) and helps to foster transparency, accountability, and NRA management oversight.

Figure 2: RBI Tool Landing Page



As noted in the Benefits of the RBI Tool section, the tool can be used to:

- Facilitate inspection: planning, scheduling, conduct, and post-inspection follow-up.
- Harmonize assessment questions and minimize inspection bias between inspectors.
- Generate a company-level inspection report with implementation level score, compliance score, and an overall facility risk.
- Generate measurable CAPA and quality improvement plans.
- Create evidence-based reinspection schedules.
- Generate comparative analysis reports between the manufacturers.
- Maintain inspection history.
- Generate inspection-related regulatory data and documents.
- Build a manufacturers database.

- Create inspectors and subject matter expert pools.
- Serve as a database of potential suppliers for procurement purposes (i.e., public tenders).

The RBI Tool is designed to facilitate the risk- and system-based regulatory compliance assessment process by presenting defined systems and elements for assessment. These elements have predefined numeric risk ratings to measure severity of noncompliance related to the hazard based on failure mode analysis. The RBI Tool also assists with knowledge management by establishing an effective risk-based decision-making process in the implementation of regulatory inspections including planning, conducting, reporting and CAPA follow-up.

GMP and GSDP inspections share basic RBI requirements. Therefore, GMP and GSDP RBI can be accomplished by a single RBI Tool. The RBI Tool is based on **systems** and their associated **elements** that are applicable to GMP and GSDP. These systems and elements are based on risk-and system-based concepts and the impact of departure from established requirements on patient health. As the specific systems and elements that apply to pharmaceutical manufacturers differ from those applicable to storage and distribution facilities, the RBI Tool is composed of two independent modules for GMP and GSDP inspections, each with its own defined system and elements.

The following sections describe the building blocks of the RBI Tool, their function in risk assessment, and the determination of GxP implementation levels and facility compliance scores.

The GMP and GSDP Systems and Elements of the RBI Tool

Prior to deploying the RBI Tool, the NRA must know and understand the applicable international guidelines to identify the interrelated processes and requirements that define a **system** and its **elements**. Similar to the identification of hazards and hazardous situations in QRM, the RBI Tool includes a set of systems and elements applicable to GMP and GSDP inspections. The source information for the systems and elements in the RBI Tool are the applicable WHO TRS guidelines covering GMP and GSDP as described below (see References).

The GMP module of the RBI Tool is based on seventeen sections of WHO TRS 986 grouped into eight interrelated **systems**: quality management system, material system, production system, QC physicochemical system, QC microbiological system, water system, HVAC system, and documentation (validation) system (Table 3). These systems are selected based on their interrelated functionalities and impact at individual and/or combined level to prevent hazardous situations. Each system is comprised of **elements** expressed as objective statements that describe countermeasures to control a hazard. Each system has a defined number of elements. In the RBI Tool, there are a total of 202 elements for the GMP module as summarized in Table 3 and described in detail in Appendix 1.

Table 3. The GMP systems and elements of the RBI Tool

GMP Systems	Number of Elements
Quality management system	22
Material system	24
Production System	23
QC physicochemical system	27

GMP Systems	Number of Elements
QC microbiological system	35
Water systems	23
HVAC system	27
Documentation (validation) system	21
Total	**202**

The GSDP module of the RBI Tool is based on 21 sections of WHO TRS 1025 Annex 7 grouped into four systems and 187 associated elements (Table 4). In addition, for time- and temperature-sensitive pharmaceutical products (TTSPP), 12 sections of WHO TRS 961 Annex 9 grouped into four systems and 98 associated elements are applied (Table 5). Facilities within a country's pharmaceutical distribution chain can be inspected against the elements applicable to specific facilities to ensure compliance with acceptable international best practices. All GSDP systems and the 285 elements are described in detail in Appendix 2.

NRAs should review and objectively adopt the system and elements listed in Appendix 1 (GMP) and Appendix 2 (GSDP), partly or entirely, prior to adopting the RBI Tool for implementation.

Table 4: The GSDP Systems and number of elements

GSDP Systems	Number of Elements
Quality Management System	57
Documentation	14
Facility	42
Operations and Product Management	74
Total	**187**

Table 5: The TTSPP Systems and number of elements

Systems	Number of Elements
Cold Chain - Quality Management System	21
Cold Chain – Documentation	11
Cold Chain – Facility	62
Cold Chain - Operations and Product Management	4
Total	**98**

RBI Tool-based Assessments

Risk Assessment

Before initiating a risk assessment, it is important to define the appropriate **risk severity** to use in the assessment questions. The traditional approach to GxP assessments is highly subjective as the process of observation finding is not systematic and consistent, but prone to biases derived from subjectivity. Moreover, this approach does not apply quantitative measures to demonstrate extent of compliance and severity.

"ISO 19011:2018 - Guidelines for auditing management systems" notes that: "Nonconformities can be graded using quantitative and qualitative grading." In principle, variables that can be measured and quantified define *severity* and provide the evidence necessary for risk-based decision-making. This can be accomplished by assigning representative values with varying degrees of severity rating. However, no universal quantitative measures demonstrate the extent of compliance and severity of risks, and the choice of definitive measuring methods for the variables of interest is not straightforward unless there is a purposely defined inspection plan.

The RBI Tool, based on the embedded algorithm for risk calculation, provides a solution to the adoption of qualitative and quantitative measurements of GxP assessments, with built-in functions that fulfill regulatory requirements, present objective statements, and provide grading methods optimized to facilitate RBI. The biases resulting from inconsistent interpretation of regulatory requirements and assessment questions are minimized through purposely defined distinctive objective statements with quantified risk ratings. Table 6 provides an example of how a general GMP principle from WHO TRS 986, Annex 2 is translated into a measurable objective statement with an associated risk rating in the RBI Tool. During GxP assessments, inspectors verify the compliance of the company against each system assessed by confirming the acceptability of the distinctive objective statements.

Table 6. Example - GMP Principle and the Corresponding RBI Tool Objective Statement and Risk Rating

General GMP Principle		RBI Tool (*reverse* FMEA model)			
GMP Principle	**Reference**	**System**	**Element Number**	**Objective Statement**	**Risk Rating**
The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy.	WHO TRS 986, Annex 2 Pharmaceutical Quality System (sections 1.1 to 1.7)	Quality Management System (Elements 1 to 22)	2	The PQS exists and functional and it covers all elements of PQS	3 (high risk with potential harm)

Risk Rating

During the inspection planning phase, each GxP element included in the RBI Tool should be assessed based on a FMEA and assigned a risk rating score of 1 (low risk), 2 (medium risk), or 3 (high risk) commensurate with the severity of the harm that may result from the hazard/hazardous situation. Elements with a high consequence (i.e., impact of the failure to meet the requirement and its consequences on the patient) are considered to have higher risks and are assigned a risk rating of 3; those deemed medium risk are scored 2, while those deemed low risk are scored 1. Table 7 includes examples of hazard/hazardous situations, corresponding risk categorization, and risk rating.

The selection of systems, elements, and risk ratings forms the basis of the risk-based assessment. By default, the RBI Tool includes risk ratings of 1 to 3 for all 202 GMP and 285 GSDP elements. It is the responsibility of the NRA user to review, modify, and confirm each element and its associated risk rating before starting to use the RBI Tool. Appendices 1 (for GMP) and 2 (for GSDP) are templates for this exercise. To minimize the subjectivity of any individual inspector, the assignment of element risk ratings should be undertaken by a NRA expert working group whose members have expertise in key technical areas such as epidemiology; pharmacology; regulatory; chemistry, manufacturing, and controls (CMC); and

QRM and by following relevant standard operation procedures. The element risk ratings may also be modified as necessary by the NRA's responsible person based on the applicable elements for a specific facility.

Table 7. Example GxP Hazardous Situations Descriptions, Consequences, and Risk Ratings

Severity	Hazardous Situation Description	Harm/ Consequences of Harm	Risk Rating
High	None to low level of GxP implementation with systematic departure from requirement that potentially or evidently results in potential product quality failure	Life-threatening condition	3
Medium	Reasonable compliance with frequent nonsystematic departure that has a low risk of product quality failure	Non-life-threatening condition; minor illness	2
Low	Fully implemented and consistently meets the expectation	No harm; inconvenience	1

GXP Point and Assessment

Similarly, the RBI Tool includes three levels (1 to 3) to measure the degree of compliance or implementation of each element (i.e., **GxP point**) based on whether an element has been fully (3 points), partially (2 points), or not implemented (Ni, 1 point).

During and/or after the inspection process, each element selected for assessment is addressed by assigning a quantitative GxP rating and qualitative activities such as drafting observation statements, based on the closeness of the observation to the objective statement. Again, the objective statement (i.e., the element) is not the same as the traditional statement of inspection finding or objective evidence. The objective statements are risk-based. Table 8 provides examples of the three statements cases: inspection finding, objective evidence, and objective statement of the RBI Tool element.

Table 8. Examples of Three GMP Statement Cases

Statement of Inspection Finding	Statement of Objective Evidence	Objective Statement (the RBI Tool Element)	GMP Point
The quality management system of the company fails to address the data integrity issues of computerized systems used in QC laboratory	There are no standard operating procedures (SOPs) that define the roles and responsibilities of multiple users of HPLC machines with respect to access privilege and data security	The quality management system covers all areas of QC and production with defined procedures to ensure data integrity: accuracy, legibility, access control, security, and audit trail	3

The GxP point is determined during inspection as each element is assessed. Therefore, there are nine possible combinations (3x3 matrix) of risk-based categorization for each element assessed during inspection, as Table 9 shows. The overall risk rating ultimately depends on the risk rating of the element assessed. The NRA may use the combined facility matrix as a guide to determine if a facility is compliant or to determine the reinspection cadence.

Table 9. GxP Risk Matrix

Risk Rating		Low [1]	Medium [2]	High [3]
GxP Point	Full implementation [3]	Low - Full	Medium - Full	High - Full
	Partial implementation [2]	Low - Partial	Medium - Partial	High - Partial
	No implementation (Ni) [1]	Low - Ni	Medium - Ni	High - Ni
Overall Risk Level		**Low [1]**	**Medium [2]**	**High [3]**

Assessment and Scoring

The RBI Tool includes three ways for recording the RBI observations:

- Quantitative grading using numerical values (1 to 3) to assign a RBI GxP point
- Observation recording with statement of inspection findings and objective evidence, as performed in the traditional inspection process
- Qualitative observation categorization: critical, major, and other, also as performed in the traditional inspection process.

As discussed in the RBI Tool Failure Mode Approach section, the relevant risk assessment factors within the RBI Tool are derived from FMEA with the application of linear and quotient equations. Risk in the equation is defined as Y = f(x), where Y is the consequence of harm from the hazard (x). The value of Y is a risk-profile number (RPN) on FMECA. In principle, the RPN is the product of occurrence (O) and severity (S) multiplied with the third factor, detection (D), the ability to detect the hazard.

RPN = Occurrence (O) x Severity (S) x Detection (D)

Frequency (f) is the probability of occurrence of harm. In *reverse* FMEA, this is determined by placing the inspection element on a failure mode by considering each departure from GxP as a source of hazard. Traditional GxP observations are categorized into three levels — critical, major, minor — to differentiate the extent of departure from GxP compliance. In RBI, the frequency counts the occurrence of risk per inspection event and the numerical rating corresponds to the degree or extent of departure from compliance.

The RBI Tool generates compliance scores both at the system level and as an overall compliance score (OCS) of the manufacturer or facility under inspection based on the following formulas:

System level score: The system level score is reported for each GxP system included in the inspection. To calculate the **system level GxP point:**

System GxP Point = $\sum_i^n 3\ x\ fi + 2\ x\ pi + 1\ x\ Ni$

where,

fi = number of GxP elements rated as fully implemented (3)

pi = number of GxP elements rated partially implemented (2)

Ni = number of GxP elements rated not implemented (1)

OCS: The OCS is calculated as a percentage of the total possible GxP compliance points. The following algorithm is applied to calculate the OCS:

- To calculate the **grand GxP point** of all the systems assessed**:**

  Grand GxP point = $\sum_i^n System\ GxP\ Point$

- To calculate the **total possible GXP point** based on all the elements assessed if they were all fully implemented:

  Possible GxP point = total # elements x 3

  where 3 is to the highest possible GxP point for each element

- To calculate the **overall GxP risk rating**:

Overall GxP risk rating = $\sum_i^n \square\ Grand\ GMP\ point \times Risk\ Rating$

- To calculate the **OCS:**

  OCS = total point assessed/total possible GXP points × 100

  where the total points assessed is the overall GxP risk rating

  $OCS = \frac{\sum_i^n \square Grand\ GxP\ point \times Risk\ Rating}{Total\ possible\ GXP\ points} \times 100$

Depending on the nature of the product and manufacturing process to be assessed, additional risk multiplying factors may be considered and entered in the equation or into the RBI Tool prior to an assessment. Risk multiplying factors can be added to the system level and/or OCS calculations during the risk rating definition stage or, if additional risks are identified, during the inspection based on risk-based thinking. The following are examples of possible scenarios and justifications to add risk multiplying factors from the perspective of the manufacturers.

- **Product and/or process complexity:** *High risk if* the process is difficult to understand and/or difficult to control, or product is unstable.
- **Public health risk concerns:** *High risk if* the manufacturer is producing priority and prescription medicines supplied to the larger population of patients nationally and globally. Examples include products intended for the treatment of tuberculosis, malaria, HIV/AIDS, neglected tropical diseases, maternal and child health.
- **History of inspection**: *Low risk if* the manufacturer is audited and is compliant with and/or accepted by WHO or SRA region regulators.

GxP Implementation Level

Manufacturers and facilities inspected are scored by the inspector following a determination of the extent to which a facility has implemented any applicable elements. The combined compliance score at the system level determines the organization's overall compliance level (i.e., OCS). Based on the value of OCS, there are three levels of organizational risk categorization or implementation levels (Table 10).

Table 10. GxP Implementation Level

Facility Implementation Level	Risk Level	OCS (%)
Level I	High	0-50%
Level II	Medium	51-79%
Level III	Low	≥80%

GxP Final Compliance Decision

A GxP facility's assessment is concluded as either "site accepted" or "site rejected." In the RBI Tool, the final compliance is based on the combination of the OCS value and number of critical and major observations recorded by the inspector during the assessment. The site is accepted if the OCS is equal or greater than 80% and there are no critical and no more than five major observations. Irrespective of the OCS, the site is rejected if there is one or more critical or greater than five major observations (Table 11).

Table 11. Criteria to accept or reject a GxP facility

Site accepted/rejected		Number of major observations	OCS
Accepted	0	0-5	≥80%
Rejected	≥1	>5	N/A

Application of the RBI Tool

The purpose of this section is to provide step-by-step instructions on the application of the RBI Tool once the user reviews and accepts it.

Adoption of the RBI Tool

The adoption/adaptation of the RBI Tool is subject to the decision of the NRA or interested organization's leadership. The software and associated documentation, as well as detailed information for the deployment, user acceptance testing and the operational manuals, can be accessed through https://bitbucket.org/uspwebdev/rbi-tool/src/master/. For successful use of the RBI Tool, the team responsible for the execution of the tool should have an understanding of the QRM principles and process, identification of hazard, risk analysis, and risk-based decision-making. The following points discussed in ICHQ9 on QRM are helpful during the RBI Tool adoption process:

- The probabilistic nature of risk and risk assessment is abstract. However, this can have a positive influence because it can lead to logical and critical thinking. Likewise, the application of this tool and the risk-based inspection process requires analysis of a complex process by applying critical thinking. This differs from the conventional and traditional inspection process that doesn't take risk into account and is purely qualitative and subjective.
- With the right mix of perspective and experience, and when subjectivity is managed correctly, critical hazards can be identified and their risks effectively managed.
- When assessing the risks posed by hazard, it is important to express and consider a variety of perspectives.
- Multi-disciplinary teams are useful in risk assessments. This is because multi-disciplinary collaboration leads to creative thinking, problem solving, idea generation, discussing options, gaining alignment, and decision-making.

Using the RBI Tool

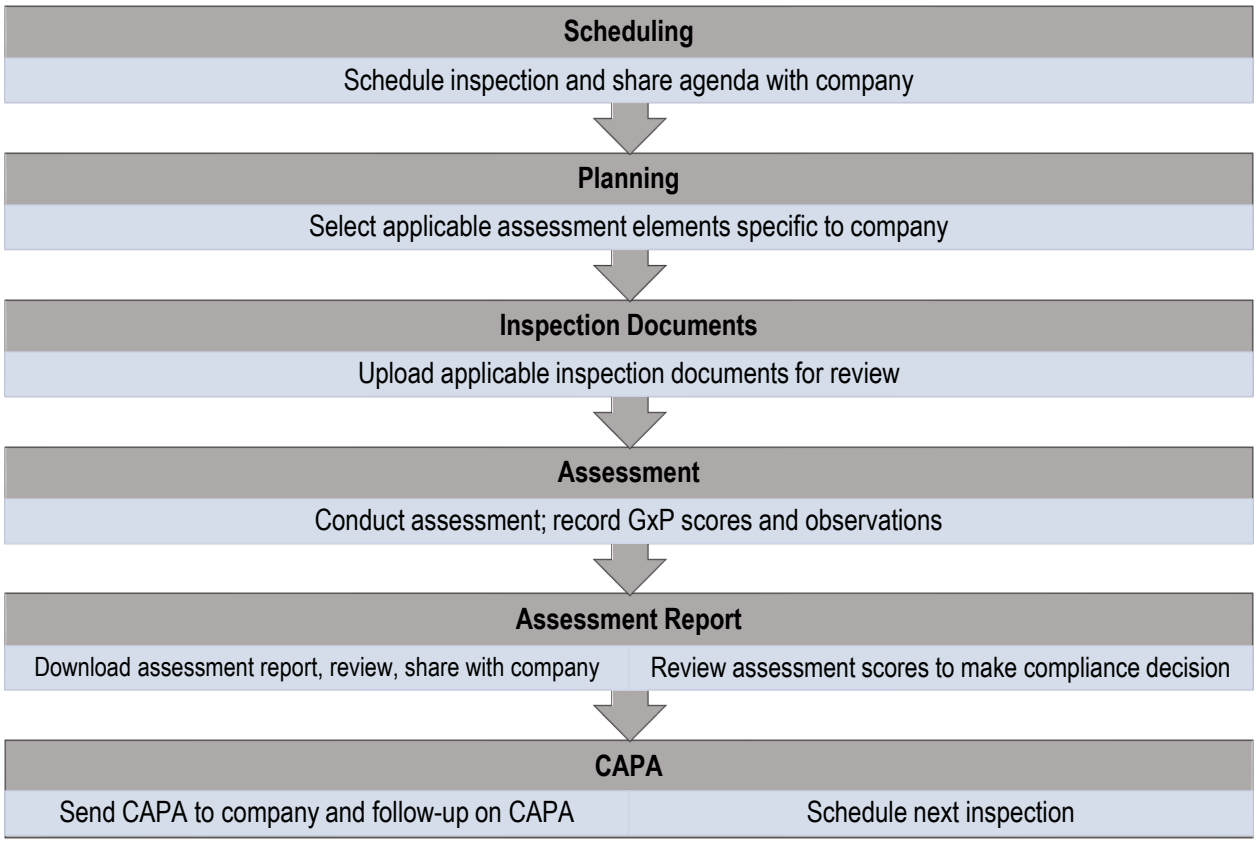
This section provides an overview of the RBI inspection process and the RBI Tool GMP and GSDP module functions. The GMP and GSDP operations manual provided as part of the RBI Tool software package should be consulted for detailed tool deployment instructions.

Risk-based GMP and GSDP inspections are conducted following the common process that Figure 3 outlines. While mostly the same, minor differences exist between the GMP and GSDP module functions to address the inspection type-specific requirements.

The GMP and GSDP modules are organized into the following main sections:

- Pre-inspection
- Scheduling
- Planning
- Assessment
- Assessment Report
- CAPA

Figure 3. RBI Tool GxP Inspection Process Flow



Pre-Inspection

The pre-inspection phase is the preparatory phase for conducting GMP and/or GSDP RBIs. The NRA GMP and/or GSDP administrator, hereafter referred to as the NRA GxP admin, is the person responsible for administering and managing the respective inspection activities on behalf of the regulatory authority. The NRA admin starts populating the RBI Tool by creating the manufacturers and facilities databases.

The manufacturers database is created in the GMP module and contains detailed information about the manufacturing companies, including name, address, contact information, website, and company category. Manufacturer specific primary and supporting documents, such as site master files, marketing authorization submissions, and quality information summaries are included in the manufacturers database for review in preparation for inspection.

The storage and distribution facilities database is created in the GSDP module and contains similar company data, as well as information product types stored or distributed and licensing

fee status. In addition, given the large number of facilities involved in the storage and distribution of pharmaceuticals, it is important for NRAs to identify and appropriately categorize the facilities that make up a country's pharmaceutical distribution chain for proper management and oversight of GSDP inspection activities. Due to the complex matrix of products that are stored and/or distributed, facility categorization can become complicated if solely based on product type. The RBI Tool provides a simplified approach that categorizes facilities into three distinct groups, based on the role of the facility within the distribution chain: 1) Importers, wholesalers and distributors, 2) Retail Pharmacies, and 3) Healthcare facility outlets (Table 12). This categorization allows NRAs to prioritize facility inspections using the same standards or elements that are applicable to each group, which can be further tailored to the specific facility based on its product matrix.

Table 12. GSDP Facility Categorization and Groups

Group	Facility Type	Examples	Applicable Standards
1	Importers, wholesalers, and distributors	- Points of entry public or private importer warehouse - Distributor warehouse - Central medical stores - Regional medical stores - NGO/Faith based warehouses - Wholesale pharmacies	Applicable elements from *WHO TRS 1025 Annex 7* or *WHO TRS 961 Annex 9* (if a facility stores or transports cold chain (TTSPP) products)
2	Retail pharmacies	- Private or public retail pharmacies - Drug stores - Patent medicine vendors	
3	Healthcare facility outlets	- Public or private hospital pharmacies - Community clinics - Health centers	

The NRA GxP admin also generates the inspectors database, which comprises the NRA's pool of experts for conducting inspections. The inspectors database captures information about each inspector's role and responsibilities within the NRA, years of experience, and areas of specialty. This information facilitates assignment of the appropriate inspector as the lead inspector and for the roles of observer, assistant, and support during the inspection scheduling process.

Scheduling

Scheduling a GxP inspection starts with selecting a company from the manufacturers or facilities database and assigning inspectors. The NRA GxP admin schedules a new inspection by first selecting its type and form and start and end dates. To complete the inspection scheduling, the NRA GxP admin selects the lead and accompanying inspectors from the panel pool. Once inspectors are assigned, the inspection can be saved as scheduled.

Planning

Inspection planning is the responsibility of the assigned lead inspector. The lead inspector reviews the GMP and GSDP systems and elements included in the RBI Tool, as discussed under The GMP and GSDP Systems and Elements of the RBI Tool. In the RBI Tool all elements are selected by default; the lead inspector's responsibility is to select those systems and elements that are relevant and applicable to the scheduled inspection based on desk review of submitted documentation and/or risk assessments from previous inspection reports. Once the

systems and elements to be inspected are selected, the inspector submits the inspection, which saves it in the system. This is confirmation of the inspection scheduled by the NRA GxP admin.

Assessment

Assessment is the actual RBI of the manufacturer, using the RBI Tool, against the systems and elements selected during the inspection planning stage. During the assessment, the inspector uses the dropdown menus of the RBI Tool to assign a GxP point (1, 2, 3) to each element assessed and to categorize observations using the traditional classification (critical, major, other) system. During the assessment, the inspector also records the written observations and drafts the deficiencies statement.

Assessment Report

The purpose of assessment or inspection report is to provide a factual and objective record of the inspection that needs to be communicated to the manufacturer using a defined reporting template as described in WHO TRS 996, Annex 4. After completing and submitting the assessment, the assessment report can be automatically published through the RBI Tool into the NRA's pre-selected inspection reporting template, which can be customized as needed. The system generated assessment report can be downloaded to review and edit as necessary the assessment ratings and observations entered by the inspectors. All the information entered in the RBI Tool during the assessment, including the GxP point, observation comments/notes, observation categorization, scoring and risk-based categorization are all available for revision. Once finalized, the assessment report is provided to the inspected organization.

CAPA and Reinspection

Following a GxP RBI, a CAPA is generated based on the identified gaps or deficiencies identified during the assessment. The RBI Tool provides a CAPA template, which can be customized as needed, that is pre-filled with observations made during the assessment that facilitates follow-up with the manufacturer or facility.

The OCS can be used to monitor a company's performance improvement by viewing the manufacturer's score before and after CAPA implementation. Moreover, the next inspection date can be scheduled using the CAPA functions after review of the CAPA responses submitted by the company. The re-inspection cadence is country specific as determined by national guidelines. Typically, a low-risk facility has a longer re-inspection interval than a medium or high-risk facility.

Summary

Resource constraints in LMICs hinder NRA inspectorates' ability to conduct comprehensive and routine GxP inspections of pharmaceutical manufacturers and storage and distribution facilities, processes, and operations to ensure their compliance with both national regulatory requirements and international practices. The risk-based thinking described in this guide is a paradigm shift from the traditional, paper-based inspection approaches that are inefficient and prone to bias and subjectivity. Carefully deliberated and implemented RBI approaches provide a means to facilitate NRA's fulfilling their regulatory responsibilities.

This guide provides a background of the core principles and concepts of quality management and QRM which tether the RBI approach. The RBI Tool described in this guide is an example of the practical application of these principles to facilitate the RBI process. The RBI Tool provides NRAs in LMICs with a simplified, yet technically sound approach to conducting risk-based inspections of manufacturing sites and storage and distribution facilities within a country's medical product supply and distribution chains. The tool allows for the careful planning, implementation, reporting, and follow up of GxP inspections. NRAs can choose to adopt this tool to facilitate the institutionalization of the RBI concept to modernize the traditional inspection process.

PQM+ hopes that NRAs will find the RBI Tool useful and helpful to address their RBI needs and ultimately improve their inspection functions.

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Appendix 1: GMP Systems and Elements of the RBI Tool

Note: In addition to providing the complete list of the system and elements included in the RBI Tool, the following table can be used by NRAs as a template to select the systems and elements appropriate for their own specific RBI processes and assign a risk rating and GMP point for each element to calculate the respective element scores.

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
Quality Management System	1	9.6 WHO TRS986, Annex 2	Organizational charts include key personnel: heads of production, quality unit, and authorized person with responsibility and decision making clearly defined			
	2	1.1-1.7, WHO TRS986, Annex 2	The PQS exists and functional and it covers all elements of PQS			
	3	1.6 WHO TRS986, Annex 2	There is periodic quality management review with detailed and authorized SOPs that cover relevant manufacturing activities			
	4	8.7-8.9, WHO TRS986, Annex 2	Procedures to ensure the quality of starting materials including the correct use of packaging materials and approved supplier's lists are available			
	5	12.15 WHOTRS961, Annex 3	Procedures and arrangements for appropriate storage and distribution of intermediate materials are satisfactory			
	6	2.1 WHO TRS961, Annex 3	Procedures to ensure products are manufactured in line with approved specifications and marketing authorization requirement exists and adequate			
	7	1 WHO TRS986, Annex 2	Evidence and commitment exist that shows only products that meets the required safety, efficacy and quality approved by authorized person are released for use			
	8	1.5 WHO TRS986, Annex 2	There are procedures in place for planned change control, review, approval, implementation, and effectiveness evaluation			
	9	1.5 WHO TRS986, Annex 2	The QC laboratory deviation management and implementation for effectiveness of changes after deviation are periodically reviewed			
	10	16.3 WHO TRS986, Annex 2	Deviation management, review, and CAPA implementation for production related activities are reviewed by management			
	11	ICHQ9 & WHO TRS981, Annex 2	There are adequate procedures in place to identify, evaluate, assess, control/mitigate, and communicate risks related to the product and manufacturing process activities			
	12	1.4, WHO TRS986, Annex 2	Product development and quality trends are linked to manufacturing process and quality improvement throughout product life cycle			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	13	1.10, WHO TRS986, Annex 2	Annual product quality review procedures, trending, frequency, content) and records are adequate			
	14	7, WHO TRS986, Annex 2	Contract manufacturing agreements, responsibilities and communication (where applicable) are available and adequate			
	15	3, WHO TRS986, Annex 2	There is adequate and integrated cross contamination and dust containment procedures, sanitation, gowning, cleaning, and cleaning validation			
	16	4.1-4.11, WHO TRS986, Annex 2	Validation and validation master plan and related qualification or revaluation/requalification document for premises, equipment, utilities, process, computers, etc., exists and adequate			
	17	5, WHO TRS986, Annex 2	Complaints handling procedures and investigation to identify the root cause, reporting of potential quality defects and corrective actions are adequate			
	18	US FDA Investigating OOS	The out of specification (OOS) handling, reporting, investigations, and actions following investigation are recorded and adequate			
	19	14.33, WHO TRS 1033, Annex 7; WHO TRS, 986, 2.1 Annex 2	Recall and return procedures, effectiveness evaluation of recall system, and operational functionality are satisfactory			
	20	8.2-8.5, WHO TRS986, Annex 2	Self-inspection procedure, schedule, and approaches are adequately applied			
	21	9.2-9.5 WHO TRS986, Annex 2	Number of personnel and training for personnel are adequate and training includes induction training and evaluation of training effectiveness on the job			
	22	11.1 WHO TRS986, Annex 2; 13.8 WHO TRS961, Annex 6	Personnel undergo medical examination, and validation of the examination, when necessary, (e.g., IPC visual inspector) are available			
Material System	23	14.1-14.23, WHO TRS986, Annex 2	The SOPs and documentation for material receipt, handling, sampling, testing, release, and distribution of all incoming materials are available and adequate			
	24	12.15, WHO TRS986, Annex 2	Storage areas have sufficient capacity and suitable to allow the orderly storage of the various categories of GMP materials and products			
	25	12.16, WHO TRS986, Annex 2	Storage areas been designed or adapted to ensure good storage conditions in particular clean, dry, and maintained within acceptable T/RH limits			
	26	12.17 WHO TRS986, Annex 2	Receiving and dispatch bays are designed and equipped to protect materials including finished products from the weather exposure			
	27	14.5 WHO TRS986, Annex 2	Procedures stock rotation of materials is available and permits material segregation as applicable: by FIFO principles, inventory control dates, retest dates, and expiration dates			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	28	14.13 WHO TRS961, Annex 3	Materials are properly labeled to identity their status (i.e., sampled, released, quarantined, approved etc.) with identifying code for each batch or lot by consignment			
	29	15.14 WHO TRS986, Annex 2	The identity of the contents of each container of starting materials are sampled and verified before use			
	30	14 WHO TRS986, Annex 2	Access restriction and control are available for materials in the storage room, retention room, stock room and other areas			
	31	14.2 WHO TRS986, Annex 2	Materials are controlled as per GMP requirement and includes starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials			
	32	14.6 WHO TRS986, Annex 2	Water used in the manufacture of pharmaceutical products is suitable for its intended use			
	33	14.8, WHO TRS986, Annex 2	Starting materials are purchased only from approved suppliers and, where possible, directly from the producer			
	34	14.11 WHO TRS986, Annex 2	Damaged containers and any other problem that might adversely affect the quality of materials are recorded and reported			
	35	14.13, WHO TRS986, Annex 2	Starting materials in the storage areas are appropriately labelled and includes name, batch number, status and expiry date where applicable			
	36	14.15, WHO TRS986, Annex 2	Only starting materials released by the QC department that are within their shelf-life are used for production			
	37	14.16, WHO TRS986, Annex 2	Starting materials are dispensed only by designated persons, following a written procedure, and stored and transferred in properly labelled containers			
	38	14.17-14.18, WHO TRS986, Annex 2	Dispensed materials are independently checked for weight and volume and dispensed materials for each batch of the final product are kept together and conspicuously labelled			
	39	14.19, WHO TRS986, Annex 2	The purchase, handling, and control of primary and printed packaging materials are the same as for the procedure of starting materials			
	40	14.20 WHO TRS986, Annex 2	Particular attention is given to printed packaging materials and are stored in secure conditions so as to exclude the possibility of unauthorized access			
	41	14.21 WHO TRS986, Annex 2	Each delivery or batch of printed or primary packaging materials are given a specific reference number or identification mark			
	42	14.24-14.25 WHO TRS986, Annex 2	Intermediate and bulk products purchased are handled on receipt as though they were starting materials			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	43	14.26.14.27, WHO TRS986, Annex 2	Finished products are held in quarantine until their final release, after which they are stored as usable stock			
	44	14.28-14.31, WHO TRS986, Annex 2	Rejected materials and products are clearly marked as such and stored separately in restricted areas until a decision is taken on their fate			
	45	6.8, WHO TRS986, Annex 2	Recalled products are identified and stored separately in a secure area until a decision is taken on their fate			
	46	14.33, WHO TRS986, Annex 2	Products returned from the market are destroyed unless it is certain that their quality is satisfactory			
Production System	47	12.1-12.2, WHO TRS986, Annex 2	Premises are designed in a logical order to minimize risk of errors, permit effective cleaning, and avoid cross contamination			
	48	12.3, WHO TRS986, Annex 2	In areas where dust is generated (e.g., weighing, sampling, processing operation etc.), there are dust extraction measures to avoid cross-contamination and facilitated cleaning			
	49	12.6, WHO TRS986, Annex 2	Premises is well maintained, and maintenance operations do not pose any hazard to the quality of the product			
	50	12.7, WHO TRS986, Annex 2	Records of cleaning, disinfection, and sanitizations are maintained and available			
	51	12.8, WHO TRS986, Annex 2	Electrical lighting, pipework, drains, light fittings, ventilation points and other service don't affect product quality directly or indirectly			
	52	12.4, WHO TRS986, Annex 2	Temperature and humidity measurement and records are available in all controlled manufacturing and storage areas			
	53	12.9, WHO TRS986, Annex 2	Premises equipped with maximum protection against entry of insects, birds and other animals			
	54	12.11, WHO TRS986, Annex 2	Rest and refreshment areas are separate and don't pose its risks on manufacturing and control areas			
	55	12.12, WHO TRS986, Annex 2	Facilities for change rooms, buffer areas and toilets are available and adequate; entry and exit to these areas doesn't permit cross contamination			
	56	12.15, WHO TRS986, Annex 2	Storage and holding areas (space, segregation, condition, and maintenance) are adequate and allows sufficient material segregation			
	57	12.7, WHO TRS986, Annex 2	Receiving bays, quarantine areas, and approved areas are labelled to indicate their status			
	58	12.23, WHO TRS986, Annex 2	Weighing and sampling procedures, segregation, and related operation prevents mix-ups and ensure integrity of quality			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	59	12.24, WHO TRS986, Annex 2	Dedicated facilities for highly sensitive material (penicillin, biological, hormones, cytotoxic, certain hormones, non-pharmaceuticals) are available to minimize cross-contamination			
	60	12.27, WHO TRS986, Annex 2	Where materials are exposed to environment, working space and in-process areas are smooth and free from cracks (walls, floors, and ceiling) and should not shed particulate matter			
	61	12.30, WHO TRS986, Annex 2	Production areas are supplied with air ventilation supplied from AHU with HVAC, air flow, temperature, humidity, and pressure differentials monitored			
	62	12.31, WHO TRS986, Annex 2	Premises for packaging of final products are specifically designed to prevent risks of mix-ups, contamination, or cross-contamination during operation			
	63	13.1-13.13, WHO TRS986, Annex 2	Equipment is located and installed in such a way to minimize risks of errors, to permit effective cleaning and maintenance and to avoid cross contamination			
	64	13.3, WHO TRS986, Annex 2	Fixed pipework is clearly labelled to identify the contents and direction of flow materials			
	65	15.46, WHO TRS986, Annex 2	Measuring and reading control panel labeling and calibration are up to date and validated			
	66	13.16, WHO TRS986, Annex 2	Production equipment and area cleaning record and status labelling are available			
	67	16.36, WHO TRS986, Annex 2	Production records are available for order request, incoming materials handling, staging, storage condition monitoring, material reconciliation, and control			
	68	16.9, WHO TRS986, Annex 2	In-process monitoring is performed in production areas and records are available for sampling, and monitoring, and checking for completeness			
	69	15.25-15.30, WHO TRS986, Annex 2	Batch processing and packaging records are available with evidence for any deviation that is verified by second person with actions undertaken to control deviation			
QC Physicochemical System	70	17.1-17.3, WHO TRS986, Annex 7, WHO TRS957, Annex 1	Quality control laboratory premises design, location, maintenance and physical separation from production areas are designed suitable			
	71	12.33-12.36, WHO TRS986, Annex 2	Quality control laboratory premises for physico-chemical testing areas and microbiological testing areas have adequate separation and equipped with required air handling design and supply			
	72	12.36, WHO TRS986, Annex 2	The QC laboratory room design is appropriate for sensitive instruments and protects them against external factors, electrical interference, vibration and contact with excessive moisture			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	73	6, WHO TRS986, Annex 2	The QC laboratory organizational chart shows responsibility, reporting lines and hierarchy for approval of testing decision			
	74	15.31-15.48, WHO TRS986, Annex 2	Laboratory logbook, SOPs, and analyst notebooks and applicable templates are adequate			
	75	14, WHO TRS937, Annex 1	Procedure for sample receiving, staging, storage, distribution, testing, and retention ensures traceability of samples and integrity data			
	76	2.2, WHO TRS937, Annex 1	Quality manual or equivalent document provides statement of quality policy, procedures of quality reporting, operational activities, documentation, and internal test procedure and quality management principles within the company			
	77	9, WHO TRS937, Annex 1	When the laboratory sub-contracts testing activity, there is clearly defined responsibility with respect to analytical validation, record maintenance with proficiency testing records to demonstrate competency			
	78	17.6, WHO TRS986, Annex 2	The QC laboratory SOP for analytical testing, verification, calibration, reporting, review, and approval are adequate			
	79	18, WHO TRS937, Annex 1	Test results are evaluated and there are procedures for deviation reporting, review, investigation, and trend analysis			
	80	3.3, WHO TRS937, Annex 1	Procedure for change control within the laboratory states process for change request, review, approval and change implementation			
	81	16, WHO TRS937, Annex 1	Procedures for analytical method development and method validation are suitable for the intended purpose			
	82	13.7, WHO TRS986, Annex 2; 12, WHO TRS 937, Annex 1	Laboratory equipment and instrument location, installation, qualification, calibration, requalification, and recalibration			
	83	7, WHO TRS986, Annex 2	Where applicable, contract agreement exists with details of contract accepter and giver with respect to testing, test type, sample management, test record and approval management			
	84	6, WHO TRS937, Annex 1	The QC laboratory is equipped with adequate human resources with regard to personnel qualification, number, experience, and training records are available			
	85	9.3, WHO TRS986, Annex 2	The QC personnel job description, authority, and delegation of responsibility for testing, reporting, checking, approval and release are clearly defined and documented			
	86	17.7, WHO TRS986, Annex 2	The sampling procedure for starting materials, intermediates, bulk, and finished product assures representative of the batch with detailed information of samples and batches or lots			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	87	17.11, WHO TRS986, Annex 2	The samples are properly labelled and recorded in the logbook of samples with details of sample information including number of the samples, date of receipt, and responsible person for the sampling			
	88	14.12, WHO TRS937, Annex 1	The storage conditions and space for samples including the test samples, reference standards, solvents, reagents and retention samples are properly maintained and controlled			
	89	12.16, WHO TRS986, Annex 2	The QC room temperature, humidity, air conditioning, and other QC areas are monitored regularly			
	90	13.5, WHO TRS986, Annex 2	Balances and other measuring equipment of an appropriate range and precisions available for QC operations and calibrated according to a fixed schedule			
	91	13.10, WHO TRS986, Annex 2	Defective equipment and instruments are removed from QC areas and are labelled accordingly to prevent any accidental use			
	92	17.20, WHO TRS986, Annex 2	The QC records are reviewed in line with BMR and any updates to SOP, calibration, and verification procedures and status labelling are properly documented			
	93	17.21, WHO TRS986, Annex 2	Retention sample policy, storage conditions, and monitoring of retention records are adequate			
	94	21.3, WHO TRS937, Annex 1	Laboratory safety measures including safety showers, safe handling of glassware, corrosive reagents, and solvents, safe disposal wastes are adequate			
	95	17.22-17.25, WHO TRS986, Annex 2	The QC laboratory is involved in the stability study program, equipped with qualified stability study chambers, and stability data monitoring and review of trends			
	96	15.9, WHO TRS986, Annex 2; WHO TRS996, Annex 5	Procedures to ensure data integrity: accuracy, legibility, access control, security, and audit trail are available			
QC Microbiological System	97	17.9-17.10, WHO TRS986, Annex 2	The microbiology QC laboratory and sampling activities for the purpose of quality control tests prevents mix ups, contamination and cross-contamination. There is sufficient space for sample, reference organisms, media, and records storage			
	98	17.3, WHO TRS986, Annex 2	The QC laboratory is under the control of qualified person with access restricted only to authorized personnel			
	99	17.2, WHO TRS986, Annex 2	The QC laboratory function is independent from production area and the premises separate with dedicated			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	100	12.35, WHO TRS986, Annex 2	The laboratory is supplied with quality air and there is separate air handling system dedicated to QC areas with controlled temperature and humidity			
	101	12.33-12.36, WHO TRS986, Annex 2	The design for area classification is based on the criticality of the product and the operation being carried out in the area			
	102	16.14, WHO TRS986, Annex 2	There are periodic environmental monitoring program and procedures and records are available (example, air settling, contact plates, temperature/pressure differential monitoring			
	103	16.16, 16.22 WHO TRS986, Annex 2	There are test records with trending review for possible microbiological contamination with alert and action limits for water, materials, and environmental monitoring			
	104	3.1, 15.31, 15.48, WHO TRS986, Annex 2	Cleaning procedures and maintenance of the area to keep it clean; the disinfection and spillage removal procedures avoids risks of cross contamination			
	105	12.2, WHO TRS957, Annex 1	Laboratory instrument and equipment identification and status labelling available and traceable			
	106	12.2, WHO TRS986, Annex 2	Records such as analyst logbooks, SOPs, and calibrations are available in close proximity for all instruments in the laboratory			
	107	12.16, WHO TRS986, Annex 2	Storage conditions and special temperature-controlled instruments are monitored and controlled			
	108	4 WHO TRS986, Annex 2; WHO TRS 961, Annex 2	The autoclaves in the microbiology laboratory are suitable for use and qualified for specified time, temperature, and pressure for the intended use to sterilize media			
	109	WHO TRS 961, Annex 2	Records of culture media prepared in the laboratory is available; dedicated autoclave for media sterilization and decontamination are used			
	110	WHO TRS 961, Annex 2	Internal quality assurance system covers microbiological test that includes approval of results and documentation on handling of deviations and analysis of trending			
	111	WHO TRS 961, Annex 2	Number of staff, job description, qualification, competence, training, and reporting structure represents assigned responsibility for analyst, supervisor, and manager in microbiological laboratory			
	112	WHO TRS 961, Annex 2	Culture media sourced from approved suppliers are tested for growth promotion and test reports are available on all media received			
	113	WHO TRS 961, Annex 2	Culture media performance checked for suitability using positive and negative control: recovery using target organisms, inhibition, biochemical properties, other tests such as pH, volume, and sterility			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	114	WHO TRS 961, Annex 2	Dry media are stored under correct storage conditions (e.g., cool, dry, and dark) and are sealed tightly			
	115	15.1, WHO TRS986, Annex 2; WHO TRS 961, Annex 2	Records that show sample preparation are traceable to all test steps, batches of the sample, persons, conditions of test, and the like			
	116	WHO TRS 961, Annex 2	Dedicated glassware is used for media containing antimetabolites or inhibitors (If not, washing procedures for glassware should be validated)			
	117	WHO TRS 961, Annex 2	Transfer of media after sterilization is done under unidirectional airflow (UDAF) and the sterilizer is equipped with interlocking double door system to maintain sterility and prevent contamination			
	118	WHO TRS 961, Annex 2	Batches of media are identifiable with records that they meet quality specifications; stored as per storage condition obtained during shelf-life determination			
	119	14.34-14.36, WHO TRS986, Annex 2; WHO TRS 961, Annex 2	All reagents/media are adequately labelled: identity, concentration, storage conditions, preparation date, expiry date and/or recommended storage periods			
	120	14.37-14.43, WHO TRS986, Annex 2; WHO TRS 961, Annex 2	Primary reference standards and certified reference materials are used to qualify, verify and calibrate equipment or media and analytical methods			
	121	WHO TRS 961, Annex 2	Reference cultures and strains are traceable and are subculture in accordance with an SOP that meets the requirements			
	122	WHO TRS 986, Annex 2	Reference stocks are stored in aliquots (deep-frozen or lyophilized). Reference stocks once thawed are not refrozen and reused			
	123	WHO TRS 986, Annex 2	Working cultures for routine use are primary subcultures prepared from the reference stock and working stocks are not sub cultured			
	124	WHO TRS 937, Annex 4, Appendix 4	Sampling of materials (e.g., water, starting materials, air) is done by trained personnel as per defined SOP			
	125	WHO TRS 937, Annex 4, Appendix 4	Incoming sample records are maintained for sampling procedure, environmental conditions for storage, time of sampling, and samplers' detail			
	126	WHO TRS 937, Annex 4, Appendix 4	Sterility testing is performed in a dedicated, classified areas (e.g., Grade A or an isolator) under aseptic conditions			
	127	WHO TRS 937, Annex 4, Appendix 4	Verification and revalidation are performed where appropriate for example, when there are changes in process for synthesis of drug substance, changes in production, procedures, method transfer			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	128	WHO TRS 937, Annex 4, Appendix 4	Room pressure readings and records and pressure gauges are labelled and indicate the area served and the acceptable limits			
	129	WHO TRS 937, Annex 4, Appendix 4	Environmental monitoring of the sterility test zone is done regularly and includes air sampling; settle plates, contact plates, swabs and glove prints			
	130	WHO TRS 937, Annex 4, Appendix 4	Analytical validation covers, where appropriate, determining accuracy, precision, specificity, limit of detection, limit of quantitation, linearity and robustness			
	131	WHO TRS 937, Annex 4, Appendix 4	Pharmacopeial specifications are used and where in-house testing procedures are used, appropriately validated and can be considered equivalent			
Water System	132	WHO TRS 937, Annex 4, Appendix 2	Water production, storage, and distribution are designed, installed, qualified, and maintained to ensure the desired quality of water for pharmaceutical use			
	133	WHO TRS 937, Annex 4, Appendix 2	The capacity of the water system is sufficient to meet the average and the peak flow demand of the current user operation at the facility			
	134	WHO TRS 937, Annex 4, Appendix 2	The water system is recirculated, and the turnover is sufficient to assure the system is suitably controlled to supply quality water for end user			
	135	WHO TRS 937, Annex 4, Appendix 2	Modification to the system is approved by the responsible quality assurance (QA) department using applicable change control documentation system			
	136	WHO TRS 937, Annex 4, Appendix 2	Source water is treated to meet the requirements of drinking water and monitored regularly (on a routine basis) for quality and endotoxin			
	137	WHO TRS 937, Annex 4, Appendix 2	The performance of water system is monitored regularly, and action is taken based on alert limits and action limits			
	138	WHO TRS 937, Annex 4, Appendix 2	There is suitable water treatment method with logical sequence of purification steps			
	139	WHO TRS 937, Annex 4, Appendix 2	The documentation associated with the User Requirement Specification (URS) shows the final water quality, the component system, and source condition			
	140	WHO TRS 937, Annex 4, Appendix 2	The system is designed and installed in a manner to facilitate and accommodate sampling, access for maintenance, regeneration, and sanitization			
	141	WHO TRS 937, Annex 4, Appendix 2	Water storage tanks, protected vents, and pipe systems allow for visual inspection			
	142	WHO TRS 937, Annex 4, Appendix 2	Sand filters, carbon beds and water softeners are monitored and controlled to prevent microbiological contamination			
	143	WHO TRS 937, Annex 4, Appendix 2	The water quality manual indicates water systems, length of pipework, dead legs, pressure gauges, hygienic diaphragm valves, and drainable steam system			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	144	WHO TRS 937, Annex 4, Appendix 2	Drinking water is the source water used to produce purified water. The processes are controlled by SOPs that cover filtration, softening, disinfection, etc.			
	145	WHO TRS 937, Annex 4, Appendix 2	Purified water is produced by at least a method involving ion exchange, reverse osmosis, ultrafiltration and/or electro-deionization processes and distillation			
	146	WHO TRS 937, Annex 4, Appendix 2	Systems are in place to inhibit the growth of microorganisms: e.g., UV light sources and periodic superheated hot water and suitable chemical sanitization			
	147	WHO TRS 937, Annex 4, Appendix 2	There is a specified flow rate maintained through the water production and distribution system			
	148	WHO TRS 937, Annex 4, Appendix 2	The materials that come into contact with purified water for pharmaceutical use, including pipework, valves and fittings, seals, diaphragms and instruments, are suitable for use			
	149	WHO TRS 937, Annex 4, Appendix 2	Bacteria retentive hydrophobic vent filters are fitted to the water storage vessels where applicable			
	150	WHO TRS 937, Annex 4, Appendix 2	There are properly planned and well-documented qualification reports that includes as for example the DQ, IQ, and OQ			
	151	WHO TRS 937, Annex 4, Appendix 2	The performance qualification covers three phases: phase 1 for investigational phase, phase 2 test for short-term control, and phase 3 long-term control			
	152	WHO TRS 937, Annex 4, Appendix 2	Samples are taken and tested in accordance with an SOP as identified in the schematic drawing of the system			
	153	WHO TRS 937, Annex 4, Appendix 2	There are SOPs for preventive maintenance of the water system and the SOP defines the frequency, activity and records that demonstrates compliance with the requirements			
	154	WHO TRS 937, Annex 4, Appendix 2	Water quality manual and review trend of trend analysis is available where results are interpreted to validate system performance following changes, failure, OOS, and CAPA			
HVAC System	155	WHO TRS 937, Annex 4, Appendix 1	The manufacturing areas are classified based on an acceptable level of protection (production area, sampling room, weighing room, general area etc.)			
	156	WHO TRS 937, Annex 4, Appendix 1	Premises and process rooms (production, sampling, testing, etc.) are qualified and validated as “as-built,” “at-rest,” and “in operation” condition			
	157	WHO TRS 937, Annex 4, Appendix 1	AHU design components and relevant process and product factors are considered during validation: air filtration, air change, room pressure, location air filters, temperature, humidity, process, occupancy, and product			
	158	WHO TRS 937, Annex 4, Appendix 1	Procedure and records for the startup and shut down sequence of AHUs are available, and the correct sequence is described to prevent cross-contamination			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	159	WHO TRS 986, Annex 2	Production areas are well ventilated where air change rates are designed properly and supported with validation and qualification to ensure that the defined clean area is maintained			
	160	WHO TRS 986, Annex 2	Cross-contamination from particulate matters is prevented with appropriate degree of air filtration and controlled to acceptable levels at rest and during operation			
	161	WHO TRS 986, Annex 2	Contamination risk is adequately controlled with its effective ventilation system (including appropriate levels of filtration, dilution, flushing and or by displacement airflow) are properly qualified			
	162	WHO TRS 986, Annex 2	Where air is recirculated from process areas and mixed with fresh air, components of the AHU include primary, secondary plus tertiary filters are designed properly, qualified and calibrated (e.g., EN779 G4 plus F8 plus EN1822 H13 filters)			
	163	WHO TRS 986, Annex 2	Production operation rooms and airflow patterns are designed to protect the products and operators and are effective for dust containment.			
	164	WHO TRS 986, Annex 2	Possibility of contaminated and unfiltered air to enter from outside to the production areas are avoided by design and practice.			
	165	WHO TRS 986, Annex 2	In a multiproduct manufacturing facility, measures undertaken to ensure that dust cannot move from one cubicle to another cubicle where different materials are processed.			
	166	WHO TRS 986, Annex 2	Pressure cascade system is maintained in accordance with the design and qualification requirement to ensure dust containment.			
	167	WHO TRS 986, Annex 2	The corridor pressure design relative to the cubicles, and the cubicles pressure relative to atmospheric pressure are properly defined and suitable for cross-contamination containments			
	168	12.8, WHO TRS 986, Annex 2	Production area ceilings and walls smooth and doors are sealed and provided with adequate lighting, temperature and humidity suitable to maintain the area clean			
	169	WHO TRS 986, Annex 2	Pressure control and monitoring devices used are appropriate in design, scale, and are calibrated. Zero checks are done at regular intervals			
	170	WHO TRS 986, Annex 2	Air locks, buffer rooms, and hatch boxes are properly designed and qualified			
	171	WHO TRS 986, Annex 2	Doors opening to the high-pressure side and are provided with self-closers. Sliding doors are not used			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	172	WHO TRS 986, Annex 2	Temperature and relative humidity are controlled, monitored, and recorded, and where relevant, maximum and minimum values are defined			
	173	WHO TRS 986, Annex 2	Central dust extraction systems are interlocked with the appropriate air handling systems, and they operate simultaneously			
	174	WHO TRS 986, Annex 2	Exhaust air from equipment and facilities (e.g., Fluidized bed dryer and coaters) pass through appropriate filters to prevent contamination of the ambient air			
	175	WHO TRS 986, Annex 2	Appropriate alarm systems are in place to alert personnel if a critical air supply system and critical fans fail to function and alarms for such out of trends are investigated and subject to CAPA			
	176	WHO TRS 986, Annex 2	Where applicable, filter banks are provided with pressure differential gauges for monitoring and control marked with the clean filter and the change-out filter			
	177	WHO TRS 986, Annex 2	Systems are in place to prevent failure of a supply air fan, return air fan, exhaust air fan, and dust extract system fans			
	178	WHO TRS 986, Annex 2	The AHU system qualification includes environmental monitoring for: particle count, pressure differential, air volume, air velocity, air change, filter leakage, and smoke test for air visualization			
	179	WHO TRS937, Annex 4, Appendix 1	Change control procedure and change management impacting the HVAC system and AHU components are available			
	180	WHO TRS937, Annex 4, Appendix 1	The AHU and HVAC system operating parameters are monitored; out-of-limit results are recorded, investigated, and subjected to CAPA			
	181	WHO TRS937, Annex 4	Procedures for periodic requalification with records on planned preventive and maintenance system and requalification after changes are available			
Documentation and Validation System	182	WHO TRS937, Annex 4	The VMP describes sufficient detail regarding the approach, philosophy and policy regarding validation and qualification process and procedure as per the GMP requirement			
	183	WHO TRS937, Annex 4	Validation protocol and responsible team consisting of personnel with appropriate qualifications and experience representing different areas of operation are available			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	184	WHO TRS937, Annex 4	Documented evidence is available with the applicable SOPs and protocols that supports the outcome of qualification and validation reports			
	185	WHO TRS937, Annex 4	Detailed qualification protocols and reports for: design, installation, operation and performance are available for key equipment, instrument, and facility			
	186	WHO TRS981, Annex 2	The risk management and risk assessment conducted shows the extent of required evidence for risk control and mitigation of risk that is in commensurate to the level of risks associated from materials, process, product, premises, environment, personnel, and utilities			
	187	9, 15 WHO TRS986, Annex 2	The SOPs for validation, calibrations and training records are part of the documented evidence during qualification and validation			
	188	WHO TRS1033, Annex 2	The standard operating procedures used for cleaning and cleaning validation are consistent and satisfactory			
	189	WHO TRS937, Annex 4, Appendix 3	Cleaning validation holding time of cleaned equipment, sampling, and product matrixing of cleaning validation represents the worst-case conditions			
	190	WHO TRS937, Annex 4, Appendix 3	Cleaning validation meets acceptance criteria and cleaning procedure is developed on the basis of evidence			
	191	WHO TRS937, Annex 4	Validation of the analytical methods used for cleaning validation was done and covers relevant parameters including accuracy, linearity, precision, selectivity, LOD, LOQ, etc.			
	192	4.10, WHO TRS986, Annex 2	Manufacturing processes and analytical methods are validated, and raw data are verified and tabulated for evaluation			
	193	WHO TRS937, Annex 4, Appendix 5	Computer systems are validated and any modifications to commercial software and hardware are appropriately qualified			
	194	WHO TRS937, Annex 4, Appendix 1	The AHU validation covers relevant parameters including temperature, humidity, pressure, air quantity, air flow pattern, HEPA filters, particle count, room recovery			
	195	WHO TRS937, Annex 4, Appendix 2	Validation of water systems covers the three phases of water system that includes phase 1 for investigational, phase 1 for short-term control and phase 3 for long-term control			
	196	15.46, WHO TRS986, Annex 2	Full validation for in-house analytical methods and records are available for applicable validation parameters			
	197	4.2-4.3, WHO TRS986, Annex 2	Key production equipment their qualification protocols and reports are available: DQ, IQ, OQ, and PQ			
	198	WHO TRS992, Annex 3	Validation and validation records and policy of revalidation and requalification following changes that requires revalidation and requalification are satisfactory			

System	Element Number	Reference	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	199	WHO TRS961, Annex 14	Updated site master file that reflects authorized production line and marketing authorization			
	200	WHO TRS1010, Annex 10	Stability study protocol includes ongoing monitoring of at least one production batch manufactured per year			
	201	WHO TRS1010, Annex 10	Hold time stability study for intermediate and bulk products are available			
	202	4.1-4.11, WHO TRS986, Annex 2; WHO TRS 937, Annex 4	Manufacturing process validation protocols and reports for each product with detailed evidence of validation for relevant process and product related aspects as per the marketing authorization are available			

Appendix 2: GSDP Systems and Elements of the RBI Tool[1]

Note: In addition to providing the complete list of the system and elements included in the RBI Tool, the following table can be used by NRAs as a template to select the systems and elements appropriate for their own specific RBI processes and assign a risk rating and GMP point for each element to calculate the respective element scores.

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
Quality Management System	1	Entities involved in the storage and distribution of medical products should have a comprehensively designed, documented and correctly implemented quality system that incorporates GSP, GDP, principles of quality risk management and management review.			
	2	Senior management has the ultimate responsibility to ensure that an effective quality system is established, resourced, implemented and maintained.			
	3	The quality system should ensure that: 5.3.1 GSP and GDP are adopted and implemented to ensure that the quality of medical products is maintained throughout their shelf-life in the supply chain; and medical products are appropriately procured, stored, distributed and delivered (in compliance with the legislation) to the appropriate recipients (see Section 18.1)			
	4	The quality system should ensure that: operations are clearly specified in written procedures;			
	5	The quality system should ensure that: responsibilities are clearly specified in job descriptions;			
	6	The quality system should ensure that: all risks are identified and necessary, effective controls are implemented;			
	7	The quality system should ensure that: processes are in place to assure the management of outsourced activities;			
	8	The quality system should ensure that: there is a procedure for self-inspection and quality audits;			
	9	The quality system should ensure that: there is a system for quality risk management;			
	10	The quality system should ensure that: there are systems for managing returns, complaints and recalls; and			
	11	The quality system should ensure that: there are systems to manage changes, deviations, and corrective and preventive actions (CAPAs).			

[1] Adapted from WHO TRS 1025 Annex 7 and WHO TRS 961 Annex 9.

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	12	There should be an authorized, written quality policy describing the overall intentions and requirements regarding quality. This may be reflected in a quality manual.			
	13	There should be an appropriate organizational structure. This should be presented in an authorized organizational chart. The responsibility, authority and interrelationships of personnel should be clearly indicated.			
	14	Roles and responsibilities should be clearly defined and understood by the individuals concerned and recorded as written job descriptions.			
	15	The quality system should include appropriate procedures, processes and resources.			
	16	There should be a system to assess, control, communicate and review risks identified at all stages in the supply chain.			
	17	The evaluation of risk should be based on scientific knowledge and experience and ultimately be linked to the protection of the patient.			
	18	Appropriate controls should be developed and implemented to address all risks. The effectiveness of the controls implemented should be evaluated at periodic intervals.			
	19	There should be a system for periodic management review. The review should include at least:			
	20	The review should include at least: Senior management;			
	21	Review of the quality system and its effectiveness by using quality metrics and key performance indicators.			
	22	Identification of opportunities for continual improvement; and			
	23	Follow-up on recommendations from previous management review meetings.			
	24	Minutes and related documentation from management review meetings should be available.			
	25	There should be a written procedure for the handling of complaints. In the case of a complaint about the quality of a medical product or its packaging, the original manufacturer and/or marketing authorization holder should be informed as soon as possible.			
	26	All complaints should be recorded and appropriately investigated. The root cause should be identified, and the impact (e.g., on other batches or products) risk-assessed. Appropriate CAPAs should be taken.			
	27	Where required, the information should be shared with the NRA and a recall initiated where appropriate.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	28	A distinction should be made between complaints about a medical product or its packaging and those relating to distribution.			
	29	The relevant information, such as the results of the investigation of the complaint, should be shared with the relevant entities.			
	30	Medical product quality problems and suspected cases of substandard or falsified products identified should be handled according to relevant authorized procedures. The information should be shared with the manufacturer and appropriate national and/or regional regulatory authorities, without delay.			
	31	There should be a written procedure, in compliance with national or regional requirements, to effectively and promptly recall medical products.			
	32	The effectiveness of the procedure should be checked annually and updated as necessary.			
	33	The original manufacturer and/or marketing authorization holder, or other relevant contract party, should be informed in the event of a recall.			
	34	Information on a recall should be shared with the appropriate national or regional regulatory authority.			
	35	All recalled products should be secure, segregated, transported and stored under appropriate conditions. These should be clearly labelled as recalled products. The particular storage conditions applicable to the product should be maintained where possible.			
	36	All customers and competent authorities of all countries to which a given medical product may have been distributed should be informed promptly of the recall of the product.			
	37	All records, including distribution records, should be readily accessible to the designated person(s) responsible for recalls. These records should contain sufficient information on products supplied to customers (e.g., name, address, contact detail, batch numbers, quantities and safety features – including exported products).			
	38	The progress of a recall process should be recorded and a final report issued, which includes a reconciliation between delivered and recovered quantities of medical products.			
	39	The quality system should include self-inspections. These should be conducted to monitor the implementation, compliance with and effectiveness of SOPs, as well as compliance with regulations, GSP, GDP and other appropriate guides.			
	40	Self-inspections should be conducted periodically, according to an annual schedule.			

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	41	The team conducting the inspection should be free from bias and individual members should have appropriate knowledge and experience.			
	42	The results of all self-inspections should be recorded. Reports should contain all observations made during the inspection and presented to the relevant personnel and management.			
	43	Necessary CAPAs should be taken and their effectiveness should be reviewed within a defined timeframe.			
	44	There should be an adequate number of personnel.			
	45	Personnel should have appropriate educational qualification, experience and training relative to the activities undertaken.			
	46	A designated person within the organization, with appropriate qualification and training, should have the defined authority and responsibility for ensuring that a quality management system is implemented and maintained. This person should preferably be independent from the person responsible for operations and should ensure compliance with GSP and GDP.			
	47	Personnel should have the authority and resources needed to carry out their duties and to follow the quality systems, as well as to identify and correct deviations from the established procedures.			
	48	There should be arrangements in place to ensure that management and personnel are not subjected to commercial, political, financial or other pressures or conflict of interest that may have an adverse effect on the quality of service provided or on the integrity of medical products.			
	49	Safety procedures should be in place relating to all relevant personnel and property, environmental protection and product integrity.			
	50	Personnel should receive initial and continued training in accordance with a written training program. The training should cover the requirements of GSP and GDP (as applicable), as well as on-the-job training. Other topics should be included, such as product security, product identification and the detection of falsified products.			
	51	Personnel dealing with hazardous products (such as highly active materials, radioactive materials, narcotics and other hazardous, environmentally sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion) should be given specific training.			
	52	Personnel should be trained in, and observe high levels of, personal hygiene and sanitation.			
	53	Records of all training, attendance and assessments should be kept.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
Facility	54	Premises should be suitably located, designed, constructed and maintained, to ensure appropriate operations such as receiving, storage, picking, packing and dispatch of medical products.			
	55	There should be sufficient space, lighting and ventilation to ensure required segregation, appropriate storage conditions and cleanliness.			
	56	Sufficient security should be provided and access should be controlled.			
	57	Appropriate controls and segregation should be provided for products requiring specific handling or storage conditions, such as radioactive materials, products containing hazardous substances and products to be stored under controlled temperature and relative humidity conditions.			
	58	Where possible, receiving and dispatch bays should be separate, to avoid mix-ups. Bays should protect products from weather conditions.			
	59	Activities relating to receiving and dispatch should be done in accordance with authorized procedures. Areas should be suitably equipped for the operations.			
	60	Premises should be kept clean. Cleaning equipment and cleaning agents should not become possible sources of contamination.			
	61	Premises should be protected from the entry of birds, rodents, insects and other animals. A rodent and pest control program should be in place.			
	62	Toilets, washing, rest and canteen facilities should be separate from areas where products are handled. Food, eating, drinking and smoking should be prohibited in all areas where medical products are stored or handled.			
	63	Each incoming delivery should be checked against the relevant documentation, to ensure that the correct product is delivered from the correct supplier. This may include, for example, the purchase order, containers, label description, batch number, expiry date, product and quantity.			
	64	The consignment should be examined for uniformity of the containers and, if necessary, should be subdivided according to the supplier's batch number should the delivery comprise more than one batch. Each batch should be dealt with separately.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	65	Each consignment should be carefully checked for possible contamination, tampering and damage. A representative number of containers in a consignment should be sampled and checked according to a written procedure. Any suspect containers or, if necessary, the entire delivery, should be quarantined for further investigation.			
	66	Receiving areas should be of sufficient size to allow the cleaning of incoming medical products.			
	67	When required, samples of medical products should be taken by appropriately trained and qualified personnel and in strict accordance with a written sampling procedure and sampling plans. Containers from which samples have been taken should be labelled accordingly.			
	68	Following sampling, the goods should be subject to quarantine. Batch segregation should be maintained during quarantine and all subsequent storage.			
	69	Materials and products requiring transport and storage under controlled conditions of temperature and relative humidity, as applicable, should be handled as a priority. The transportation temperature data, where appropriate, should be reviewed upon receipt, to ensure that the required conditions had been maintained. Where applicable, cold-chain materials and products should be handled according to the approved conditions by the authority, or as recommended by the manufacturer, as appropriate.			
	70	Medical products should not be transferred to saleable stock until an authorized release is obtained.			
	71	Measures should be taken to ensure that rejected medical products cannot be used. They should be segregated and securely stored while awaiting destruction or return to the supplier.			
	72	Precautions should be taken to prevent unauthorized persons from entering storage areas.			
	73	Storage areas should be of sufficient capacity to allow orderly storage of the various categories of medical products.			
	74	Storage areas should be appropriately designed, constructed, maintained or adapted. They should be kept clean and there should be sufficient space and lighting.			
	75	Storage areas should be maintained within acceptable and specified temperature limits. Where the labels show special storage conditions are required (e.g. temperature, relative humidity), these should be provided, controlled, monitored and recorded.			

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	76	Materials and medical products should be stored off the floor, away from walls and ceilings, protected from direct sunlight and suitably spaced, to permit ventilation, cleaning and inspection. Suitable pallets should be used and kept in a good state of cleanliness and repair.			
	77	A written sanitation program should be available, indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas.			
	78	There should be appropriate procedures for the clean-up of any spillage, to ensure complete removal of any risk of contamination.			
	79	Where the status is ensured by storage in separate areas, these areas should be clearly marked and their access restricted to authorized personnel. Any system replacing physical separation and labeling or demarcation should provide equivalent security. For example, computerized systems can be used, provided that they are validated to demonstrate security of access			
	80	Sampling should be done under controlled conditions and conducted in such a way that there is no risk of contamination or cross-contamination. Adequate cleaning procedures should be followed after sampling.			
	81	Certain materials and products, such as highly active and radioactive materials, narcotics and other hazardous, sensitive and/or dangerous materials and products, as well as substances presenting special risks of abuse, fire or explosion (e.g., combustible liquids and solids and pressurized gases), should be stored in a dedicated area that is subject to appropriate additional safety and security measures, and in accordance with national legislation.			
	82	Materials and medical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.			
	83	Materials and medical products should be stored in conditions that assure that their quality is maintained. Stock should be appropriately rotated. The “first expired/first out” (FEFO) principle should be followed.			
	84	Narcotic medical products should be stored in compliance with international conventions, national laws and regulations on narcotics.			
	85	Broken or damaged items should be withdrawn from usable stock and separated.			
	86	There should be a written procedure for fire control, including prevention of fire, fire detection and fire drills. Fire-detection and firefighting equipment should be available and should be serviced regularly.			

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	87	The storage conditions for medical products should be in compliance with their labelling and information provided by the manufacturer.			
	88	Heating, ventilation and air conditioning systems should be appropriately designed, installed, qualified and maintained, to ensure that the required storage conditions are upheld.			
	89	Mapping studies for temperature, and relative humidity where appropriate, should be done, for example in storage areas, refrigerators and freezers.			
	90	Temperature and relative humidity, as appropriate, should be controlled and monitored at regular intervals. Data should be recorded and the records should be reviewed. The equipment used for monitoring should be calibrated and be suitable for its intended use. All records pertaining to mapping and monitoring should be kept for a suitable period of time and as required by national legislation. See Appendix 1 for recommended storage conditions.			
	91	Equipment, including computerized systems, should be suitable for its intended use. All equipment should be appropriately designed, located, installed, qualified and maintained.			
	92	Computerized systems should be capable of achieving the desired output and results.			
	93	Where electronic commerce (e-commerce) is used, i.e., electronic means for any of the steps, defined procedures and adequate systems should be in place to ensure traceability and confidence in the supply chain and products concerned.			
	94	Electronic transactions (including those conducted via the Internet) relating to the distribution of medical products should be performed only by authorized persons, according to defined and authorized access and privileges.			
	95	Where GXP systems are used, these should meet the requirements of WHO or other appropriate guides on computerized systems.			
Documentation	96	The scope and extent of qualification, and validation where appropriate, should be determined using documented risk management principles.			
	97	Premises, utilities, equipment and instruments, processes and procedures should be considered.			

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	98	Qualification and validation should be done following procedures and protocols. The results and outcome of the qualification and validation should be recorded in reports. Deviations should be investigated and the completion of the qualification and validation should be concluded and approved.			
	99	Documentation includes all procedures, records and data, whether in paper or electronic form. Documents should be appropriately designed, completed, reviewed, authorized, distributed and kept as required. Documents should be readily available.			
	100	Written procedures should be followed for the preparation, review, approval, use of and control of all documents relating to the policies and activities for the process of storage and distribution of medical products.			
	101	Documents should be laid out in an orderly fashion and be easy to complete, review and check. The title, scope, objective and purpose of each document should be clear.			
	102	All documents should be completed, signed and dated as required by authorized person(s) and should not be changed without the necessary authorization.			
	103	Documentation should be prepared and maintained in accordance with the national legislation and principles of good documentation practices.			
	104	Records should be accurate, legible, traceable, attributable and unambiguous. Electronic data should be backed-up in accordance with written procedures. Records should be maintained for the back-up and restoration of data.			
	105	Procedures for the identification, collection, indexing, retrieval, storage, maintenance, disposal of and access to all applicable documentation should be followed.			
	106	Documents should be reviewed regularly and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.			
	107	All records should be stored and retained using facilities that prevent unauthorized access, modification, damage, deterioration and/or loss of documentation during the entire life cycle of the record. Records must be readily retrievable.			

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	108	Comprehensive records should be maintained for all receipts, storage, issues and distribution. The records should include, for example: • 17.10.1 Date (e.g., receipt or dispatch, as appropriate) • 17.10.2 Name and description of the product • 17.10.3 Quantity received, or supplied • 17.10.4 Name and address of the supplier and customer • 17.10.5 Batch number(s) • 17.10.6 Expiry date • 17.10.7 Suitability of the supplier • 17.10.8 Qualification of suppliers; and • 17.10.9 Customer qualification			
	109	All containers should be clearly labelled with at least the name of the medical product, batch number, expiry date or retest date, and the specified storage conditions.			
Operations and Product Management	110	Returned medical products should be handled in accordance with authorized procedures.			
	111	All returned medical products should be placed in quarantine upon receipt. The status of the goods should be clear. Precautions should be taken to prevent access and distribution until a decision has been taken with regard to their disposition. The particular storage conditions applicable to the medical products should be maintained until their disposition.			
	112	Medical products returned should be destroyed unless it is certain that their quality is satisfactory, after they have been critically assessed in accordance with a written and authorized procedure.			
	113	The nature of the medical product, any special storage conditions it requires, its condition and history and the time lapse since it was issued, should all be taken into account in this assessment. Where any doubt arises over the quality of the medical product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	114	When handling returned goods, the following considerations at least should be taken: • 9.5.1 a risk-based process should be followed when deciding on the fate of the returned goods. This should include, but not be limited to, the nature of the product, storage conditions, condition of the product history, time-lapse since distribution and the manner and condition of transport while being returned • 9.5.2 the terms and conditions of the agreement between the parties; and • 9.5.3 examination of the returned goods, with decisions taken by suitably qualified, experienced and authorized persons			
	115	Where products are rejected, authorized procedures should be followed, including safe transport.			
	116	Destruction of products should be done in accordance with international, national and local requirements regarding disposal of such products, and with due consideration to the protection of the environment.			
	117	Records of all returned, rejected and destroyed medical products should be kept for a defined period, in accordance with national requirements.			
	118	Records of stock levels for all medical products in store should be maintained, in either paper or electronic format. These records should be updated after each operation (e.g., entries, issues, losses, adjustments). These records should be kept for a suitable period of time and as required by national legislation. Periodic stock reconciliation should be performed at defined intervals, by comparing the actual and recorded stock.			
	119	The root cause for stock discrepancies should be identified and appropriate CAPAs taken to prevent recurrence.			
	120	When damaged containers are received, this should be brought to the attention of the person responsible for quality. Any action taken should be documented. (These containers should not be issued unless the quality of the medical products has been shown to be unaffected.)			
	121	All stock should be checked at regular intervals, to identify those items that are close to their retest or expiry date. Appropriate action should be taken, such as removal of these items from useable stock.			
	122	All activities and operations should be conducted in accordance with national legislation, GSP, GDP and associated guides.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	123	Storage and distribution of medical products should be done by persons authorized to do so, in accordance with national legislation.			
	124	Activities and operations should be performed in accordance with documented procedures.			
	125	Automated storage and retrieval systems and operations should comply with current GSP, GDP, and GXP guides, as well as the recommendations in this guide.			
	126	Medical products should be procured from appropriately authorized suppliers.			
	127	Deliveries should be examined for damage, seal intactness, signs of tampering, labelling, completeness of order and other related aspects (e.g., availability of a certificate of analysis, where applicable), at the time of receiving.			
	128	Containers and consignments that do not meet acceptance criteria at the time of receipt should be labelled, kept separate and investigated. This includes suspected falsified products.			
	129	Medical products requiring specific storage conditions, or controlled access (e.g., narcotics), should be processed without delay and stored in accordance with their requirements.			
	130	Appropriate controls should be implemented to prevent contamination and/or mix-ups during storage.			
	131	Controls and procedures should be in place to prevent and handle spillage and breakage.			
	132	Repackaging and relabeling of materials and products are not recommended. Where repackaging and relabeling occur, these activities should only be performed by entities appropriately authorized to do so and in compliance with the applicable national, regional and international requirements, and in accordance with GMP.			
	133	Procedures should be in place for the controlled disposal of original packaging, to prevent re-use thereof.			
	134	Medical products should be transported in accordance with the conditions stated on the labels and described by the manufacturer. The risk to the quality of the medical product during transport and distribution should be eliminated or minimized to an acceptable level.			
	135	Product, batch and container identity should be maintained at all times.			
	136	All labels should remain legible.			
	137	Distribution records should be sufficiently detailed to allow for a recall when required.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	138	Drivers of vehicles should be identified and present appropriate documentation to demonstrate that they are authorized to transport medical products.			
	139	Vehicles should be suitable for their purpose, with sufficient space and appropriately equipped to protect medical products.			
	140	The design and use of vehicles and equipment must aim to minimize the risk of errors and permit effective cleaning and/or maintenance, to avoid contamination, build-up of dust or dirt and/or any adverse effect on the quality of the products.			
	141	Where feasible, consideration should be given to adding technology, such as global positioning system (GPS) electronic tracking devices and engine-kill buttons to vehicles, which would enhance the security and traceability of vehicles with products.			
	142	Where possible, dedicated vehicles and equipment should be used for medical products. Where non-dedicated vehicles and equipment are used, procedures should be in place to ensure that the quality of the products will not be compromised. Defective vehicles and equipment should not be used. These should either be labelled as such or removed from service.			
	143	There should be procedures in place for the operation and maintenance of all vehicles and equipment.			
	144	Equipment and materials used for the cleaning of vehicles should not become a source of contamination or have an adverse effect on product quality.			
	145	Vehicles used for transportation of medical products should be qualified, where applicable, to demonstrate their capability to maintain the required transport conditions. There should be a maintenance program for the cooling/heating system.			
	146	Appropriate environmental conditions should be maintained, monitored and recorded. All monitoring records should be kept for a defined period of time, as required by national legislation. Records of monitoring data should be made available for inspection by the regulatory or other oversight body.			
	147	Instruments used for monitoring conditions, for example, temperature and humidity, within vehicles and containers should be calibrated at regular intervals. 18.26 Rejected, recalled and returned products, as well as those suspected as being falsified, should be securely packaged, clearly labelled and accompanied by the appropriate supporting documentation.			

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	148	Measures should be in place to prevent unauthorized persons from entering and/or tampering with vehicles and/or equipment, as well as to prevent the theft or misappropriation thereof.			
	149	Shipment containers should have no adverse effect on the quality of the medical products and should offer adequate protection to materials and these products. Containers should be labelled indicating, for example, handling and storage conditions, precautions, contents and source, and safety symbols, as appropriate.			
	150	Special care should be taken when using dry ice and liquid nitrogen in shipment containers, owing to safety issues and possible adverse effects on the quality of medical products.			
	151	Written procedures should be available for the handling of damaged and/ or broken shipment containers. Particular attention should be paid to those containing potentially toxic and hazardous products.			
	152	There should be documented, detailed procedures for the dispatch of products.			
	153	Medical products should only be sold and/or distributed to persons or entities that are authorized to acquire such products in accordance with the applicable national legislation and marketing authorization. Written proof of such authorization, or an import permit or equivalent where there is no marketing authorization, must be obtained prior to the distribution of products to such persons or entities.			
	154	Dispatch and transportation should be undertaken only after the receipt of a valid order, which should be documented.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	155	Records for the dispatch of products should be prepared and should include information such as, but not limited to: • 18.35.1 Date of dispatch • 18.35.2 Complete business name and address (no acronyms), type of entity responsible for the transportation, telephone number, names of contact persons • 18.35.3 Status of the addressee (e.g., retail pharmacy, hospital or community clinic) • 18.35.4 A description of the products, including, for example, name, dosage form and strength (if applicable) • 18.35.5 Quantity of the products, i.e., number of containers and quantity per container (if applicable) • 18.35.6 Applicable transport and storage conditions • 18.35.7 A unique number to allow identification of the delivery order; and • 18.35.8 Assigned batch number and expiry date (where not possible at dispatch, this information should at least be kept at receipt, to facilitate traceability)			
	156	Records of dispatch should contain sufficient information to enable traceability of the product. Such records should facilitate the recall of a batch of a product, if necessary, as well as the investigation of falsified or potentially falsified products. In addition, the assigned batch number and expiry date of products should be recorded at the point of receipt, to facilitate traceability.			
	157	Vehicles and containers should be loaded carefully and systematically on a last-in/first-out (LIFO) basis, to save time when unloading, to prevent physical damage and to reduce security risks. Extra care should be taken during loading and unloading of cartons, to avoid damage.			
	158	Medical products should not be supplied or received after their expiry date, or so close to the expiry date that this date is likely to be reached before the products are used by the consumer.			
	159	Medical products and shipment containers should be secured in order to prevent or to provide evidence of unauthorized access. Vehicles and operators should be provided with additional security where necessary, to prevent theft and other misappropriation of products during transportation.			
	160	Medical products should be stored and transported in accordance with procedures such that: • 18.40.1 The identity of the product is not lost • 18.40.2 The product does not contaminate and is not contaminated by other products			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
		• 18.40.3 Adequate precautions are taken against spillage, breakage, misappropriation and theft; and • 18.40.4 Appropriate environmental conditions are maintained, for example, using cold-chain for thermolabile products.			
	161	Written procedures should be in place for investigating and dealing with any failure to comply with storage requirements, for example, temperature deviations. If a deviation has been noticed during transportation, by the person or entity responsible for transportation, this should be reported to the supplier, distributor and recipient. In cases where the recipient notices the deviation, it should be reported to the distributor.			
	162	Transportation of products containing hazardous substances or narcotics and other dependence-producing substances, should be transported in safe, suitably designed, secured containers and vehicles. In addition, the requirements of applicable international agreements and national legislation should be met.			
	163	Spillages should be cleaned up as soon as possible, in order to prevent possible contamination, cross-contamination and hazards. Written procedures should be in place for the handling of such occurrences.			
	164	Damage to containers and any other event or problem that occurs during transit must be recorded and reported to the relevant department, entity or authority and investigated.			
	165	Products in transit must be accompanied by the appropriate documentation.			
	166	Any activity relating to the storage and distribution of a medical product that is delegated to another person or entity should be performed by the appropriately authorized parties, in accordance with national legislation and the terms of a written contract.			
	167	There should be a written contract between the entities. The contract should define the responsibilities of each entity (contract giver and contract acceptor) and cover at least the following: • 19.2.1 Compliance with this guide and the principles of GSP and GDP; • 19.2.2 The responsibilities of all entities for measures to avoid the entry of substandard and falsified products into the distribution chain • 19.2.3 Training of personnel • 19.2.4 Conditions of subcontracting subject to the written approval of the contract giver; and			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
		• 19.2.5 Periodic audits			
	168	The contract giver should assess the contract acceptor before entering into the contract, e.g. through on-site audits, documentation and licensing status review.			
	169	The contract giver should provide to the contract acceptor all relevant information relating to the material and medical products.			
	170	The contract acceptor should have adequate resources (e.g., premises, equipment, personnel, knowledge, experience and vehicles, as appropriate) to carry out the work.			
	171	The contract acceptor should refrain from performing any activity that may adversely affect the materials or products handled.			
	172	The quality system should include procedures to assist in identifying and handling medical products that are suspected to be substandard and/or falsified.			
	173	Where such medical products are identified, the holder of the marketing authorization, the manufacturer and the appropriate national, regional and international regulatory bodies (as appropriate), as well as other relevant competent authorities, should be informed.			
	174	Such products should be stored in a secure, segregated area and clearly identified to prevent further distribution or sale. Access should be controlled.			
	175	Records should be maintained reflecting the investigations and action taken, such as disposal of the product. Falsified products should not re- enter the market.			
	176	Storage and distribution facilities should be inspected by inspectors authorized by national legislation. This should be done at determined, periodic intervals.			
	177	Inspectors should have appropriate educational qualifications, knowledge and experience.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	178	An inspection should normally be conducted by a team of inspectors.			
	179	Inspectors should assess compliance with national legislation, GSP, GDP and related guides (GXP), as appropriate.			
	180	Inspections should cover the premises, equipment, personnel, activities, quality system, qualification and validation and other related aspects, as contained in this guide.			
	181	An inspection report should be prepared and provided to the inspected entity within a defined period of time from the last day of the inspection. Observations may be categorized based on risk assessment.			
Quality Management System	182	Personnel handling products should wear garments suitable for the activities that they perform. Personnel dealing with hazardous pharmaceutical products, including products containing materials that are highly active, toxic, infectious or sensitizing, should be provided with protective garments as necessary.			
	183	Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, should be established and observed. Such procedures should cover health, hygiene and the clothing of personnel.			
	184	Procedures and conditions of employment for employees, including contract and temporary staff, and other personnel having access to medical products, must be designed and implemented to assist in minimizing the possibility of such products coming into the possession of unauthorized persons or entities.			
	185	Codes of practice and procedures should be in place to prevent and address situations where persons involved in the storage and distribution of medical products are suspected of, or found to be implicated in, any activities relating to the misappropriation, tampering, diversion or falsification of any product.			
Operations and Product Management	186	CAPA for observations listed as non-compliances in the inspection report, with the national legislation and guides, should be submitted for review by the inspectors within the defined period, as stated by the inspectors.			
	187	Inspections should be closed with a conclusion after the review of the CAPAs.			

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Cold Chain - Operations and Product Management	188	Port handling and customs clearance 1.1.1 Port of entry Import TTSPPs through a port of entry that is equipped to handle such products. Where this is not possible, ensure that arrangements are in place to provide the necessary level of protection and security. Reason: To minimize the risk of damage.			
	189	Offloading: As soon as possible after arrival, remove TTSPP shipments from the wharf or airport apron to a safe and suitable temperature-controlled storage location. Reason: To minimize the risk of theft and to avoid exposure to adverse ambient conditions.			
	190	Temporary storage at port of entry: Store TTSPP shipments in a secure warehouse under the conditions recommended by the product manufacturer, until the shipment has been authorized for removal by customs. Reason: To avoid risk of theft or damage during temporary storage. In some situations, arrangements can be made for formal customs clearance to take place away from the port of entry - for example, at a national vaccine store. In situations where the port of entry is not equipped with suitable cold storage facilities, this can reduce the risk of temperature excursions.			
	191	Customs clearance: Draw up procedures and memoranda of understanding to ensure that TTSPP shipments are cleared through customs as rapidly as possible. This can be facilitated by a pre-clearance procedure carried out by the local health agency, clearing agent or freight forwarder in collaboration with customs. Alternatively, the clearance process should be conducted by customs staff, supported by personnel with suitable pharmaceutical training, especially when clearance involves the opening and resealing of temperature- controlled packaging. Reason: To avoid delays during customs clearance that may cause temperature excursions and place TTSPPs at risk.			
Cold Chain - Facility	192	Natural hazards Select and/or develop storage sites to minimize risks from natural hazards such as floods, landslides and earthquakes and extreme weather conditions such as hurricanes and tornadoes. Reason: To protect against loss of valuable pharmaceutical products, to ensure continued supply to patients in the market and to protect personnel working in the store.			
	193	Site access: Provide vehicular access to storage buildings sufficient to accommodate the largest vehicles visiting the site, including emergency vehicles. Reason: To ensure convenient operation of the facility.			
	194	Site security: Provide perimeter protection to ensure security of the grounds and storage buildings against anticipated risks. Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and the value of goods stored there.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	195	Site cleanliness: Keep the site free of accumulated dust, dirt, waste and debris. Ensure that pests are kept under control within the site area. Collect waste in designated closed containers and arrange for safe disposal at frequent intervals. Reason: To help protect storage buildings against ingress by dust, dirt and pests.			
	196	Construction standards: Construct or procure storage buildings that are: • purpose-designed for the storage of TTSPPs, or well-adapted for this purpose; • designed to suit the prevailing climate, making maximum use of passive heating, cooling and ventilation; • designed and equipped to minimize the consumption of electricity and other fuel sources; • constructed using materials and finishes that are robust, easy to clean and which are selected to minimize long-term maintenance; • constructed using locally available materials and building technologies; and • built to minimize hiding and nesting places for pests. Reasons: Storage in unsuitable and poorly designed buildings places TTSPPs at risk and increases storage costs. Buildings constructed using inappropriate materials and technologies are difficult to operate and maintain in resource-constrained settings.			
	197	Accommodation and layout: Ensure that the storage buildings are well laid out and contain all the necessary storage areas, goods assembly, receiving and dispatch bays and office accommodation needed for efficient operation of the TTSPP store.			
	198	Loading bays: Ensure that receiving and dispatch bays are designed to avoid conflict between incoming and outgoing goods and are protected from direct sunlight, dust, dirt, rain, snow and wind, and from extremes of heat, cold, and solar radiation that could damage TTSPPs, and measures are taken to minimize pest activity in these areas. Reason: Protection against damage and maintenance of product quality.			
	199	Receiving bays: Provide receiving areas with suitable equipment to clean reusable transport containers after their contents have been unloaded, and before the containers are stored for re-use. Reason: Protection against contamination of outgoing TTSPPs.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	200	Goods assembly areas: Provide sufficient space to receive, assemble and pack TTSPPs for dispatch under temperature-modified conditions. Preferably, these areas should be physically close to the temperature-controlled storage area. Reason: Protection of TTSPPs during arrival, order assembly and dispatch.			
	201	Holding area for incoming goods: Provide a temperature-controlled holding area for incoming TTSPPs pending their acceptance into the main storage area. The holding area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement. Where goods are held in bond in the warehouse, awaiting customs clearance, they must be physically separated and secured. Reason: Incoming items may need inspection and/or regulatory clearance, including laboratory testing.			
	202	Quarantine area: Provide a quarantine area for the isolation of returned, faulty, recalled and otherwise withdrawn goods pending a decision on disposal or re-stocking by the qualified person or department. Materials within quarantine areas must be clearly identified with their status. • with temperature control, for items returned for re-stocking; • with temperature control, for items recalled for testing; • without temperature control, for items awaiting disposal. The quarantine area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement. Reason: Items for re-stocking, testing and disposal should be kept separate to avoid the risk of inappropriate use.			
	203	Environmental control of ancillary areas: Ensure, where possible, that ancillary areas where TTSPPs are temporarily held during arrival, order assembly or dispatch are: ● maintained within the temperature range specified for the goods being handled; ● maintained within the humidity range specified for goods that are adversely affected by high relative humidity and are not sufficiently protected by their packaging; ● protected from undue exposure to direct sunlight; ● protected from the weather; ● protected against dust, dirt and waste accumulation; ● adequately ventilated; ● adequately lit to enable operations to be carried out accurately and safely; ● monitored during the times when TTSPPs are handled; and monitored during the times when TTSPPs are handled (see 4.5.1-4.5.4). Reason: Protection of TTSPP quality during arrival, order assembly or dispatch. Active environmental control of ancillary areas may not be needed if all TTSPPs are kept in			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
		temperature- controlled packaging and/or humidity-protective packaging when passing through these areas.			
	204	General building security: Ensure that buildings used to store TTSPPs have sufficient security to prevent unauthorized access and to prevent misappropriation of goods. Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and to the value of goods stored there.			
	205	Controlled and hazardous substances areas: Ensure that all areas that are used to store controlled or hazardous TTSPPs are: • dedicated, securely locked facilities that comply fully with all legislative and regulatory requirements applicable in the country where the store is located; • only accessible to authorized staff; • protected by automatic intruder and/or fire and smoke, and/or chemical and/or radiological sensor alarm systems appropriate to the type(s) of product being stored; • designed to be explosion-proof, where explosive TTSPPs are stored; and • continuously monitored by security staff. Reason: Protection of property and life. Zoned sprinkler systems are recommended to control fires and to localize product damage in the event of system activation. Explosion-proof stores must have a blast roof or wall. Preferably, explosive substances should be stored in an independent building, well separated from the main store.			

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	206	Fire protection equipment: Provide suitable fire detection and fire-fighting equipment, including fire hydrants, in all TTSPP storage areas and ensure that: ● systems and equipment are appropriate for the class of occupancy and product storage arrangements and are approved by the local fire authority; and ● equipment is regularly serviced in accordance with the equipment manufacturers ● recommendations and local regulations. Reason: Protection of property and life.			
	207	Fire prevention, detection and control procedures: Follow SOPs for fire prevention, detection and control. Train staff and carry out regular fire drills. Prohibit smoking in all areas. Reason: Protection of property and life.			
	208	Building cleanliness: Implement a cleaning program for all areas: do not allow the accumulation of dust, dirt and waste, including packaging waste; take precautions against spillage or breakage, and cross-contamination; collect waste in designated closed containers and arrange for safe disposal at frequent intervals; do not permit consumption of food or beverages other than in designated areas; and maintain cleaning records to demonstrate compliance. Reason: Protection against damage and contamination of TTSPPs and to minimize the risk of pest infestation.			
	209	Pest control: Implement a program to keep all areas free of pests. This should include enclosed receiving and loading bays. Maintain records to demonstrate compliance with a robust pest control program. Reason: Protection against damage and contamination of TTSPPs.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	210	Uninterrupted power supply: Where possible, and where necessary,9 ensure that all temperature-controlling equipment for TTSPP storage (i.e. refrigerators, freezers, building management systems, heating, ventilation and air-conditioning (HVAC) systems, compressors, air-handling units, monitoring systems, alarms and related computer equipment) are connected to an uninterrupted power supply (UPS) system. Where a generator and associated control equipment is used it should: • be able to manage the combined start-up load of all connected temperature-controlling and temperature-monitoring equipment; • not exceed the defined parameters of the mains power supply; • be equipped with automatic mains failure start-up and automatic shutdown when power is restored; and • have adequate fuel tank capacity and sufficient fuel to cover a prolonged power outage. Regularly test and service UPS equipment and generators. Maintain records to demonstrate compliance. Reason: Loss prevention. UPS systems may be unnecessary in countries with a very reliable electricity supply. In smaller stores in countries where electricity is only available for a limited period each day, or is entirely absent, an alternative approach to UPS is to use refrigeration equipment with extended holdover capacity, for example, ice-lined refrigerators, or gas, kerosene or solar-powered refrigerators. The installed capacity of the UPS system can be minimized by fitting electronic controls which reduce compressor start-up loads			
	211	Power failure contingency plan: Develop and maintain a contingency plan to protect TTSPPs in the event of power failure which places products at risk. Alternative emergency cooling systems (e.g., liquid nitrogen or dry ice) are acceptable. Reason: Loss prevention.			
	212	Building maintenance: Implement a planned preventive maintenance program to ensure that storage buildings and building utilities are well maintained. Keep records to demonstrate compliance with the program. Reason: To ensure that storage buildings continue to protect stored products against damage.			
	213	Normative references: EN 60068-3 parts 5, 6, 7 and 11: Environmental testing. Guide. Confirmation of the performance of temperature chambers International Air Transport Association (IATA) Perishable cargo regulations chapter 17. 10th ed, July 2010 USP <1079> Good storage and shipping practices USP <1118> Monitoring devices time, temperature and humidity			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	214	Storage capacity of temperature-controlled stores: Ensure that the net storage capacity of the temperature-controlled stores is sufficient to accommodate peak TTSPP stock levels and their associated transit temperature protection components (i.e., freezer blocks, flexible ice blankets, refrigerated gel packs, phase change materials and insulated packaging, if retained), under correct temperature conditions and in a manner which enables efficient and correct stock management operations to take place. Reason: To avoid the risks associated with overstocking and to ensure that good warehousing practices can be adopted (i.e., first in-first out (FIFO) or earliest expiry-first out (EEFO)). Overstocking makes FIFO or EEFO handling difficult or impossible and hinders accurate physical stock counts.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	215	Temperature-controlled storage: Ensure that TTSPPs are stored in temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers which comply with the following requirements. Temperature-controlled rooms, cold rooms and freezer rooms should be: capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced at the store location; preferably equipped with an auto-defrost circuit which has a minimal effect on temperature within the unit during the defrost cycle and maintains temperature within specification for this period; equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPPs that are damaged by exposure to low temperatures; connected to a UPS as described in clause 3.9.1; equipped with a calibrated continuous temperature monitoring system with sensors located at points representing greatest temperature variability and temperature extremes; preferably equipped with continuous humidity monitoring devices with sensors located at points representing humidity extremes; equipped with alarms to indicate temperature excursions and/or refrigeration failure; fitted with lockable doors, or an access control system, as necessary; locks must have a safety device so that doors can be freely opened from the inside; and qualified as defined in clause 4.7. Refrigerators and freezers should be: purpose-designed for the storage of TTSPPs; household-style units are only acceptable if they have been independently tested and found to comply with the temperature control requirements of a recognized standard for pharmaceutical refrigerators and freezers; capable of maintaining the temperature range specified by the TTSPP manufacturer over the full annual ambient temperature range experienced at the storage site; equipped with calibrated temperature monitoring devices appropriate to the level of risk but preferably capable of continuous recording and with sensor(s) located at a point or points within the cabinet which most accurately represents the temperature profile of the equipment during normal operation; preferably equipped with alarms to indicate temperature excursions and/ or refrigeration failure; fitted with lockable doors or lids, or access control system, as necessary; and qualified and/or tested as defined in clause 4.7. Reason: To maintain labelled TTSPP storage temperatures during long- term storage. For example, WHO PQS standards for refrigerators and freezers are available at: http://www.who. int/immunization_standards/vaccine_quality/pqs_e03_fridges_freezers/en/index.html.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	216	Temperature-controlled storage for controlled and hazardous products: Ensure that controlled and hazardous TTSPPs are securely stored: Provide dedicated temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers for these TTSPPs, in separate secure areas, as described in clause 3.6.2. Alternatively, but only if acceptable to the regulatory authority, bulk stocks of TTSPPs with high illicit-value may be stored in a securely locked section of a general temperature-controlled storage area. Reason: To protect this category of TTSPPs against theft and misuse and to safeguard workers and general storage areas in the event of an accident involving hazardous substances.			
	217	Temperature control: Provide thermostatic temperature control systems for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements: system able continuously to maintain air temperatures within the set point limits throughout the validated storage volume; control sensors accurate to ± 0.5 °C or better; control sensors calibrated as described in clause 4.10.1; control sensors located in areas where greatest variability in temperature is expected to occur in order to maximize available safe storage volume; control sensors positioned at the hot and cold spots determined by temperature mapping, even if affected by door opening, unless recommendations are being made not to store products in such areas; and control sensors independent of the temperature monitoring system.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	218	Temperature monitoring: Provide air temperature monitoring systems and devices for all temperature- controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements: General requirements Monitoring sensors accurate to ± 0.5 °C or better for electronic devices and ± 1 °C or better for alcohol, bi-metal gas or vapor pressure thermometers. Monitoring sensors calibrated as described in clause 4.10.1. Monitoring sensors located in areas where greatest variability in temperature is expected to occur within the qualified and/or tested storage volume as defined in clause 4.7. Monitoring sensors positioned so as to be minimally affected by transient events such as door opening. Temperature monitoring devices, temperature traces or electronic temperature records manually checked at least twice a day, in the morning and evening, seven days a week, including public holidays. Temperature-controlled rooms, cold rooms and freezer rooms Provide a temperature record with a minimum recording frequency of six times per hour for each monitoring sensor position. Provide documentation for each monitoring sensor position which can be stored and accessed. Continue to operate independently in the event of a power failure. Refrigerators and freezers Preferably, connect refrigerators and freezers to a multipoint monitoring system with a minimum recording frequency of six times per hour for each sensor position which can operate independently in the event of a power failure. Alternatively use battery-powered portable temperature monitoring devices with a minimum recording frequency of six times per hour. The least preferred option is a thermometer or maximum/minimum thermometer. Provide documentation for each appliance which can be stored and accessed. Reasons: To maintain labelled TTSPP temperatures during long- term storage. Thermometers provide only limited and discontinuous temperature information. For this reason, continuous recording devices are preferable. Where there is no UPS, the autonomy period for the device should be matched to the maximum length of anticipated power outages.			
	219	Humidity control: Provide humidity control in temperature-controlled rooms that are used to store TTSPPs which are adversely affected by high relative humidity and are not sufficiently protected by their packaging. Such products are typically labelled “store in a dry place” or carry similar wording and require a humidity-controlled environment.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	220	Humidity monitoring: Provide humidity monitoring systems and devices in temperature-controlled rooms that are used to store TTSPPs which require a humidity-controlled environment. Comply with the following minimum requirements: sensors accurate to ± 5% RH; sensors calibrated as per clause 4.10.2; sensors located to monitor worst-case humidity levels within the qualified storage volume defined in clause 4.7; sensors positioned so as to be minimally affected by transient events such as door opening; provides a humidity record with a minimum recording frequency of six times per hour for each sensor position; provides documentation for each sensor position which can be stored and accessed; and continues to operate independently in the event of a power failure. Reason: To maintain labelled TTSPP humidity conditions during long-term storage. Where there is no UPS the autonomy period for the device should be matched to the maximum length of anticipated power outages.			
	221	Temperature alarms: Provide temperature alarm systems for temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements: General requirements • Sensors accurate to ± 0.5 °C. • Sensors calibrated as described in clause 4.10.1. • Sensors located to monitor worst-case temperatures within the validated storage volume defined in clause 4.7; where the alarm system is not integrated with the temperature monitoring system, sensors should be located close to the temperature monitoring sensors. • Sensors positioned so as to be minimally affected by transient events such as door opening. Temperature-controlled rooms, cold rooms and freezer rooms • High/low alarms set points to trigger appropriately located visual alarm(s). • Preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s). • Preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours. Refrigerators and freezers • Preferably there should be a visual and/or audible alarm system; this may be integrated with a portable continuous temperature monitoring device. Reason: Loss prevention.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	222	Humidity alarms: Provide humidity alarm systems for temperature-controlled rooms used to store TTSPPs that require a humidity-controlled environment. Comply with the following minimum requirements: • Sensors accurate to ± 5% relative humidity (RH); • Sensors calibrated as described in clause 4.10.2; • Sensors located to monitor worst-case humidity levels within the validated storage volume defined in clause 4.7; where the alarm system is not integrated with the humidity monitoring system, sensors should be located close to the humidity monitoring sensors; • Sensors positioned so as to be minimally affected by transient events such as door opening; • High/low alarms set points to trigger appropriately located visual alarm(s); • Preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s); and • Preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours. Reason: Loss prevention.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	223	Qualification of temperature-controlled stores: Qualify new temperature-controlled storage areas and new refrigeration equipment before it becomes operational. The qualification procedure should: • demonstrate the air temperature profile throughout the storage area or equipment cabinet, when empty and in a normal loaded condition; • define zones which should not be used for storage of TTSPPs (for example areas in close proximity to cooling coils, cold air streams or heat sources); and • demonstrate the time taken for temperatures to exceed the designated limits in the event of power failure. Fully document the initial qualification. Carry out additional qualification exercises whenever modifications are made to the storage area that may increase loading or affect air circulation, or when changes are made to the refrigeration equipment, such as a change in the set point. Consider the need for re-qualification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal. Qualification may not be required for equipment which requires little or no site assembly or commissioning, such as vaccine refrigerators and freezers that have been independently tested and found suitable for the storage of TTSPPs. Independent testing must be carried out between the chosen set points and under the ambient temperature conditions to which the equipment will be exposed during operation. Prequalified equipment of this type must be correctly installed in each location in accordance with written guide. Reason: To ensure that labelled TTSPP temperatures can be maintained during long-term storage and that the facility can demonstrate to the regulatory authorities and other interested parties that due diligence has been observed.			
	224	Cleanliness of temperature-controlled stores: Implement a cleaning and decontamination program for all temperature- controlled rooms: • Ensure that floor areas are fully accessible for cleaning. Do not store goods directly on the floor. • Do not permit storage of any non-pharmaceutical products except transport-related items such as icepacks, gel packs and the like. • Do not allow the accumulation of dust, dirt and waste, including packaging waste. • Take precautions against spillage or breakage, and cross-contamination. • Do not allow accumulation of frost and ice, particularly ice contaminated by spillages. • Collect waste in designated closed containers and arrange for safe disposal at frequent intervals. Maintain cleaning records to demonstrate compliance. Reason: Protection against damage and contamination of TTSPPs and hazards to workers, arising from spillage or breakage.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	225	Refrigeration equipment maintenance: Implement a maintenance program for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers: • Carry out regular planned preventive maintenance on all temperature-controlling equipment. • Make arrangements to ensure that emergency maintenance is carried out within a time period that does not place TTSPPs at risk of damage. • Ensure that there is a contingency plan to move products stored in non-functioning equipment to a safe location before damage to the product occurs in the event that equipment cannot be repaired in a timely manner. Maintain records to demonstrate compliance. Reason: Loss prevention.			
	226	Calibration of temperature control and monitoring devices: Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified. Calibration should demonstrate the accuracy of the unit across the entire temperature range over which the device is designed to be used. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated.			
	227	Calibration of humidity control and monitoring devices: Calibrate devices against a certified, traceable reference standard at least once a year unless otherwise justified. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated.			
	228	Alarm equipment verification: Check functionality of temperature and humidity alarms at least once every six months at the designated set points. Maintain records to demonstrate compliance. Reason: To ensure that labelled TTSPP storage temperatures and humidity control can be maintained during long-term storage and that the store can demonstrate to the regulatory authorities and other interested parties that due diligence has been observed.			
	229	Materials handling equipment: Where powered materials handling equipment is used in temperature- controlled rooms, cold rooms or freezer rooms, select equipment which is certified for safe use in confined spaces. Reason: Protection of the workforce.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	230	Normative references • Directive 94/62/EC. European Parliament and Council Directive of 20 December 1994 on packaging and packaging waste.1994. • EN 13428:2004. Packaging. Requirements specific to manufacturing and composition. Prevention by source reduction. • EN 13430:2004. Packaging. Requirements for packaging recoverable by material recycling. • EN 13431:2004. Packaging. Requirements for packaging recoverable in the form of energy recovery, including specification of minimum inferior calorific value. • EN 13432:2000. Packaging. Requirements for packaging recoverable through composting and biodegradation. Test scheme and evaluation criteria for the final acceptance of packaging. • IATA Perishable Cargo Regulations Chapter 17, 9th Edition, July 2009. - Isothermal and refrigerating containers for health products - Thermal performance qualification method. • ISTA - 5B: Focused Simulation Guide for Thermal Performance Testing of Temperature Controlled Transport Packaging. • ISTA - 7D: Thermal Controlled Transport Packaging for Parcel Delivery System Shipment. Basic Requirements: atmospheric conditioning, vibration and shock testing. • WHO Technical Report Series, No. 937, 2006. Annex 5: Good distribution practices for pharmaceutical products.			
	231	Product stability profiles: Transport TTSPPs in such a manner that transport temperatures meet local regulatory requirements at the sending and receiving sites and/or so that temperature excursions above or below the manufacturer's labelled storage temperature range do not adversely affect product quality. Product stability data must demonstrate the acceptable temperature excursion time during transport. Reason: Protection of TTSPPs against degradation.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	232	Transport route profiling and qualification: Profile and qualify transport routes: • Select the most suitable methods for protecting TTSPPs against anticipated ambient temperature and humidity conditions throughout the year. • Use suitable methods, including published standards, weather data, laboratory tests and field tests to select suitable transport equipment and shipping containers. Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defied for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.			
	233	Air and sea transport: Ensure that any carrier contracted to transport TTSPPs by air or by sea operates under the terms of a formal service level agreement (SLA) drawn up between the parties. The carrier is to be made responsible for maintaining load temperatures within the transport temperature profile defined for each product. Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties. Temperature-controlled road vehicles operated by common carriers: Temperature control in vehicles operated by a common carrier must be qualified and the details and responsibilities for this process should be set out in a formal SLA drawn up between the parties. Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	234	Temperature-controlled road vehicles generally: Ensure that temperature-controlled road vehicles used for the transport of TTSPPs are: • capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced over known distribution routes and when the vehicle is in motion, or parked with the main engine stopped; • equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPPs that are damaged by exposure to low temperatures; • equipped with calibrated temperature monitoring devices with sensors located at points representing temperature extremes; • equipped with alarms to alert the driver in the event of temperature excursions and/or refrigeration unit failure; • fitted with doors with security seals and/or security locks that protect against unauthorized access during transit; • qualified as defined in clause 6.6; and • regularly calibrated and maintained and records kept to demonstrate compliance. Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.			
	235	Transport of controlled TTSPPs and TTSPPs with high illicit value: Ensure that controlled TTSPPs and TTSPPs with high illicit value are transported in the following manner: • Transport practices comply with all relevant local legislation and regulations. • Vehicles are equipped with lockable doors and an intruder alarm. • Vehicles use unique seal lock indicating devices such as cable seal locks with unique identifiers that are tamper-resistant to protect against unauthorized access during transit. • Security-cleared delivery drivers are employed. • All deliveries are documented and tracked. - Signed dispatch and arrival records are kept. • Shipments are fitted with security equipment appropriate to the product being transported and the assessed security risk, such as global positioning system (GPS) devices located in the vehicle and/or hidden in the product.			

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		• Drivers are informed about the perishability of the product and the maximum acceptable transport time. Reason: To prevent theft and misappropriation of this category of TTSPP and to ensure the security and safety of the driver. Refer to ISO/PAS 17712: Freight containers - Mechanical seals.			
	236	Temperature control in temperature-controlled road vehicles: Provide thermostatic temperature control systems for all temperature- controlled vehicles used to transport TTSPPs. Comply with the following minimum requirements • System able continuously to maintain air temperatures within the set point limits throughout the validated storage volume defined in clause 6.6; • Control sensors accurate to ± 0.5°C; • Control sensors calibrated as described in clause 6.7.1; • Control sensors located to control worst-case temperatures in order to maximize available safe storage volume; • Control sensors positioned in the return air stream; and • Control sensors independent of the temperature monitoring system.			
	237	Temperature monitoring in temperature-controlled road vehicles: Provide air temperature monitoring systems and devices for vehicles used to transport TTSPPs. Comply with the following minimum requirements: • Monitoring sensors accurate to ± 0.5 °C; • Monitoring sensors calibrated as described in clause 6.7.2; • Monitoring sensors located to monitor worst-case temperatures within the qualified storage zone defined in clause 6.6; • Monitoring sensors positioned so as to monitor worst-case positions; • Provide a temperature record with a minimum recording frequency of six times per hour for each sensor position; and • Provide documentation which can be stored and accessed. Establish transit temperature specifications and document transit temperatures for every internal and external shipment. Recording frequency should take account of the storage capacity of the data logger and the expected transport period.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	238	Humidity monitoring in temperature-controlled road vehicles: Preferably provide humidity monitoring systems and devices for temperature-controlled vehicles which are used to transport TTSPPs that require a humidity-controlled environment. Systems and devices should comply with the following minimum requirements: • Sensors accurate to ± 5% RH; • Sensors calibrated as described in clause 6.7.3; • Sensors located to monitor worst-case humidity levels within the qualified storage zone defined in clause 6.6; • Sensors positioned so as to be minimally affected by transient events such as door opening; • Provide a humidity record with a minimum recording frequency of six times per hour for each sensor position; and • Provide documentation which can be stored and accessed. Establish transit humidity specifications and document transit humidity conditions for internal and external shipments where required.			
	239	Temperature monitoring in passive and active shipping containers: Use chemical or electronic freeze indicators, electronic loggers (with or without alarms) and/or other suitable indicators to monitor temperature and/or humidity exposure during internal distribution. Preferably use these devices for external distribution. Monitor and document indicator status upon arrival. Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	240	Qualification of temperature-controlled road vehicles: Where temperature-controlled vehicles are directly owned and/or operated, qualify each vehicle before it becomes operational, wherever possible. The qualification procedure should: • Demonstrate that the air temperature distribution is maintained within the limits specified throughout the temperature-controlled compartment for both air and product temperatures for commonly used load layouts and at the ambient temperature extremes anticipated during normal operation over known routes; • Demonstrate the humidity distribution throughout the temperature- controlled compartment for commonly used load layouts, where products are being transported that require a humidity-controlled environment; • Define zones within the vehicle's payload area which should not be packed with TTSPPs (for example areas in close proximity to cooling coils or cold air streams); • Demonstrate the time taken for temperatures to exceed the designated maximum in the event that the temperature-controlling unit fails; and • Document the qualification exercise. An alternative approach is to perform an initial full qualification on each trailer/refrigeration unit type combined with an installation qualification (IQ) for each example when a new vehicle becomes operational. Carry out additional qualification exercises whenever significant modifications are made to the vehicle. Consider the need for re-qualification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal. Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.			
	241	Calibration of transport temperature control devices: Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified.			
	242	Calibration of transport temperature monitoring devices: Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified.			
	243	Calibration of transport humidity monitoring devices: Calibrate devices against a certified, traceable, reference standard at least once a year, unless otherwise justified.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	244	Verification of transport alarm equipment: Check functionality of temperature and humidity alarms at the designated set points. Check functionality of security alarm systems. Carry out these checks at least once a year, unless otherwise justified. Maintain records to demonstrate compliance. Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.			
	245	Shipping containers 6.8.1 Container selection generally: Select shipping containers that: • comply with applicable national and international standards relevant to the product type and the chosen transport route and mode(s); • protect personnel and the general public from hazards arising from spillage, leakage or excessive internal pressure; • protect the product being transported against mechanical damage and the anticipated ambient temperature range that will be encountered in transit; and • can be closed in a manner that allows the recipient of the consignment to establish that the product has not been tampered with during transport. Reason: Quality assurance and safety.			
	246	Uninsulated containers: Ensure that uninsulated containers are correctly used, in a manner which protects their contents: • Transport uninsulated containers in a qualified temperature-controlled environment such as an actively or passively temperature-controlled vehicle; • Ensure that the transport system is able to maintain the temperature of the TTSPP within the product's stability profile as stated by the product manufacturer and/or to maintain the TTSPP within the transit temperature specification requirements specified by the regulatory authorities at both the sending and receiving locations. Reason: Quality assurance and safety.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	247	Qualification of insulated passive containers: Qualify insulated passive containers, including any and all necessary ancillary packaging such as temperature stabilizing medium, dry ice, ice or gel packs, cool water packs or warm packs, phase change materials, partitions, bubble wrap and dunnage: Ensure that the qualified packaging system is capable of maintaining the TTSPP within the temperature range needed to meet the product stability profile as stated by the product manufacturer. Container qualification should include full details of the packaging assembly, the thermal conditioning regime and the minimum and maximum shipping volume, weight and thermal mass that can safely be accommodated in the container. Qualification should also include the correct placement of temperature monitors where these are used; - take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient's temperature-controlled store. Reason: To ensure that TTSPPs can safely be transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.			
	248	Qualification of active containers: Qualify active containers: • Ensure that the container is capable of maintaining the TTSPP within the temperature range needed to meet the product stability profile as stated by the product manufacturer; • Take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient's temperature-controlled store. Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	249	Shipping container packing: Pack TTSPP shipping containers to: • the exact specified configuration to ensure that the correct TTSPP temperature range is maintained; • minimize the risk of theft and fraud and assure the recipient that the goods have not been tampered with while in transit, for example by using locked containers or shrink-wrapped pallets; • minimize the risk of mechanical damage during transport; • protect freeze-sensitive products against temperatures below 0°C when frozen packs are used; • protect products against light, moisture and contamination or attack by microorganisms and pests; • protect products against adverse effects when dry ice is used as a coolant; • clearly label containers to identify the correct transport temperature range and to show correct orientation for handling; and • ensure that packages containing dangerous goods (including dry ice) are labelled in compliance with relevant transport regulations and requirements. Reason: To ensure that shipping containers are systematically used in the manner defined during the container qualification process and that this can be demonstrated to the regulatory authorities and other interested parties.			
	250	Product handling during packing and transport: Handle TTSPPs correctly during packing and transport: • pack TTSPPs in an area set aside for the assembly and packaging of these products as specified in clause 3.3.1; • take precautions against spillage or breakage, contamination and cross- contamination; • deliver TTSPPs to outside recipients by the most suitable mode(s) of transport available in order to minimize delivery time; and • ensure that patients receiving TTSPP deliveries are given clear advice on correct storage of the product before use. Reason: To maintain TTSPP quality during transport.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	251	Cleaning road vehicles and transport containers: Implement a cleaning and decontamination program for all road vehicles and reusable shipping containers used to transport TTSPPs: • ensure that all internal surfaces of load compartments are regularly cleaned; • do not allow the accumulation of dust, dirt and waste, including packaging waste in load compartments, or in reusable shipping containers; • take precautions against spillage or breakage, and cross-contamination; • do not allow accumulation of frost and ice in refrigerated vehicles, particularly ice contaminated by spillages; and • collect waste in designated closed containers and arrange for safe disposal at frequent intervals. Maintain cleaning records for vehicles and reusable shipping containers to demonstrate compliance. Reason: Protection against damage and contamination of TTSPPs and hazards to workers arising from spillage or breakage.			
	252	Transport of returned TTSPPs: Ensure that that returned TTSPPs are transported under the same conditions as those used for the initial delivery: • the sender and recipient must work together so that that the product is maintained within the temperature range needed to meet the manufacturer's stated product stability profile; • take account of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of return; and • quarantine returned TTSPPs in temperature-controlled storage pending a decision by the quality control department or qualified person to dispose of the product or to return it to stock. Reason: To ensure that returned and recalled TTSPPs are maintained within the correct transport temperature profile so that they can safely be re-stocked if a decision to do so is made.			
	253	Transport of recalled TTSPPs: Ensure that recalled TTSPPs are: • marked for disposal as either "recalled" or "withdrawn"; • transported back from the recipient and quarantined under secure conditions pending a final decision on disposal as described in clause 8.6.3.			
	254	Normative references: IATA Perishable Cargo Regulations Chapter 179th Edition, July 2009. Clauses 17.10.5 and 17.10.6.			

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	255	Labelling generally: Label internal shipping and external distribution containers containing TTSPPs as follows: • identify the product in accordance with all national and international labelling requirements relevant to the container content, transport route and mode(s); • identify hazardous products in accordance with relevant national and international labelling conventions; and • indicate the appropriate temperature and humidity ranges within which the product is to be transported and/or stored.			
	256	Labelling air-freighted shipments: In cases where TTSPPs are to be air-freighted, the package(s) should be labelled using the standard International Air Transport Association (IATA) time and temperature-sensitive symbol, in accordance with the conditions outlined in Chapter 17 of the IATA Perishable Cargo Regulations. Apply the label to the outer surface of individual shipping packages, overpacks or bulk containers. Reason: To ensure that products are correctly and safely handled at all points in the supply chain.			
	257	Stock control systems 8.1.1 General stock control systems and procedures: TTSPP stock control systems and procedures meet the following minimum requirements: • allow access only to authorized persons; • record all receipts and dispatches; • record batch numbers and expiry dates; • record short-dated and expired products; • record product status (i.e. released, quarantined, hold, reject); • record all product returns, recalls, withdrawals, damage and disposals; • manage the issue of products in EEFO order; and • take regular physical inventories and reconcile stock records with the actual physical count. Investigate and report on stock discrepancies in accordance with agreed procedures. Preferably physical counts should be made at least twice a year. Reason: To ensure that accurate and complete stock records are kept at all times.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	258	Stock control procedures for controlled and hazardous TTSPPs: In addition to the requirements set out in clause 8.1.1, implement the following procedures: • Institute a customer verification process to ensure that all recipients of these products are authorized to receive them. • Maintain stock records which specifically identify products in these categories. • Carry out regular audits and make audit reports available to the responsible authorities. • Comply with all record-keeping procedures specified in local legislation and regulations. Retain product transaction and delivery records for at least the minimum time period required by local regulations. Reason: To ensure that accurate and complete stock records are kept at all times and to satisfy the requirements of the regulatory authorities.			
	259	Product arrival checks: Check and record the following for all incoming TTSPPs: • product name, item code (identifier), strength, and batch/lot number; • quantity received against order; • name and address of the supplying site; • examine containers for tampering, damage or contamination; • examine expiry dates • accept short-dated products only if prior agreement has been reached with the supplier; do not accept products that have expired or which are so close to their expiry date that this date is likely to occur before use by the consumer; • delays encountered during transport; • status of any attached temperature recording device(s) and/or time/ temperature indicators; and • verify that required storage and transport conditions have been maintained.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	260	Actions following arrival checks: • Enter product details, including product name/number, strength, batch numbers, quantities received, expiry dates and acceptance status into the stock recording system. • Store checked goods under the correct temperature and security regime immediately upon receipt. • Quarantine defective or potentially defective products, products with incomplete or missing paperwork, products that experienced unacceptable temperature excursions during transport, or products suspected to be counterfeit. Do not release until checks have been completed satisfactorily. All unacceptable temperature excursions should be evaluated to determine their effect on the product. • Report any defects to the supplying store or holder of the marketing authorization. • Do not transfer to saleable stock until all relevant disposition procedures have been completed. Reason: To ensure that incoming TTSPPs are in acceptable condition, accurately recorded and correctly stored and that defective and/or incorrect shipments are followed up with the supplier.			
	261	Management of outgoing goods Implement outgoing goods procedures to ensure that: • Transport vehicle conformity, including conformity with SLA or QA agreements, is checked before loading goods. • Expired products are never issued. • Products with short expiry dates are not issued unless the recipient accepts that they can be consumed before the expiry date is reached. • Products are distributed in strict EEFO order unless a product-based time-temperature exposure indicator, such as a vaccine vial monitor, demonstrates that a batch should be distributed ahead of its EEFO order. • Details of any temperature monitoring devices packed with the external distributions are recorded. • Details of outgoing products, including product name/number, strength, batch numbers, expiry dates and quantities distributed, are entered into the stock recording system.			
	262	Actions following dispatch: Monitor TTSPPs following dispatch in order to: • trace products to their intended destination; • record and retain records to provide assurance of goods arrival status. A suitable delivery report from the carrier is an acceptable alternative; and			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
		• take appropriate action in the event of returns, recalls or complaints. Reason: To ensure that outgoing TTSPPs are in acceptable condition, that short-dated stock does not accumulate in the store and that evidence is kept to demonstrate that correct quantities are distributed and received in good condition.			
	263	Product complaint procedures: Manage product complaints as follows: • If a product defect is discovered or suspected in a batch of TTSPPs, cooperate with the regulatory authority to determine whether other batches are affected and recall products if required to do so by the regulatory authority. • Where complaints or defects relate to a product or its packaging, immediately notify the holder of the marketing authorization for the product. • Where complaints or defects arise as a result of errors or omissions within the organization, immediately evaluate the causes and take remedial measures to prevent a recurrence. • Record all complaints and the remedial actions taken. Monitor and analyze trends in the complaint records. Reason: Protection of the public and of the reputation of the supplying organization.			
	264	Suspect products: Implement systems for identifying and managing suspect products found in the supply chain as follows: • Physically segregate any suspect TTSPPs found in the supply chain and store securely until legal investigations are complete. • Label them clearly as “not for use” or other similar phrase; • Immediately notify the regulatory authority or authorities and any other relevant authorities, as well as the holder of the marketing authorization of the product. • Cooperate with regulatory authorities to assist with investigating the source of suspect products and implement appropriate remedial action(s). • Document the decision-making process for disposal or return of condemned or defective TTSPPs and make these records available to the relevant authorities. Reason: Protection of the public, protection of legitimate suppliers and manufacturers and conformity with regulatory requirements.			
	265	Return procedures: Manage product returns as follows: • Quarantine returned TTSPPs in a suitable temperature-controlled area and under the security conditions applicable to the product type.			

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		• Do not return to saleable stock unless storage and transport temperature conditions after dispatch from the distribution site have been fully verified and documented, including the return leg to the distribution site.			
	266	Where appropriate, obtain written advice from the holder of the marketing authorization regarding handling and/or disposal of the returned TTSPP. • If returned stock is re-issued, distribute in EEFO order or in accordance with the exposure status of any product-mounted time-temperature indicator device. • Quarantine returned TTSPPs that have been exposed to unacceptable storage and/or transport temperatures and mark for disposal. • Maintain records of all returned TTSPPs. Reason: Protection of the public. 8.6.2 Recall procedures Manage product recalls as follows: • Conduct urgent and non-urgent TTSPP recalls in accordance with an agreed emergency plan. • Notify the local regulatory authority or authorities. • Notify overseas regulatory counterparts where the product has been exported. • Notify all affected customers as applicable. • Quarantine any remaining inventory of recalled TTSPPs and mark for further investigation before disposal. • Maintain records of all TTSPP recalls, including reconciliation of quantity sold, quantity returned, quantity remaining or quantity consumed. Reason: Protection of the public and conformity with regulatory requirements.			
	267	Disposal procedures: Manage product awaiting board of survey or disposal as follows: • Ensure that rejected and/or recalled or withdrawn TTSPPs cannot be used, released or cause contamination to other products. Store separately from other products, in accordance with local regulations, to await destruction or return to the supplier. • Safely dispose of rejected and/or recalled/withdrawn products in accordance with local regulations, including where relevant, regulations covering the disposal of hazardous and controlled drugs. • Maintain disposal records. Reason: Protection of the public and the environment.			

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	268	Traceability or stock tracking: Ensure that stock and distribution records enable traceability, or stock tracking, of TTSPPs from the point of supply to the end-user or patient. Traceability should include records of the temperature exposure of the product during internal shipping and storage. These records should include: • for incoming goods: status of shipping indicators used (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of receipt; • for outgoing goods: type of shipping indicators used (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of dispatch. Monitor, record, and investigate discrepancies. Reason: To demonstrate that TTSPPs have been correctly distributed and to facilitate product recalls and detect theft and fraud.			
	269	Emergencies and contingency planning: Make contingency arrangements for the safe storage of TTSPPs in the event of emergencies, including, but not confined to: • extended power supply outages; • equipment failure; and • vehicle breakdown during transport of TTSPPs. Prepare action plans to deal with products subjected to temperature excursions. Ensure that the responsible staff know, and have rehearsed, the appropriate actions to be taken in the event of the identified emergency scenarios. Reason: Loss prevention.			
	270	Record-keeping: Maintain comprehensive records and ensure that they are laid out in an orderly fashion and are easy to check. Paper records must be: • stored and maintained so that they are accessible and easily retrievable; • labelled, dated and filed for easy identification; • protected against deterioration and loss due to fire, flood or other hazards; • kept secure and protected against unauthorized access; and • signed and dated by authorized persons and not changed without due authorization. Computer records must be: • logically filed for easy identification and retrieval; • kept secure and protected against unauthorized access; • where feasible, manually signed, dated and scanned or when electronically archived dated, encrypted and with check-sum;			

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		• regularly backed-up and archived on media that are independent of the record-keeping computer system(s). Back-up media may be a separate secure server, a separate hard disc, a flash drive or other digital media appropriate to the scale of the operation. Electronic records from data loggers are usually encrypted and protected by check-sums. This ensures compliance with FDA Title 21 CFR Part 11:Electronic Records; Electronic Signatures; Final Rule (1997).			
	271	Content of records: Ensure that the following traceability data is recorded for each TTSPP batch number, as applicable: • status of product on arrival; • temperature and humidity records including records of excursions outside labelled storage and/or transit temperature specification conditions; • general TTSPP stock transactions, including purchase and sale records; • controlled drug audits; • audits for products with high illicit value; • audits for hazardous products; • stock tracking; • return, recall, withdrawal and disposal reports, where relevant; • product complaint reports, where relevant; and • counterfeit product reports, where relevant. Maintain all records in accordance with local legislation and regulations.			
	272	Record review and retention: Ensure that records are reviewed and approved on a regular basis by a designated member of the quality management team. Ensure that records are accessible for review by end-users, the regulatory authority and other interested parties. Retain records for the minimum period required under local legislation, but for not less than three years. Reason: Internal quality control, transparency and external inspection by the regulatory authorities and other interested parties.			
	273	Temperature records: Monitor and record storage temperatures in all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, as follows: • Check and record temperatures at least twice daily: in the morning and evening; preferably continuously. • Review temperature records monthly and take action to rectify systematic excursions. • Systematically file temperature records for each storage environment or piece of equipment to ensure traceability.			

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		Keep records for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.			
	274	Humidity records: When storing products which are adversely affected by high relative humidity (see clause 4.5.3), monitor and record humidity levels in all temperature-controlled rooms as follows: • Record humidity at least twice every 24 hours or preferably continuously. • Check humidity records daily. • Review humidity records monthly and take action to rectify systematic excursions. • Systematically file humidity records for each temperature-controlled room to ensure traceability. Keep records for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation. Reason: Internal quality assurance and availability of records for review by the regulatory authorities and other interested parties.			
	275	Normative references: • ISO 14001: 2004. Environmental management systems - Requirements with guide for use. • The Montreal Protocol on Substances that Deplete the Ozone Layer. UNEP, 2000.			
	276	Environmental management of refrigeration equipment: Ensure that all new refrigeration equipment for temperature-controlled storage and transport is specified to: • use refrigerants that comply with the Montreal Protocol; • minimize or eliminate the use of refrigerants with high global warming potential (GWP); and • minimize CO2 emissions during operation. Select equipment to minimize whole-life environmental impact and employ best practice to eliminate leakage of refrigerant into the environment during installation, maintenance and decommissioning of refrigeration equipment. Reason: Compliance with international protocols and accords on climate change and environmental protection.			

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	277	Normative references • ICH, 2005: ICH Harmonized Tripartite Guide: Quality risk management Q9 • ISO 9000:2005. Quality management systems - Fundamentals and vocabulary • ISO 9001:2008. Quality management systems - Requirements • ISO 9004:2000. Quality management systems - Guides for performance improvements • ISO 10005:2005. Quality management systems - Guides for quality plans • ISO 19011:2002. Guides for quality and/or environmental management systems auditing			
	278	Organizational structure: Establish, document and maintain an organizational structure for the TTSPP storage and shipping and distribution operations which clearly identifies all key management responsibilities, and the personnel who are accountable. Reason: Quality management.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	279	Quality system: Establish, document and maintain a quality system for the management of TTSPPs including, the following, as applicable: • standard quality system(s) and associated auditing procedures; • written procedures and specifications; • record storage, record retention and record destruction program; • risk management; • calibration program; • stability program; • qualification and validation program; • deviation and root cause investigation program; • corrective and preventive action (CAPA) procedures; • training program; • periodic temperature-controlled process assessment; • change control program; • maintenance program; • management controls; • product return and recall/withdrawal policies, including emergency recalls; • product complaint policies; • material destruction program; • warehouse and storage program; • shipping and distribution program; • notification systems for regulatory agencies; boards of health and ministries of health; • self-inspection program and continuous quality improvement. Carry out annual reviews of the quality management system to ensure that it remains appropriate, relevant, and effective. Reason: Quality assurance.			
	280	Self inspections: Conduct regular self-inspections to ensure continuing compliance with quality management standards GSP and GDP; record results, follow-up with the corrective actions needed to rectify areas of non-compliance and document the changes made.			
	281	Contractors subject to service level agreements: Ensure that every contractor with whom there is an SLA provides periodic evidence of compliance with the GSP and/or GDP standards			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
		incorporated into the SLA. Reason: To demonstrate compliance with applicable quality management standards.			
	282	SOPs: Develop and maintain SOPs covering correct storage, internal shipping and external distribution of TTSPPs, including, but not limited to, the following topics: • security, including management of controlled and hazardous TTSPPs; • safe handling of TTSPPs; • temperature monitoring; • calibration of temperature and humidity monitoring devices and alarm systems; • qualification and validation procedures, including temperature mapping; • maintenance of controlled-temperature equipment; • facility cleaning and pest control; • facility maintenance; • product arrival (receiving) procedures and records; • stock storage and warehousing procedures (put away, replenishment, order fulfilment, packing); • stock control procedures and records; • distribution procedures and records; • management of temperature excursions; • product return and recall/withdrawal procedures and records; • product complaint procedures and records; • safe disposal of damaged, expired and quarantined products and records which are no longer required; • temperature-controlled packaging and route qualification; • temperature-controlled vehicle operation, including management of security locks and seals; • emergency response procedures; and • environmental management. Ensure that all documents are clear and unambiguous and that document change control procedures are in place as specified in clause 11.5. Reason: Quality management and staff training.			

System	Element Number	Description of Elements	Risk Rating (RR)	GMP Point (GP)	Element Score (RR x GP)
	283	Document control: Ensure that all quality manuals, SOPs and similar documents are: • authorized by an appropriate person; • recorded in a document register; • regularly reviewed and kept up to date, with all changes recorded and authorized; • version controlled; • issued to all relevant personnel; and • withdrawn when superseded. Withdraw superseded documents and retain record copies for document history files and for the minimum period(s) required by the regulatory authorities and for duty-of-care purposes. Reason: Good quality management practice.			
	284	General training: Provide regular and systematic training for all relevant personnel responsible for storage, loading and unloading areas used for non-hazardous TTSPPs, covering the following: • applicable pharmaceutical legislation and regulations; • SOPs and safety issues; and • response to emergencies. Ensure that each employee understands his or her specific responsibilities. Provide similar training for drivers who are responsible for transporting these substances. Maintain individual training records to demonstrate compliance and regularly evaluate the effectiveness of training programs. Reason: To ensure that all relevant personnel are competent to carry out their duties.			
	285	Specialist training: In addition to the training described in clause 12.1.1, provide regular and systematic additional training for relevant personnel responsible for storage, loading and unloading of controlled or hazardous TTSPPs. Training should cover the following: • applicable legislation and regulations; • security and safety risks; and • response to emergencies. Ensure that each employee understands his or her specific responsibilities. Maintain training records to demonstrate compliance and perform effectiveness checks on training. Provide similar training for drivers who are responsible for transporting these substances. Reason: To ensure that all relevant personnel are competent to handle controlled or hazardous TTSPPs.			