

A Risk Management approach to non-sterile compounding of medicines

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AFTER COMPLETING THIS ACTIVITY, PHARMACISTS SHOULD BE ABLE TO:

1. Describe the different guidelines and systems available to assess and manage risk when compounding
2. Describe factors that should be considered when conducting a risk assessment.

The 2016 Standards addressed by this activity include: 1.1, 1.2, 1.3, 1.6, 3.4 and 3.5

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Introduction

The purpose of Risk Management (RM) is to assess, control, communicate and review the risks of a product (or service) in order to raise the level of protection to the end user, to the operator, to the environment and to ensure regulatory compliance. The fundamental procedures of Risk Management are identification, assessment, mitigation of risk; and ultimately a review as to whether a particular activity should be undertaken or not.

By definition, a hazard is anything that may cause harm. Risk is the chance, whether it be high, moderate or low, that a person could be harmed by a hazard (or breach regulatory compliance), together with an indication of how serious the harm (or breach) could be.

Practical Aspects in Compounding Pharmacy

In compounding of non-sterile medications, risk is defined as that which poses a possible, imminent, and/or potential danger to the operation of a compounding practice, before, during, and/or after the performance of a task. The danger may be to the patient, caregiver, personnel, environment,

or breach of laws, guidelines and standards. Since risk management is a critical component of every compounding practice, a written Risk Management Policy and Procedure Guideline must be established, which includes the following:¹

- Function of the Risk Assessment Policy and Procedure
- General Responsibilities of Members of a Risk Assessment Committee
- Personnel and Risk Assessment Committee Infrastructure, which discriminates between their roles and responsibilities
- Frequency of Risk Assessment Task Implementation
- Risk Management Methods
- Reporting and Recording Methods and Frequency
- Review of decisions and practices

The features of the physical environment, technology, preparatory procedures, patient and personnel which contribute to risk, may be considered by an approach which is proactive, reactive, routine and random.

Environmental risk

Environmental risk requires classification of the type of compounding performed in:

- Primary engineering controls (PEC),
- Secondary engineering controls (SEC),
- Containment primary engineering controls (C-PEC) and
- Containment secondary engineering controls (C-SEC).

Plausible risks that might occur in that environment need to be identified and solutions suggested. For example, it is identified that all active pharmaceutical ingredients (API) and excipients pose a potential risk. Proactively, chemicals for hazardous drug compounding may be weighed in a C-PEC located in a C-SEC. The C-SEC is externally vented, physically separated, has an appropriate air exchange and negative pressure.² Due to the diversity in potential risks, other risk-related solutions include:

- a visible binder and/or electronic access to safety data sheets
- training of personnel
- appropriate personnel protective equipment
- appropriate spill kits and emergency procedures
- placing the primary engineering control for the weighing of chemicals for non-hazardous drug compounding on the opposite side of this room or ideally in another designated room
- use of supplemental engineering controls such as closed-system drug-transfer devices.

Technological risk

Technological risk requires identifying risk associated with specific technologies used in support of, and in the formulation of compounded preparations including:

- Electromechanical,
- Reusable,
- Disposable,
- Protective,
- Safety,
- Testing and
- Deactivation/decontamination and disinfection.

measures may themselves pose a new risk. For example, where the activity is the weighing of chemicals on a balance, the identified risk is that the weighed mass is inaccurate. Since the risks potentially affect the dose of API delivered to the patient, the suggested risk-related solutions include:

- the use of a trade-certified electronic balance which displays three decimal places
- daily verification of internal calibration of the balance
- regular external certification of the balance by a third party provider
- training of personnel

Another risk with the use of the proposed balance, relates to the leveling of the balance. The suggested risk-related solutions include:

- the use of electronic balance which displays that it is level (such as a bubble)
- daily verification that the balance is level
- placing the weighing equipment on a bench which is built level

Procedural risk

Procedural risk is defined as those activities that surround, and are in support of, the actual formulation of a compounded preparation. For example handling hazardous drugs

has an inherent risk that a chemical spill may occur, which could affect the health of personnel, cross contaminate other medications (and areas used in compounding medications) intended for patients and also affect the environment.

Risk-related solutions include:

- separate storage of hazardous chemicals
- utilize an on-site spill kit
- train personnel on storage, handling and emergency procedures related to hazardous drugs.

Patient risk

Patient risk considerations include:

- how the patient will administer (and possibly measure) the dose
- storage of the medication
- expiry-date and disposal of any medication at the end of its lifecycle
- individual patient considerations such as age, medical history and family history
- privacy.

Personnel risk

Personnel risk relates to the risks posed to the personnel, in addition to those posed by the personnel. It considers the:

- appropriateness of their training
- practice and validation of their skill set

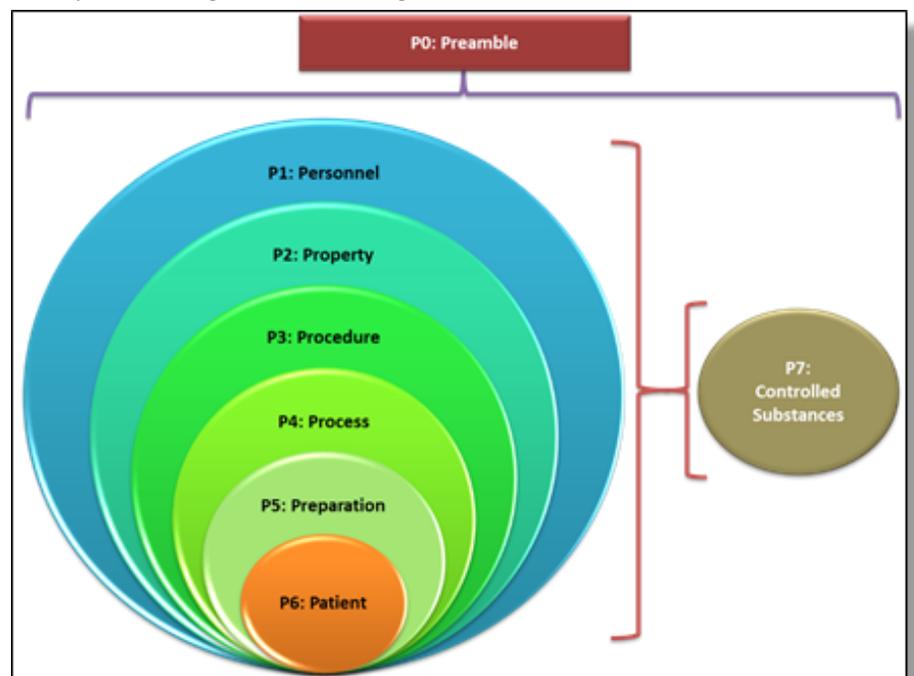


Diagram 1: System P™⁴ ©LP3 Network Inc. Reproduced with permission 2018

It should be noted that corrective

- policies related to illnesses and health conditions
- monitoring of exposure to chemicals
- personal attire (shoes, clothing, hair, jewellery, nails)

System P™

System P™ refers to a system especially suitable for compounding pharmacies as it provides a categorical breakdown of all required standards of practice: Personnel, Property, Procedure, Process, Preparation, and Patient, Preamble and Controlled Substances (the equivalent of Schedule 8 drugs in Australia). Each category is clearly defined with established parameters.

Personnel, Property and Procedure, combined, make up the support infrastructure to manage an operation (the compounding practice). Process, Preparation, and Patient make up the step-wise approach resulting in an approved formulation of record specific to a medication (the Master Formulation Record) that can then become a Compounding Record whereby a pharmacist-physician-patient relationship has been established.

System P™ places the patient at the centre of the model, thereby emphasising patient safety through quality assurance and quality control and the implementation of standard operating procedures (refer to Diagram 1). It is therefore equally relevant in Risk Management, where compounding pharmacists must consider all the components of the system to address risk.³

Property in the compounding setting includes:

- Facility, equipment, and utilities (including traffic flow and design and material surfaces and finishes)
- Heating, ventilation, air conditioning (HVAC), area classification, specifications, design
- Environment: temperature, pressure and humidity, air changes per hour
- Raw materials, equipment and devices and their storage areas (receiving, quarantine, on hold, rejected, accepted, bulk, returns)

Processes and Procedures include:

- Verification, validation, qualification of processes

- Periodic review of procedures and processes
- Change control to any validated/ approved systems/documents
- Deviations, out-of-specification results, investigations and CAPAs
- Procurement, operation, maintenance, monitoring, cleaning and testing of the environment, HVAC
- Procurement, operation, maintenance, monitoring, cleaning and testing of equipment, and devices
- Pest control
- Equipment calibration
- Computer network access, use and maintenance
- Control of storage areas of raw materials, equipment and devices
- Supplier qualification and raw material supply chain robustness and supply chain traceability
- Procurement process of raw materials (quality, manufacturer, distributor, compendial grade)
- In-house testing, testing equipment, methods and method validation, reference materials, primary standards
- Selection and use of personnel protective equipment

Table 1: The Components of System P™³

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Name of Category as per System P™	Description of Category
P0: Preambles	Prerequisites for operating a compounding practice; includes licensing and certification, and the foundation for the implementation of current standards of practice.
P1: Personnel	All employees within your compounding practice.
P2: Property	Everything you own: facility, technology, and chemicals.
P3: Procedure	All procedures once removed and in support of the Master Formulation Records, Compounding Records and preparations.
P4: Process	All Master Formulation Records in development; synonymous with development and rehearsal of Master Formulation Records.
P5: Preparation	The Master Formulation Records, Compounding Records, and final preparations.
P6: Patient	All clients receiving compounded medications from your practice.
P7: Controlled Substances	The combination of all other P categories that would facilitate the proper control and management of narcotics and controlled substances requiring special regulatory consideration.

- Introduction of new compounded preparations
- Formulations (source, publication, efficacy, safety, stability)
- Compounding preparatory procedures and microprocedures
- Contracted testing of preparations (potency, mixing efficacy, microbiological)
- In-process monitoring
- Packaging and labelling
- Storage, dispensing, counselling and distribution of compounded medicines
- Disposal of expired raw materials and end-of-cycle materials, equipment and devices
- Complaints, returned goods and recalls

System P™ is therefore a system pertinent to the compounding pharmacy in its pursuit of Risk Management with the patient at the centre of the model.

International Standards Organisation (ISO)

Risk management quality standards under ISO 14971 considers risk from the perspectives of assessment, control, review and communication.⁵

Diagram 2 outlines the risk management approach to quality as proposed by The International Council for Harmonisation’s quality guidelines (ICH Q9 and ISO 14971).

At the core of the risk assessment, are considerations of probability, severity and detectability. At the core of risk control are considerations of mitigation and acceptance. The risk is then reviewed and communicated. Note that in the above flowchart, “Unacceptable” refers to the regulatory requirements and also requires that the risk assessment process should be revisited.

The **Risk Assessment** process includes:

1. **Identify** any potential hazards: What might go wrong or has gone wrong?

2. **Determine the probability** or likelihood of occurrence of the risk.
3. **Determine the severity** of the risk, should it occur: What are the consequences (severity)?
4. Understand whether the current resources (including structure, equipment, procedures) can detect the risk: How easy is it for the risk to be detected?
5. **Evaluate** the risk- to determine whether to accept or take action to prevent/minimise a given risk: What is the level of risk, and are there any mitigating factors?

Risk assessment is the stage of qualitative categorization and quantitative estimate of the identified hazards. Since risk assessment applies to all staff, they must be trained on the procedure prior to undertaking any activities which may expose them to the risk. There is often an escalation tree or structure which identifies who is responsible for which decisions, such as the lead and the head of department. Such structures are common in large organisations such as hospitals and drug manufacturing companies. They are

also necessary in the compounding of pharmaceutical medicines since compounding activities expose patients, operators and the environment to risk.

All staff are responsible for

1. Identifying and reporting actual or potential hazards in the work environment using the appropriate reporting system.
2. Taking immediate action to minimize risks when it is reasonably practicable to do so, as per approved procedures and work instructions.
3. Being personally responsible for not undertaking any task, or action, which would knowingly expose themselves or others to risk.

After defining the product, process or task to be assessed, the risk assessment initiator or a designee performs a risk assessment. The risk is deemed to fall into one of three categories:

1. Acceptable
2. Undesirable
3. Unacceptable

The **Risk Control** process includes:

1. **Identify hazards** which should be

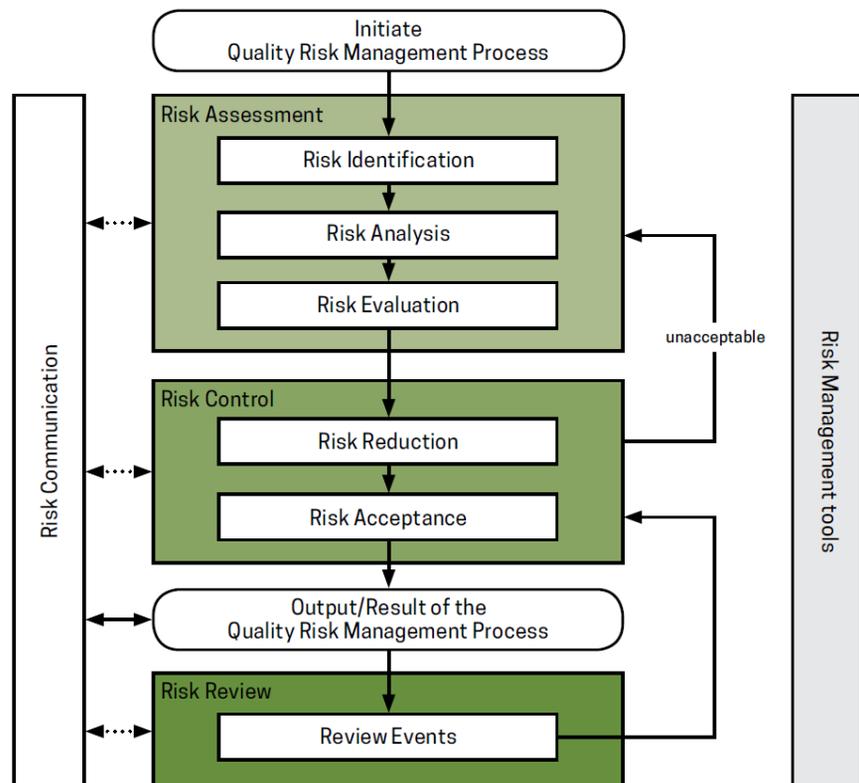


Diagram 2: A Quality Risk Management process⁶

<p>controlled</p> <ol style="list-style-type: none"> 2. <i>Identify processes</i> where hazards may occur 3. <i>Recommend controls</i> to reduce the risk 4. <i>Recommend any critical limits</i> or relevant tolerability criteria for the risk 5. <i>Devise procedures</i> for monitoring and verification 6. <i>Communicate</i> the results of the RM process 	<p>provision of compounding services:⁷</p> <p>5.2.2 Uses quality, dedicated ingredients from approved sources (i.e. ingredients from suppliers granted a licence under the Therapeutic Goods Act 1989). Risk assessment is required for ingredients sourced from suppliers not licensed under the Act or sourced from proprietary products, to determine whether the material is safe and appropriate for its intended use and meets applicable pharmacopoeial standards.</p> <p>5.3.2 Implements and maintains SOPs, which include:</p> <ul style="list-style-type: none"> • management of personal health conditions (e.g. pregnancy, illness, injury) that may increase the risk to the product or compounder • risk assessment and mitigation (including corrective actions, if required) <p>5.4.4 Promotes staff understanding of the purpose, limitations and levels of risk associated with complex compounding, and strategies to mitigate these risks.</p>	<p>to compound a product. See Appendix 7: Compounding decision support and risk assessment tool.</p> <p>5.5.4 Manages identified risks appropriately, considering evidence and best-practice guidelines (e.g. use of personal protective equipment, containers for storage and disposal of clinical and hazardous waste, adherence to relevant work health and safety [WHS] procedures, aseptic technique, infection control procedures).</p> <p>5.6.1 Documents information specific to compounding a product to enable easy access to information required for traceability and recall of the product, and reproducibility of the compounding process. This may include:</p> <ul style="list-style-type: none"> • risk assessment and mitigation <p>5.7.6 Uses personal protective equipment and additional precautions (e.g. eye protection, dust mask, powder containment systems) appropriate to the level of risk when compounding hazardous substances.</p> <p>5.7.9 Ensures that sterile compounding is undertaken:</p> <ul style="list-style-type: none"> • using isolators, laminar flow cabinets, and laminar flow workbenches that meet Australian Standards and are appropriate to risk • using protective clothing appropriate to risk
<p>The Risk Review process includes:</p> <ol style="list-style-type: none"> 1. Review the results of the monitoring and verification 2. Recommend appropriate corrective and preventative action (CAPA) where deviation occurs 3. Verify the Risk Management plan 	<p>5.5 Risk management and evaluation</p> <ul style="list-style-type: none"> • Assessing and managing risks. • Evaluating compounding services. <p>(Meets actions outlined in <i>Standard 2: Leading and Managing Pharmacy Practice, Criterion 2.8: Risk management and evaluation.</i>)</p>	<p>5.6.1 Documents information specific to compounding a product to enable easy access to information required for traceability and recall of the product, and reproducibility of the compounding process. This may include:</p> <ul style="list-style-type: none"> • risk assessment and mitigation <p>5.7.6 Uses personal protective equipment and additional precautions (e.g. eye protection, dust mask, powder containment systems) appropriate to the level of risk when compounding hazardous substances.</p> <p>5.7.9 Ensures that sterile compounding is undertaken:</p> <ul style="list-style-type: none"> • using isolators, laminar flow cabinets, and laminar flow workbenches that meet Australian Standards and are appropriate to risk • using protective clothing appropriate to risk
<p>The scope of the review should clearly establish the boundaries of the process, system, project or activity being assessed and any inherent assumptions that are made. It should consider possible interactions outside the boundary and their potential impacts.</p>	<p>5.5.2 Assesses and monitors the risks associated with preparation of the product, including:</p> <ul style="list-style-type: none"> • product-related risks (e.g. ingredients and formulation, preparation process, intended use of the product) • personnel-related risks (e.g. exposure to hazardous substances, capacity and capability of staff) • premises-related risks (e.g. equipment maintenance and calibration; suitability of surfaces, spaces, furnishings and equipment). 	<p>5.10 Compounding practice</p> <ul style="list-style-type: none"> • Compounding preparations in accordance with best-practice guidelines and patient needs. • Upholding hygiene procedures to reduce the risk of contamination. • Preparing sterile preparations in a manner that ensures the quality and sterility of the final product.
<p>All process-related risk assessments should be regularly reviewed by a designee to ensure the suitability of hazards and controls to current practices. Any changes and updates should be documented through the Master records.</p>	<p>5.5.3 Uses an appropriate decision support and risk assessment tool to determine whether the compounder is adequately skilled and resourced</p>	<p>5.10.2 Conducts a risk assessment of the compounding process, and responds appropriately (i.e. compounds the product in accordance with SOPs, contacts the prescriber or facilitates supply via an alternative provider). See Appendix 7: Compounding decision support and risk assessment tool.</p>
<p>Risk Management is an ongoing part of the compounding process. It includes the review of all events (positive or negative) relating to the RM while taking into account new knowledge and experience about the risk.</p>	<p>5.5.3 Uses an appropriate decision support and risk assessment tool to determine whether the compounder is adequately skilled and resourced</p>	<p><i>Professional Practice Standards</i>, also</p>
<p>Professional Practice Standards</p> <p>In Standard 5: Compounding of the <i>Professional Practice Standards v5 2017</i>, published by Pharmaceutical Society of Australia, one component of the patient-centred care model is risk management and evaluation (Diagram 3).</p>	<p>5.5.3 Uses an appropriate decision support and risk assessment tool to determine whether the compounder is adequately skilled and resourced</p>	<p><i>Professional Practice Standards</i>, also</p>
<p>The standard includes criteria which are directly related to risk in the</p>	<p>5.5.3 Uses an appropriate decision support and risk assessment tool to determine whether the compounder is adequately skilled and resourced</p>	<p><i>Professional Practice Standards</i>, also</p>



Diagram 3: Criteria to achieve the Compounding Standard⁷

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includes *Appendix 7: Compounding decision support and risk assessment tool*⁸. Within this, the question arises “What risks are associated with compounding this preparation?”. The pharmacist is required to identify risks related to each of the following three perspectives: product, personnel and patient. Each of the identified risks within each perspective is then considered in light of its source, mitigations, likelihood, consequence and risk rating (RR).

There are four RR matrix colour-coded categories, with each one leading to a required action by the pharmacist (Diagram 4):

1. Extreme risk (ER): Do not compound; contact prescriber (which is colour coded red)
2. High risk (HR): Seek expert guidance before compounding, or refer to alternative provider with expertise (colour coded ORANGE)
3. Medium risk (MR): Exercise caution when compounding (ensure risk mitigation strategies are in place) (colour coded yellow)
4. Low risk (LR): Compound in accordance with best practice (colour coded green)

Depending on the RR endpoint, the pharmacist may action intervention to mitigate the risk:⁸

“Minor intervention” example:

- Face mask/gloves are required if there is an unacceptable risk to compounder safety
- Substitution of a different (equivalent) ingredient.

“Significant intervention” examples:

- Additional training is required
- Expert guidance is required
- Specialist equipment is required
- Change of formulation

In conjunction with other Standards, the criteria of Standard 5 together with the *Compounding decision support and risk assessment tool* should be utilised by compounding pharmacists to “ensure timely access to a safe, efficacious and quality product.”

Pharmacy Board of Australia

In the *Guidelines on compounding of medicines*, the Pharmacy Board of Australia divides compounding into two categories: Simple and Complex. The document provides guidance and clarification on specific issues regarding compounding of medicines with the specific “aim to minimise the associated risks for patients, pharmacists and other pharmacy

staff, and improve patient outcomes and patient safety.” As risk increases, compounded medicines shift from simple to complex compounding.⁹

Complex compounding is identified as an area of practice “which requires or involves specific competencies, equipment, processes and/or facilities to manage the higher risks associated with the preparation and dispensing of these medicines”. Quantifiable features identified in the definition of Complex Compounding include when an API is in unit dosage forms containing less than 25 mg, or up to 25% by weight or volume. Qualitative features include sustained release or other modified-release preparations; sterile preparations; and where the ingredients pose an occupational health and safety hazard such as cytotoxics or hormones.

Pharmacists are required to use professional judgement grounded on risk assessment, current clinical knowledge and current pharmaceutical knowledge. This process is carried out prior to commencing any compounding to inform the pharmacist whether compounding should be undertaken, especially when there is no precedence for the formulation found in reputable sources.

The *Guidelines* discuss the requirement for standard operation procedures, including the requirement for documented risk management processes which align with:

- professional practice standards
- the current edition of the *Australian Pharmaceutical Formulary and Handbook*
- regulatory standards of the applicable jurisdictions such as State/Territory and Commonwealth.¹⁰

The aim of the processes is to manage risks associated with the

- compounded product since it is used by patients and
- workplace (for maintenance of facilities, quality assurance of

products including microbial testing, occupational health and safety adherence, professional indemnity insurance arrangements etc.).

The *Guidelines* also recognise that preparing compounded medications in batches poses the risk of potential harm to large numbers of patients and therefore discourages batch compounding. Conversely, although not specifically noted in the *Guidelines*, compounded medications which have been verified for high quality, have the potential to benefit large numbers of patients.

“A pharmacist must conduct a risk assessment and ensure that they have sufficient evidence that appropriate processes are in place and have been followed to effectively manage any additional risk associated with batch preparation (also refer to Guideline: 12. *Documentation on Page 11.*)”⁹

Pharmacists should conduct a risk assessment on the

- training and experience of staff assisting in compounding⁹
- environment
- facilities
- equipment
- specific medications such as veterinary products or hazardous substances¹¹

The need for mitigating risk has been identified in the following areas in the *Guidelines*:

- Needlestick injury
- Contamination of the compounded medication
- Staff training including use of equipment
- occupational health and safety standards
- routine health monitoring of staff handling hazardous drugs¹²

There are numerous resources regulators and organisations that identify the important role of Risk Management in the provision of pharmaceutical services and

compounding pharmacy in particular. It is incumbent upon the compounding pharmacist to incorporate Risk Management in their practice in order to address risk to patients, personnel, the environment and ensure compliance with regulations, standards of practice and guidelines.

Risk rating (RR) matrix				
Likelihood of risk	Consequence of risk			
	4. Not significant (a safe and quality product can be compounded)	3. Minor (a safe and quality product can be compounded with minor intervention)	2. Major (a safe and quality product can be compounded with significant intervention)	1. Severe (a safe and quality product cannot be compounded)
A. Almost certain (expected to occur)	LR	MR	HR	ER
B. Likely (will probably occur)	LR	MR	HR	ER
C. Possible (could occur)	LR	MR	HR	ER
D. Unlikely (not expected to occur)	LR	LR	MR	HR

Diagram 4: Risk Rating (RR) Matrix⁸ ©Pharmaceutical Society of Australia. Reproduced with permission 2018

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CPD MULTIPLE CHOICE QUESTIONS

1. Which of the following components form the structure of the Risk Management scheme as proposed by ICH Q9 and ISO 14971?
- A. Risk assessment, identification, mitigation, communication
 - B. Risk assessment, control, review, communication
 - C. Risk assessment, mitigation, evaluation, review
 - D. Risk assessment, identification, mitigation, review
2. All Staff involved in the compounding of pharmaceuticals are responsible for identifying and reporting of hazards irrespective of their position within the organisation.
- A. True
 - B. False
3. Risk assessment considers the probability, severity and detectability of the risk eventuating
- A. True
 - B. False
4. Applying Professional Practice Standards Risk Rating matrix, where the consequence of a risk is major and almost certain to occur, compounding may still be possible under certain interventions. Which of the following scenarios is unlikely to have interventions which would make compounding acceptable:
- A. A non-hazardous drug handled in the absence of full personnel protective equipment
 - B. A cytotoxic drug handled in an unclassified environment
 - C. A drug with a wide therapeutic window which cannot be delivered in a unit dose dispenser
 - D. The dose of compounded medicine which needs to be titrated according to patient response, is accompanied by limited published evidence that supports the dose titration
5. Choose which of the below statements is/are correct:
System P™ in compounding pharmacies involves:
- I. numerous factors all beginning with the letter "P"
 - II. the patient as the central consideration, and reason for being
 - III. the implementation of standard operating procedures to assure and control quality
 - IV. an appreciation of the string of processes which form the procedures
- A. All the above are correct
 - B. I, II and III are correct
 - C. II, III and IV are correct
 - D. I, II and IV are correct
6. Which of the following are important factors which need to be considered when compounding a medication for a patient, as they may potentially contribute to risk:
- A. How the patient will administer and/or measure the dose
 - B. Storage of the medication
 - C. Expiry date of the compounded product, as well as disposal of any unused medication at the end of its life cycle
 - D. The patients age, medical history and family history
 - E. All of the above