# RISK MATRIX FOR STERILE COMPOUNDED PRODUCTS: DESIGN AND VALIDATION

Spanish Group of Pharmaceutical Compounding **PP003**

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## Objective

To design and validate a matrix allowing the classification of sterile compounded preparations in different risk levels


## Material and methods

| Design | Validation |
|---|---|
| ❑ literature review<br>❑ identification of risks associated to the elaboration process (FMEA methodology)<br>❑ estimation of the severity associated to the risks detected | ❑ construct validity<br>❑ inter and intrarater reliability (target: overall agreement >95%, Light's Kappa≥0.6)<br>=>15 representative sterile preparations evaluated by 10 compounding pharmacists |

## Results

❑ 6 dimensions of risk
❑ risk severity graded from A to D

| RISK MATRIX FOR STERILE PREPARATIONS | |
|---|---|
| **NAME OF THE PREPARATION :** | |
| **1. Preparation process** | |
| 1. Combinations of **4 or more** different medications.<br>2. Preparations requiring **4 or more** punctures in the final container or which require the reconstitution and/or extraction of **4 or more** ampoules/vials to obtain the necessary dose to include in final container<br>3. Preparations which require **complex calculations**[1] in 2 or more steps to determine the dose for the patient and/or amount to prepare<br>4. Processes in which foam is formed, or entail a risk of physico-chemical instability (light, $O_2$), precipitation, turbidity, pH-dependent degradation, colorations, phase separation, during the preparation process.<br>5. Difficult reconstitution-dilution lasting **over 10-20 minutes**[2] (i.e.: non-pegylated liposomal doxorubicin, paclitaxel-albumin, Palivizumab, etc.). | C |
| 1. Combinations of 3 different medications.<br>2. Preparations requiring 3 punctures in final container or which require reconstitution and/or extraction of 3 ampoules/vials to obtain necessary dose to include in final container<br>3. Preparations which require **simple calculations**[3] in one single step to ascertain the dose for the patient and/or the amount to be prepared | B |
| 1. Combinations of **2** different medications<br>2. Preparations only requiring 1 or 2 punctures in the final container or which require the reconstitution and/or extraction of 1 or 2 ampoules/vials to obtain the necessary dose to include in the final container.<br>3. Products not requiring calculations for preparation.<br>4. Reconstitution and dilution of vials in solution, concentrates and freeze-dried powders for total use or **fractions of simple doses**[4] on the basis of injectable solutions of a known concentration<br>5. Simple unitary reconstitution-dilution lasting less than 5 minutes[2]. | A |
| **2. Route of administration** | |
| 1. Intrathecal. | D |
| 1. Intraocular (intravitreous, intracameral), central venous line (in techniques requiring a sterile field), epidural/peridural. | C |
| 1. Central venous line, peripheral intravenous, intramuscular, subcutaneous, intradermal, intrapleural, intralesional, intraperitoneal, intra-articular, inhaled, nebulised. | B |
| 1. Ophthalmic topical, otic topical, intravesical, oral, rectal, topical. | A |
| **3. Safety profile of the active ingredient** | |
| 1. Vesicant substances, irritant substances, corrosive substances, with mutagenic potential, carcinogenic properties or infectious properties[5]. | C |
| 1. Narrow therapeutical window and/or need for monitoring<br>2. Considered to be high risk in the event of error[6].<br>3. Opiates, sedatives and psychotropic substances<br>4. Clinical trial medications | B |
| 1. Rest of medication with low toxicity profile | A |
| **4. Amount of units prepared** | |
| 1. More than 25 units/batch | C |
| 1. Between 3 and 25 units/batch | B |
| 1. 1 or 2 units | A |
| **5. Susceptibility to microbiological contamination[7]** | |
| 1. Transfer of products via **open systems**[8].<br>2. Preparation using non-sterile products, containers or non-sterile transfer systems requiring terminal sterilisation at the end of the preparation. | D |
| 1. Substances which are highly susceptible to microbiological contamination which are administered via iv infusion in **8h or more.**<br>2. Eyedrop preparation **without preservatives** in sterile containers via the dropper tip (not considered open) to be used in multi-dose form. | C |
| 1. Preparations of substances with low contamination risk which are administered over 24 hours (patient-controlled pumps, elastomeric infusion devices).<br>2. Substances with low risk of microbial contamination where the time lapsed from preparation to start administration is >12 hours.<br>3. Preparation of eyedrops **with preservatives** in sterile containers via the dropper tip (not considered to be an open transfer system) to be used in multi-dose form. | B |
| 1. Simple transfer of medication in **closed systems**<br>2. Preparations with low risk of contamination for immediate administration.<br>3. Preparations whose administration duration is equal or under 24 hours. | A |
| **6. Distribution of the preparation** | |
| 1. Exclusive use for other hospitals. | C |
| 1. Combined use (for the hospital that prepares it and for other hospitals). | B |
| 1. Exclusive use by hospital that prepares it. | A |

❑ Result is a 6-letter combination with three possible risk levels: low, intermediate, high
❑ microbiological beyond-use date proposed based on risk level, preparation environment and storing conditions

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| | | | | | |

**Interpretation of result:**
**LOW RISK LEVEL:**
- **ANY COMBINATION WITH < 3 "B" OPTIONS AND NO "C" or "D" OPTIONS**

**INTERMEDIATE RISK LEVEL:**
- **ANY COMBINATION WITH ≥3 "B" OPTIONS or**
- **ANY COMBINATION WITH ≥1 "C"OPTION**

**HIGH RISK LEVEL**
- **IF IT INCLUDES ANY "D" OPTIONS**

| RISK LEVEL AND PREPARATION/CONSERVATION REQUIREMENTS | | |
|---|---|---|
| **Risk level** | **Preparation requirements** | **Storage requirements [(1)]** |
| If the set of letters contains at least a D, the preparation is considered to be **a high risk preparation.** | Pharmacy service.<br>Preparation in laminar flow cabinet in a controlled environment (clean area) | • 24 hours / room temperature<br>• 3 days / refrigerator (2˚C – 8˚C)<br>• 45 days / freezer (≤ -20˚C)<br>• 90 days/ freeze-dried |
| If the set of letters contains at least one C or three or more B (and no D), it is considered to be an **intermediate risk preparation.** | Pharmacy service.<br>Preparation in laminar flow cabinet in a controlled environment (clean area) | • 30 hours / room temperature<br>• 9 days / refrigerator (2˚C – 8˚C)<br>• 45 days in freezer (≤ -20˚C)<br>• 90 days freeze-dried |
| If the set of letters contains fewer than three B (and no C or D) it is considered to be a **low risk preparation.** | Pharmacy service.<br>Preparation in laminar flow cabinet in a controlled environment (clean area) | • 48 hours/ room temperature<br>• 14 days / refrigerator (2˚C–8˚C)<br>• 45 days / freezer (≤ -20˚C)<br>• 90 days freeze-dried |
| | Pharmacy service.<br>Preparation in laminar flow cabinet located in no controlled environment | • 12 hours / room temperature<br>• 24 hours / refrigerator (2˚C–8˚C)<br>• 7 days / freezer (≤ -20˚C) |
| | Nursing unit on ward, no controlled environment | • 1 hour / room temperature,<br>• 1 hour / refrigerator (2˚C – 8˚C)<br>• Do not freeze |

### Validation results

**Overall agreement: 96.4±10.1**

| Dimension | Light's Kappa | 95% CI |
|---|---|---|
| 1 | 0.92 | 0.65-1.0 |
| 2 | 1 | 1.0-1.0 |
| 3 | 0.75 | 0.41-0.96 |
| 4 | 1 | 1.0-1.0 |
| 5 | 0.68 | 0.43-0.92 |
| 6 | -- | -- |

## Conclusion

The risk matrix designed is a reproducible tool adapted to daily practice in hospital settings that may increase patient safety and allows a better use of resources in sterile preparations.

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