Technical and regulatory feasibility of a new sterile preparation posing health and environmental risk: the case of 30% ethanol eye drops

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INTRODUCTION

- Military hospital with 200 beds treating 90% of civilians
- Preparation activity of the hospital pharmacy: anticancer drugs reconstitution unit (10,000 bags / year) and preparation unit

- **Instillation of 30% ethanol extemporaneously diluted** from 96% ethanol to optimize de-epithelialization in refractive surgery
- ⚠ Risks of **error**, **contamination** or even **confusion** with other indications of 96% ethanol

OBJECTIVES

❑ To **ensure medication management safety**, this study aimed to **evaluate the technical and regulatory feasibility** of preparing 30% ethanol eye drops within the hospital pharmacy, considering the **sterility requirement** of ophthalmic preparations and the **safe handling** of concentrated ethanol

METHODS

Regulatory validity assessment
- According to Good Preparation Practices
- **Positioning** in the therapeutic arsenal and **added value**
- Technical feasibility (**resources**)

Process mapping
Description of the **steps** in the business, management and support processes based on incoming (**need/requirement**) and outgoing data (**expected**)

Risk mapping
- Definition of **generic hazards** categories[1]
- Identification of **dangerous situations** at the intersection of hazards and process steps

Risk assessment
Dangerous situations assessment:
- Description of the **causes** & **consequences**
- **Initial criticality** (C_i) scoring

*(consequence **s**everity * **o**ccurrence likelihood * level of existing control **m**easures)*
Based on 1-to-5 **scales**[2]

$C = S \times O \times M$

Action plan
- Decision on **risk reduction actions** (↓ likelihood or ↑ management)
- Acceptance of **residual criticality** (C_r) according to the defined scale[2]
- **Prioritizing** and **monitoring** the action plan

[1] GENERIC HAZARDS

For the patient
- Lack of treatment
- Inadequate dosage
- Microbiological contamination of the drug
- Physico-chemical degradation of the drug

For personnel
- Inhalation of ethanol vapor

For the environment
- Release of ethanol
- Fire (flammability)

Regulatory
- Barrier to preparation
- Non-compliance with good practices

[2] SCORING SCALES

Initial risks										Residual risks			
Step	Hazard	Risk	Cause	Consequence	Existing control measure	Severity	O_i	M_i	Initial criticality	Risk reduction action	O_c	M_c	Residual criticality

O_i : initial occurrence
O_c : corrected occurrence

M_i : initial management level
M_c : corrected management level

S Severity of consequence

	Regulatory	Patient	Personnel	Environment
5	Barrier	Irreversibility (death)	Death or disability	Major (fire)
4	Critical deviation	Loss of opportunity (reversible injury)	Work stoppage > 10 days	Important (pollution)
3	Major deviation	Service failure (hospitalization postponement)	Work stoppage < 10 days	Localized
2	Minor deviation	Service disruption (delay)	Injuries without work stoppage	Low
1	Remark or compliance	Without effect	Psychological impact without injury	Negligible

O Likelihood of occurrence

5	Each session
4	One session out of two
3	One session out of five
2	One session out of ten
1	Never

M Management level

5	Discovery (no action)
4	Alert (insufficient actions)
3	Organisation (procedures without assessment)
2	Forecasting (action plan and indicators)
1	Control (training, monitoring, checking)

C Criticality

Score	Level	Risk acceptability
45 à 125	To be treated	Risk situations not acceptable as they stand → Analysis and treatment actions
15 à 44	To monitor	Lower risk situations → Identification and monitoring actions
0 à 14	Acceptable	Low-risk situations acceptable as they stand

METHODS

RISK ASSESSMENT OF CONCENTRATED ETHANOL HANDLING

Estimation of the **evaporation rate** of ethanol in a **worst case** situation (spillage on the work surface and positive uncertainty)
- Estimation of ethanol **concentration** in the **working atmosphere** → Compared to **occupational exposure limits**
- Estimation of ethanol **volumetric percentage** in the **working atmosphere** → Compared to **lower flammability limit**

Based on the **formulas** issued by the **French National Institute for Research and Safety** (ED 5068), the **qualification data** for the **premises** and **equipment** (volume of the room, air change rate, work surface, etc.) and the **toxicological data sheets** for ethanol

RESULTS

Regulatory validity assessment
- **Documented medical indication** and **absence of appropriate dosage** → validity
- **Lack of control capabilities** required by the European Pharmacopoeia → **magistral** preparation
- Available technical resources: **cleanroom**[3], **class II BSC**[4] and **qualified personnel**

Process mapping
- **7 steps:**
1. Prescription
2. Control of production resources
3. Production preparation
4. Production
5. Packaging
6. Quality control
7. Storage
- **29 sub-steps**

54 risk situations identified for the 29 sub-steps and 9 generic hazards

Risk mapping

Risk assessment
- **42 situations analyzed** (others having overlapping causes or hazards)
- **14 situations** considered unacceptable and **to be addressed**

- **14 actions** including **8 priorities**

Distribution of the initial criticality of risk situations

Distribution of the residual criticality of risk situations

Action plan

[3]cleanroom : supplied with filtered air
[4]BSC : biosafety cabinet

A FEW EXAMPLES TO HELP YOU SEE THINGS MORE CLEARLY?

Step	Hazard	Risk	Cause	O	Consequence	S	Existing control measure	M	C_i	Risk reduction action	C_r
2		Non-compliance	No preparation file	O_i 5 O_c 1	Major deviation	3	Operating procedure not covered by a file	M_i 4 M_c 2	60	Drafting a preparation file	6
2		Microbiological contamination	Non-sterile primary packaging materials	O_i 5 O_c 1	Non-sterile product may cause infection	4	*None (No sterile stock)*	M_i 5 M_c 2	100	Supply of sterile primary packaging materials	8
3		Microbiological contamination	BSC cleaning not validated	O_i 5 O_c 1	Non-sterile product may cause infection	4	*None (BSC not used, so no prior validation)*	M_i 5 M_c 2	100	Microbiological validation of equipment cleaning	8

WHAT ABOUT THE HANDLING OF CONCENTRATED ETHANOL?

Use under defined working conditions → **No risk** to **personnel** or the **environment**

DISCUSSION & CONCLUSION

✓ **Implementation** of a **new magistral sterile preparation** with **controlled risk** for patients, personnel and the environment

✓ **Medication management safety** ensured

✓ It could be **further enhanced** by a **self-assessment of good practices compliance** and **direct atmospheric monitoring** of ethanol concentrations in the working area