Opinion Paper

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Preparation of alcohol-based handrub in COVID-19 Alsatian cluster

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Abstract: Alsace, in particular Haut-Rhin, is one of the main clusters of COVID-19 in France. There has been a shortage of essential supplies in the area, especially alcohol-based hand sanitizer. In this context, and in accordance with the decree dated March 6, 2020, our hospital management team asked us to start local production of alcohol-based handrub. This was a real challenge: In one week, we had to implement the production of handrub to meet the needs of a 1,400-bed hospital. The production had to comply with the French preparation guidelines and take place on specific premises, with qualified and calibrated equipment, by qualified staff, under the supervision of a pharmacist. The other big challenge we faced was the supply of pharmaceutical raw and packaging materials. During this particular critical period, all suppliers were out of stock. Here, we describe the organizational set-up and the decisions made, e. g., to use technical-grade ethanol before the publication of the decrees dated March 13 and March 23, 2020.

Keywords: alcohol-based handrub; alcohol-based hand sanitizer; Alsatian cluster; biocide; COVID-19; local production; preparation.

Introduction

Alsace, in particular Haut-Rhin, is one of the main clusters of the COVID-19 pandemic in France [1]. There is a substantial shortage of essential and basic personal protective equipment and supplies, in particular of alcohol-based hand sanitizer. According to management, our hospital pharmacy implemented the temporary local production of alcohol-based handrub to avoid running out of stock and to

fight against the spread of SARS-CoV-2 in the hospital. This was a real challenge: In one week, we had to implement the production of handrub to meet the needs of a 1,400-bed hospital. Here, we describe the organizational set-up and the decisions made to start production as soon as possible.

Chronology of a tense week

March 6: Due to the risk of a national shortage of alcohol-based hand sanitizers and the contagious nature of SARS-CoV-2, the French government published a decree authorizing all pharmacists to prepare their own alcohol-based handrub in accordance with the World Health Organization (WHO) guidelines using pharmaceutical-grade raw material [2, 3].

March 9: The stock of alcohol-based hand sanitizers in the hospital was rated at one week. No delivery had been planned. All main pharmaceutical suppliers were asked about the availability of raw material with pharmaceutical-grade ethanol, glycerin, and hydrogen peroxide. Late in the morning, all of the main pharmaceutical suppliers reported being out of stock of all concentrations of pharmaceutical-grade ethanol. Pharmaceutical-grade glycerin and hydrogen peroxide were available in sufficient quantity.

March 10: Technical-grade ethanol was still available from laboratory suppliers. A large order of 1,000 L was placed. Packaging materials were also unavailable and therefore we organized the recovery of empty bottles within the hospital.

March 11: Considering the state of emergency, a critical request for preparation of handrub from technical-grade ethanol was sent to the Regional Health Agency Grand-Est. At this time, the stock of alcohol-based hand sanitizers in the hospital was rated at three days. Delivery was not guaranteed with the main supplier reporting a six week delay.

March 12: The Regional Health Agency Grand-Est authorized us to use technical-grade ethanol. The first two batches were produced in our usual preparation room. At the same time, a new preparation room was fitted out in the old quality control laboratory located close to the storage room for flammable products.

March 13: The production line was implemented and four more batches of handrub were prepared.

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March 14: Publication of the decree dated March 13, 2020, relaxed the rules concerning the raw materials that could be used for these preparations [4].

March 16: Production was now fully operational with 12 batches of 5 L per day corresponding to 300 L per week. Normally, this is the weekly consumption at our hospital but this increased to 500 L during the COVID-19 pandemic alongside the growing needs of the hospital staff. Finally, the hospital received 600 L of industrial alcohol-based hand sanitizers. The production carried out by the hospital pharmacy during this week will constitute a buffer stock.

Why use technical-grade ethanol?

First, the exceptional context should be taken into consideration. A shortage of alcohol-based hand sanitizer was and continues to be a reality everywhere in France.

Haut-Rhin was hit hard by the COVID-19 pandemic and thus continuity in the supply of alcohol-based hand sanitizer was vital [1].

Although the decree of March 6, only granted use of pharmaceutical-grade raw material, alcohol-based hand sanitizer is a biocide product not a drug [2]. Biocide products fall under the European regulations of May 22, 2012, which do not recommend the use of pharmaceutical-grade ethanol but a high-quality ethanol supplied by a producer listed on the website of the European Chemicals Agency [5, 6]. The decree dated March 13 took this into account and the decree dated March 23, broadened the use to agricultural and natural ethanol [4, 7].

Finally, analysis of the technical-grade ethanol certificate showed specifications that are very close to those of the European Pharmacopoeia (Table 1) [8, 9]. However, we should point out the absence of information on benzene quantification, miscibility, and Iodoform testing.

Table 1: Comparison between the European Pharmacopoeia requirements and the certificate of analysis of technical-grade ethanol 96° used [8, 9].

	European Pharmacopoeia specifications	Ethanol 96°, Cristalco®, FranceAlcools® Technical grade specifications (Testing procedure)
Organoleptic characteristic	Clear, colorless liquid, volatility	Clear, colorless liquid (OIV method for alcoholic beverage analysis) Hazen coloration < 3 (NF T20-605/UV Spectro) Smell (Internal method)
Alcohol strength at 20 °C	Between 95.1 and 96.9% v/v	Limits > 96.00 % v/v (OIV method for alcoholic beverage analysis)
Identification	1st method: A (Density) and B (Infrared spectrometry) 2nd method: A (Density), C (Permanganate test) and D (Iodoform test)	Density and permanganate test (OIV method for alcoholic beverage analysis)
Miscibility	Water Methylene chloride	Not carried out
Acidity	Phenolphthalein test (30 ppm acetic acid)	<1 g acetic acid/hL Pure Alcohol (PA) (OIV method for alcoholic beverage analysis)
Density	Between 0.805 and 0.812	Between 0.805 and 0.812 (OIV method for alcoholic beverage analysis)
UV Absorption	Steadily curve UV absorption 240 nm (5 cm cell) = max 0.4 UV absorption between 250 and 260 nm (5 cm cell) = max 0.3 UV absorption between 270 and 340 nm (5 cm cell) = max 0.1	Steadily curve UV absorption 220 nm (1 cm cell) = max 0.3 UV absorption 230 nm (1 cm cell) = max 0.18 UV absorption 240 nm (1 cm cell) = max 0.08 UV absorption 270 nm (1 cm cell) = max 0.02 (OIV method for alcoholic beverage analysis)
Impurities	Methanol < 200 ppm (v/v) Acetaldehyde and acetal < 10 ppm (v/v) of acetaldehyde Benzene < 2 ppm (v/v) Total other impurities < 300 ppm (v/v)	Methanol < 2.5 g/hL PA Total aldehydes < 0.5 g acetaldehyde/hL PA Esters < 1.3 g ethyl acetate/hL PA High alcohols < 0.5 g methyl2propanol1/hL PA Furfural (Not detectable) Ammonia and nitro basis <0.1 g nitrogen/hL PA (OIV method for alcoholic beverage analysis)
Dry extract	Max 25 ppm (m/v)	<1.5 g/hL PA (OIV method for alcoholic beverage analysis)

Table 2: Procedure for alcohol-based handrub production.

Who?	Where?	How?
<i>Recovery of empty dirty bottles</i>		
Caregiver	Pharmacy	– Daily, place empty bottles of the care unit in the recycling bin at the entrance of the hospital pharmacy.
<i>Routing circuit between pharmacy and sterilization</i>		
Sterilization Staff	Pharmacy	– Daily, come to the pharmacy to place clean bottles on the shelf identified at the entrance of the pharmacy. – Collect dirty bottles and take them back to the sterilization unit.
<i>Label removal, cleaning, and disinfection process for reusable handrub bottles label removal and washing procedure</i>		
Sterilization Staff	Sterilization	– Remove the pump and rinse each part (the pumps as well as the inside of the bottles) with cold water. <u>Washing the pumps:</u> – Operate the pumps to fill them with detergent/disinfectant. – Soak the pumps in the detergent/disinfectant for 20 min. – Rinse thoroughly with water. <u>Washing the bottles:</u> – Soak bottles in hot water to allow peeling off of labels. Remove the glue with the solvent (put a mask and ventilate the room) then rinse with hot water. – Soak bottles in the detergent/disinfectant for 20 min. – Rinse with water. – Proceed to automated cleaning and disinfection of bottles. <u>Automated cleaning and disinfecting disinfection cycle parameters:</u> – Pre-cleaning: 2 min at 30 °C. – Cleaning: 7 min at 50 °C with 5 mL/L of cleaning solution (Mediclean Forte® Dr. Weigert). – Rinse twice: 2 min at 60 °C. – Thermal disinfection: 10 min at 80 °C with 0.5 mL/L of drying activator (Mediklar® Dr. Weigert). – Drying: 2 min at 90 °C and 10 min at 80 °C.
<i>Preparation of a 5-L antiseptic topical solution containing ethanol 80% (v/v)</i>		
Pharmacy technician: 2 preparers 1 controller	Preparation room	<u>Formulation 1:</u> – Ethanol 96%: 4,166 mL – Hydrogen peroxide 3%: 208 mL – Glycerol 98%: 74 mL – Sterile distilled water: 552 mL <u>Formulation 2:</u> – Ethanol 100%: 4,000 mL – Hydrogen peroxide 3%: 208 mL – Glycerol 98%: 74 mL – Sterile distilled water: 718 mL <u>Step by step preparation:</u> – Glycerol is measured with a measuring cylinder and then poured into a 6-L Erlenmeyer flask. Since glycerol is very viscous and sticks to the wall, some ethanol is added using the same measuring cylinder in order to clean it. – Ethanol, hydrogen peroxide, and sterile distilled water are added using graduated cylinders adapted to measured volumes. – A magnetic stirring bar is placed in the solution and the Erlenmeyer flask is sealed with a plastic wrap in order to prevent evaporation. – The solution is mixed for 5 min. – The 10-L tank is topped with the two 5-L batches prepared simultaneously. – The solution is divided up and placed into its final containers (e. g., 500- or 250-mL bottles). – The bottles are placed in quarantine for 72 h before use. <u>Packaging:</u> – Packaging in recycling LDPE and HDPE bottles that have been previously washed. <u>Quality control :</u> – Systematic double-check of raw materials and volumes by a third party. – Systematic pre- and post-production verification of the alcohol concentration.

Table 2: (continued)

Who?	Where?	How?
		<div> <div> <p><u>Label</u></p> </div> <div> <p><u>Back label</u></p> </div> </div>
<i>Quarantine</i>		
Pharmacy technician	Alcohol storage room	<ul style="list-style-type: none"> – Prepared batches are placed in quarantine for 72 h in orange bins before use. – Label orange bin with batch number and quarantine end date and time.
<i>Validation</i>		
Pharmacist	Alcohol storage room	<ul style="list-style-type: none"> – Pre-validation of batches in quarantine. – Daily, lift quarantine and batch release. – Place them in blue bins labelled “batch released – ready to send”.
<i>Routing circuit between pharmacy to central store</i>		
worker	Pharmacy	<ul style="list-style-type: none"> – Daily delivery to the central store of the batches.

Organizational set-up

Production depends on the resources and materials that are locally available as well as on reporternment regulations. Thus, our production had to comply with the French preparation guidelines and take place on specific premises, with qualified and calibrated equipment, by qualified staff, under the supervision of a pharmacist [10]. The organizational set-up that was implemented involved many employees and was only made possible by their cooperation. Therefore a protocol was written in order to coordinate the whole team (Table 2).

Owing to shortages in the supply of packaging material, we organized the recycling of empty bottles. The cleaning procedure was tested on high density polyethylene (HDPE), low density polyethylene (LDPE), and polyethylene terephthalate (PETE) bottles. Only LDPE and HDPE were suitable for the automated cleaning and disinfecting process (Table 2) and could be recycled.

Before production began, all raw materials and certificates of analysis were checked in order to ensure the quality of the products. Every preparation step was double-checked by a third party, as recommended in the French preparation guidelines [10].

As recommended by the WHO and the Regional Health Agency, we performed a pre-procedural and post-procedural

analysis of the alcohol concentration with calibrated alcohol meters to guarantee the titration of the alcohol. The accepted limits were fixed to $\pm 5\%$ of the target concentration. We made the necessary adjustments in volume to obtain the final recommended concentration (75–85% for ethanol). The solution was then divided and placed into its final containers. Conditioning alcohol-based handrubs were placed in quarantine for 72 h before use: This allows any spores present in the alcohol or bottles to be destroyed [3].

Conclusion

With the COVID-19 pandemic evolving rapidly, the current health crisis required everyone to make quick but thoughtful decisions. In order to release our first batches of alcohol-based handrub as soon as possible, we had to precede the publication of the decree dated March 13; we started the preparation of alcohol-based handrub from the technical-grade ethanol on March 11 [4]. This decision was discussed on the basis of the European regulations on biocides and it was authorized by the regional health agency [5]. In the same way, the difficulties to procure packaging material led us to recycle empty LDPE and HDPE bottles. This decision was validated after testing the automated cleaning and disinfecting process in collaboration with the sterilization unit.

After two weeks and with collaboration of many support departments at the hospital, 600 L of alcohol-based handrub was produced and provided to different units in our hospital.

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