Guide to Local Production:
WHO-recommended Handrub Formulations

Introduction: This Guide to Local Production of WHO-recommended Handrub Formulations is separated into two discrete but interrelated sections:

Part A provides a practical guide for use at the pharmacy bench during the actual preparation of the formulation. Users may want to display the material on the wall of the production unit.

Part B summarizes some essential background technical information and is taken from WHO Guidelines on Hand Hygiene in Health Care (2009). Within Part B the user has access to important safety and cost information and supplementary material relating to dispensers and distribution.

PART A: GUIDE TO LOCAL PRODUCTION

Part A is intended to guide a local producer in the actual preparation of the formulation.

Materials required (small volume production)

REAGENTS FOR FORMULATION 1:	REAGENTS FOR FORMULATION 2:
• Ethanol 96%	• Isopropyl alcohol 99.8%
• Hydrogen peroxide 3%	• Hydrogen peroxide 3%
• Glycerol 98%	• Glycerol 98%
• Sterile distilled or boiled cold water	• Sterile distilled or boiled cold water

- 10-litre glass or plastic bottles with screw-threaded stoppers (1), or
- 50-litre plastic tanks (preferably in polypropylene or high density polyethylene, translucent so as to see the liquid level) (2), or
- Stainless steel tanks with a capacity of 80–100 litres (for mixing without overflowing) (3 , 4)
- Wooden, plastic or metal paddles for mixing (5)
- Measuring cylinders and measuring jugs (6 , 7)
- Plastic or metal funnel
- 100 ml plastic bottles with leak-proof tops (8)
- 500 ml glass or plastic bottles with screw tops (8)
- An alcoholometer: the temperature scale is at the bottom and the ethanol concentration (percentage v/v) at the top (9 , 10 , 11)

NOTE

- Glycerol: used as humectant, but other emollients may be used for skin care, provided that they are cheap, widely available and miscible in water and alcohol and do not add to toxicity, or promote allergy.
- Hydrogen peroxide: used to inactivate contaminating bacterial spores in the solution and is not an active substance for hand antisepsis.
- Any further additive to both formulations should be clearly labelled and be non-toxic in case of accidental ingestion.
- A colorant may be added to allow differentiation from other fluids, but should not add to toxicity, promote allergy, or interfere with antimicrobial properties. The addition of perfumes or dyes is not recommended due to risk of allergic reactions.


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METHOD: 10-LITRE PREPARATIONS

These can be prepared in 10-litre glass or plastic bottles with screw-threaded stoppers.

Recommended amounts of products:

FORMULATION 1	FORMULATION 2
• Ethanol 96%: **8333 ml** • Hydrogen peroxide 3%: **417 ml** • Glycerol 98%: **145 ml**	• Isopropyl alcohol 99.8%: **7515 ml** • Hydrogen peroxide 3%: **417 ml** • Glycerol 98%: **145 ml**

Step by step preparation:

1. The alcohol for the formula to be used is poured into the large bottle or tank up to the graduated mark.

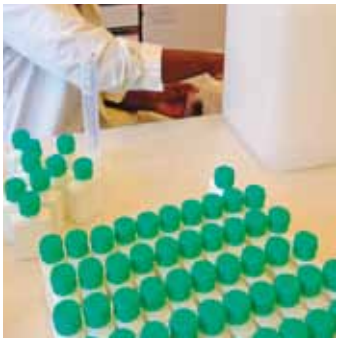
2. Hydrogen peroxide is added using the measuring cylinder.

3. Glycerol is added using a measuring cylinder. As glycerol is very viscous and sticks to the wall of the measuring cylinder, it should be rinsed with some sterile distilled or cold boiled water and then emptied into the bottle/tank.

4. The bottle/tank is then topped up to the 10-litre mark with sterile distilled or cold boiled water.

5. The lid or the screw cap is placed on the tank/bottle as soon as possible after preparation, in order to prevent evaporation.

6. The solution is mixed by shaking gently where appropriate or by using a paddle.



7. Immediately divide up the solution into its final containers (e.g. 500 or 100 ml plastic bottles), and place the bottles in quarantine for 72 hours before use. This allows time for any spores present in the alcohol or the new/re-used bottles to be destroyed.

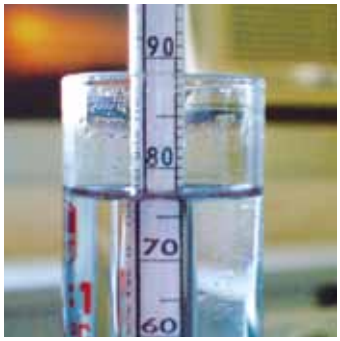
Final products

FORMULATION 1	FORMULATION 2
Final concentrations: • Ethanol 80% (v/v), • Glycerol 1.45% (v/v), • Hydrogen peroxide 0.125% (v/v)	**Final concentrations:** • Isopropyl alcohol 75% (v/v), • Glycerol 1.45% (v/v), • Hydrogen peroxide 0.125% (v/v)

Quality control

1. Pre-production analysis should be made every time an analysis certificate is not available to guarantee the titration of alcohol (i.e. local production). Verify the alcohol concentration with the alcoholmeter and make the necessary adjustments in volume in the preparation formulation to obtain the final recommended concentration.

2. Post-production analysis is mandatory if either ethanol or an isopropanol solution is used. Use the alcoholmeter to control the alcohol concentration of the final use solution. The accepted limits should be fixed to ± 5% of the target concentration (75%–85% for ethanol).



3. The alcoholmeter shown in this information pamphlet is for use with ethanol; if used to control an isopropanol solution, a 75% solution will show 77% (± 1%) on the scale at 25°C.

General information

Labelling should be in accordance with national guidelines and should include the following:

- Name of institution
- WHO-recommended handrub formulation
- For external use only
- Avoid contact with eyes
- Keep out of the reach of children
- Date of production and batch number
- Use: Apply a palmful of alcohol-based handrub and cover all surfaces of the hands. Rub hands until dry
- Composition: ethanol or isopropanol, glycerol and hydrogen peroxide
- Flammable: keep away from flame and heat

Production and storage facilities:

- Production and storage facilities should ideally be air conditioned or cool rooms. No naked flames or smoking should be permitted in these areas.
- WHO-recommended handrub formulations should not be produced in quantities exceeding 50-litres locally or in central pharmacies lacking specialised air conditioning and ventilation.
- Since undiluted ethanol is highly flammable and may ignite at temperatures as low as 10°C, production facilities should directly dilute it to the above-mentioned concentration. The flashpoints of ethanol 80% (v/v) and of isopropyl alcohol 75% (v/v) are 17.5°C and 19°C, respectively.
- National safety guidelines and local legal requirements must be adhered to the storage of ingredients and the final product.
- Additional safety information is presented in Part B of this Guide.

PART B: SUPPLEMENTARY TECHNICAL, SAFETY AND COST INFORMATION:

Part B contains important safety and cost information and incorporates information from the WHO Guidelines on Hand Hygiene in Health Care (2009).

The case for alcohol-based handrubs in health care

At present, alcohol-based handrubs are the only known means for rapidly and effectively inactivating a wide array of potentially harmful microorganisms on hands.

WHO recommends alcohol-based handrubs based on the following factors:

1. Evidence-based, intrinsic advantages of fast-acting and broad-spectrum microbicidal activity with a minimal risk of generating resistance to antimicrobial agents;
2. Suitability for use in resource-limited or remote areas with lack of accessibility to sinks or other facilities for hand hygiene (including clean water, towels, etc.);
3. Capacity to promote improved compliance with hand hygiene by making the process faster, more convenient and immediately accessible at the point of patient care;
4. Economic benefit by reducing annual costs for hand hygiene, representing approximately 1% of extra-costs generated by health care-associated infection
5. Minimization of risks from adverse events because of increased safety associated with better acceptability and tolerance than other products.

(Source: WHO Guidelines on Hand Hygiene in Health Care 2009)

Background to WHO alcohol-based handrub formulations

According to the available evidence on efficacy, tolerability and cost-effectiveness, WHO recommends using an alcohol-based handrub for routine hand antisepsis in most clinical situations. Health-care facilities currently using commercially-available handrubs, liquid soaps and skin care products sold in disposable containers should continue this practice, provided that the handrubs meet recognised standards for microbicidal efficacy (ASTM or EN standards) and are well accepted/tolerated by the health-care workers. It is obvious that these products should be regarded as acceptable, even if their contents differ from those of WHO-recommended formulations described within this document. WHO recommends the local production of the following formulations as an alternative when suitable commercial products are either unavailable or too costly.

To help countries and health-care facilities to achieve system change and adopt alcohol-based handrubs, WHO has identified formulations for their local preparation. Logistic, economic, safety, cultural and religious factors have all been carefully considered by WHO before recommending such formulations for use worldwide.

Efficacy

It is the consensus opinion of a WHO expert group that WHO-recommended handrub formulations can be used both for hygienic hand antisepsis and for presurgical hand preparation.

Hygienic handrub

The microbicidal activity of the two WHO-recommended formulations was tested by WHO reference laboratories according to EN standards (EN 1500). Their activity was found to be equivalent to the reference substance (isopropanol 60% v/v) for hygienic hand antisepsis.

Presurgical hand preparation

Both WHO-recommended handrub formulations were tested by two independent reference laboratories in different European countries to assess their suitability for use for pre-surgical hand preparation, according to the European Standard EN 12791. Although formulation I did not pass the test in both laboratories and formulation II in only one of them, the expert group is, nevertheless, of the opinion that the microbicidal activity of surgical antisepsis is still an ongoing issue for research as due to the lack of epidemiological data there is no indication that the efficacy of n-propanol (propan-1-ol) 60% v/v as a reference in EN 12791 finds a clinical correlate. It is the consensus opinion of a WHO expert group that the choice of n-propanol is inappropriate as the reference alcohol for the validation process because of its safety profile and the lack of evidence-based studies related to its potential harmfulness for humans. Indeed, only a few formulations worldwide have incorporated n-propanol for hand antisepsis.

Considering that other properties of WHO recommended formulations, such as their excellent tolerability, good acceptance by health-care workers and low cost are of high importance for a sustained clinical effect, the above results are considered acceptable and it is the consensus opinion of a WHO expert group that the two formulations can be used for surgical hand preparation. Institutions opting to use WHO-recommended formulations for surgical hand preparation should ensure that a minimum of three applications are used, if not more, for a period of 3–5 minutes. For surgical procedures of more than 2 hours duration, ideally surgeons should practise a second handrub of approximately 1 minute, even though more research is needed on this aspect.

Key lessons learned from around the world

Many settings around the world successfully undertook local production of the two WHO-recommended formulations. Throughout Part B, additional information is presented where relevant, in table form, based on feedback from 11 sites located in Bangladesh, Costa Rica, Egypt, Hong Kong SAR, Kenya, Mali, Mongolia, Pakistan (two sites), Saudi Arabia, and Spain. Further, detailed information is available within the WHO Guidelines on Hand Hygiene in Health Care (2009)

Composition of alcohol-based formulations for in-house/local production

The choice of components for WHO handrubs takes into account both cost constraints and microbiological efficacy. The procurement of raw ingredients will be influenced by the availability of sub-standard materials on the market and it is important to select local sources with care.

The following two alcohol-based handrub formulations are recommended for preparation in-house or in a local production facility, up to a maximum of 50 litres:

Formulation 1

To produce final concentrations of ethanol 80% v/v, glycerol 1.45% v/v, hydrogen peroxide (H_2O_2) 0.125% v/v.

Formulation 2

To produce final concentrations of isopropyl alcohol 75% v/v, glycerol 1.45% v/v, hydrogen peroxide (H_2O_2) 0.125% v/v:

Only pharmacopoeial quality reagents should be used (e.g. The International Pharmacopoeia) and not technical grade products.

Raw materials:

While alcohol is the active component in the formulations, certain aspects of other components should be respected. All raw materials used should be preferably free of viable bacterial spores. The raw materials for inclusion/consideration are listed in the table below:

H_2O_2	• The low concentration of H_2O_2 is intended to help eliminate contaminating spores in the bulk solutions and recipients and is not an active substance for hand antisepsis. • H_2O_2 adds an important safety aspect, however the use of 3–6% for the production might be complicated by its corrosive nature and by difficult procurement in some countries. • Further investigation is needed to assess H_2O_2 availability in different countries as well as the possibility of using a stock solution with a lower concentration.
Glycerol and other humectants or emollients	• Glycerol is added as a humectant to increase the acceptability of the product. • Other humectants or emollients may be used for skin care, provided that they are affordable, available locally, miscible (mixable) in water and alcohol, non-toxic, and hypoallergenic. • Glycerol has been chosen because it is safe and relatively inexpensive. Lowering the percentage of glycerol may be considered to further reduce stickiness of the handrub.
Use of proper water	• While sterile distilled water is preferred for making the formulations, boiled and cooled tap water may also be used as long as it is free of visible particules.
Addition of other additives	• It is strongly recommended that no ingredients other than those specified here be added to the formulations. • In the case of any additions, full justification must be provided together with documented safety of the additive, its compatibility with the other ingredients, and all relevant details should be given on the product label.
Gelling agents	• No data are available to assess the suitability of adding gelling agents to WHO-recommended liquid formulations, but this could increase potentially both production difficulties and costs, and may compromise antimicrobial efficacy.
Fragrances	• The addition of fragrances is not recommended because of the risk of allergic reactions.

All handrub containers must be labelled in accordance with national and international guidelines.

Procurement of components: key learning from around the world (based on feedback from the field)	
Ethanol	Easier to procure from local suppliers due to cost in some countries. • Can be derived from sugar cane or wheat. • Subject to licensing restrictions and strict record-keeping – an important consideration prior to embarking on production.
Isopropyl	Easier to procure in some countries.
Glycerol	Produced by local suppliers in most cases.
Hydrogen peroxide	Difficulties sourcing satisfactory H_2O_2 resulted in the need to import in five sites.

Production and storage

Manufacture of WHO-recommended handrub formulations is feasible in central pharmacies or dispensaries. Whenever possible and according to local policies, governments should encourage local production, support the quality assessment process, and keep production costs as low as possible. Special requirements apply for the production and stock piling of the formulations, as well as for the storage of the raw materials.

Because undiluted ethanol is highly flammable and may ignite at temperatures as low as 10°C, production facilities should directly dilute it to the concentrations detailed within this guide. (Refer to ***Summary table of risks and mitigation measures concerning the use of alcohol-based hand hygiene preparations***)

WHO is exploring the development of additional guidance on large-scale production to facilitate scale-up.

Production facilities and personnel: key learning from around the world (based on feedback from the field)	
Who are the main producers?	• Qualified pharmacists.
How much is produced?	• 10 litres to 600,000 litres per month was produced in test-sites.
Where does production occur?	• Hospital pharmacy. • National drug companies.
Production equipment	• Plastic, stainless steel and glass containers were used for mixing.
Dispensers for final product	• Ranges used: – 100 ml pocket bottles – 385 ml bottles – 500 ml wall-mounted dispensers – 1 litre wall mounted bottles or bags
Sources of dispensers	• Local sourcing can prove problematic, some countries had success working with local private sector suppliers.

Storage volumes:

Special requirements are applicable for the production and storage of the formulations, as well as the storage of the primary products. The quantity of locally-produced WHO handrub should not exceed 50 litres, or possibly less if regulated by local and/or national guidelines and regulations.

Cleansing and disinfection process for reusable handrub bottles:

1. Bring empty bottles to a central point for reprocessing by standard operational protocols;
2. Wash bottles thoroughly with detergent and tap water to eliminate any residual liquid;
3. If heat-resistant, thermally disinfect bottles by boiling in water. Whenever possible, thermal disinfection should be chosen in preference to chemical disinfection. The latter may increase costs and introduces an extra step to flush out the remains of the disinfectant. Chemical disinfection should include soaking the bottles in a solution containing 1000 ppm of chlorine for a minimum of 15 minutes and then rinsing with sterile/cooled boiled water;
4. After thermal or chemical disinfection, leave bottles to dry completely upside-down in a bottle rack. Dry bottles should be closed with a lid and stored, protected from dust, until use.

Quality Control:

If concentrated alcohol is obtained from local production, verify the alcohol concentration and make the necessary adjustments in volume to obtain the final recommended concentration. An alcoholmeter can be used to control the alcohol concentration of the final use solution; H_2O_2 concentration can be measured by titrimetry (oxydo-reduction reaction by iodine in acidic conditions). A higher level quality control can be performed using gas chromatography and the titrimetric method to control the alcohol and the hydrogen peroxide content, respectively. Moreover, the absence of microbial contamination (including spores) can be checked by filtration, according to the European Pharmacopeia specifications.

Quality control: key learning from around the world (based on feedback from the field)	
Method	• Local alcoholmeters used in majority of sites. • Seven sites sent samples to the University of Geneva Hospitals, Geneva, Switzerland, for quality checks by gas chromatography and the titrimetric method to control the alcohol and the hydrogen peroxide content.
Addition of fragrance	• Quality was optimal for three formulations in which either a fragrance or special humectants were added to WHO formulation I.
Extremes of climate	• Samples from Mali, which were kept in a tropical climate without air conditioning or special ventilation, were in accordance with the optimal quality parameters in all samples up to 19 months after production.

Distribution

To avoid contamination with spore-forming organisms, disposable bottles should preferably be used although reusable sterilizable bottles may reduce production costs and waste management. To prevent evaporation, containers should have a maximum capacity of 500 ml on ward and 1 litre in operating theatres, and ideally fit into a wall dispenser. Leakage-free pocket bottles with a capacity of no more than 100 ml should also be available and distributed individually to health-care workers, but it should be emphasized that the use of these products should be confined to health care only. The production or re-filling unit should follow norms on how to clean and disinfect the bottles (e.g. autoclaving, boiling, or chemical disinfection with chlorine). Autoclaving is considered the most suitable procedure. Reusable bottles should never be refilled until they have been completely emptied and then cleansed and disinfected.

Cleaning and recycling: key learning from around the world (based on feedback from the field)	
Cleaning and recycling of dispensers	• The cleaning and recycling process outlined in this document was applied in six sites. Methods used for disinfection varied and included treatment with chlorine or alcohol.

Cost issues:

The costs of WHO handrub formulations may vary according to country, resources and labour costs; studies to evaluate costs and resource use are necessary. As a comparison, examples of actual prices of commercially available alcohol-based handrubs in different countries are detailed within the Guidelines.

Costs: Key learning from around the world (based on feedback from the field)	
Production cost (including salaries but not the dispenser) per 100 ml	Formulation 1: • US$ 0.37 (Kenya) • US$ 0.30 (Mali) Formulation 2: • US$ 0.30 (Bangladesh).
Production cost (including the pocket bottle) per 100 ml	Formulation 1: • US$ 0.50 (Hong Kong) Formulation 2: • US$ 0.44 (Pakistan)
Range of cost of commercially available products per 100 ml	• US$ 2.50–5.40 (liquid) • US$ 8 (gel)

Safety Standards

With regard to skin reactions, handrubbing with alcohol based solutions is better tolerated than handwashing with soap and water. In a recent study conducted among ICU health-care workers, the short-term skin tolerability and acceptability of WHO-recommended handrub formulations were significantly higher than those of a reference product. Any additive should be as non-toxic as possible in case of accidental or intentional ingestion.

General Safety Issues:

The main safety issues relate to the flammability of alcohol-based handrubs and the adverse effects associated with accidental or deliberate ingestion. These are summarised in the ***Summary table of risks and mitigation measures concerning the use of alcohol-based hand hygiene preparations***.

Flammability – Flash-points:

The flash points of ethanol 80% (v/v) and isopropyl alcohol 75% (v/v) are 17.5°C and 19°C, respectively, and special attention should be given to proper storage in tropical climates. Production and storage facilities should be ideally air-conditioned or cool rooms. Open flames and smoking must be strictly prohibited in production and storage areas. Pharmacies and small-scale production centres supplying WHO-recommended handrub formulations are advised not to manufacture locally batches of more than 50 litres at a time.

Accidental ingestion:

In general, it is not recommended to add any bittering agents to reduce the risk of ingestion of the handrubs. Nevertheless, in exceptional cases where the risk of ingestion might be very high (paediatric or confused patients), substances such as methylethylketone and denatonium benzoate, added to some household products to make them less palatable, may be added to alcohol-based handrubs in order to reduce the risk of accidental or deliberate ingestion. However, there is no published information on the compatibility and deterrent potential of such chemicals when used in alcohol-based handrubs to discourage their abuse. It is important to note that such additives may make the products toxic and add to production costs. In addition, the bitter taste may be transferred from hands to food being handled by individuals using handrubs containing such agents. Therefore, compatibility and suitability, as well as cost, must be carefully considered before deciding on the use of such bittering agents.

A colorant may be incorporated to differentiate the handrub from other fluids as long as such an additive is safe and compatible with the essential components of the handrubs. However, the H_2O_2 in the handrubs may tend to fade any colouring agent used and prior testing is recommended.

Summary table of risks and mitigation measures concerning the use of alcohol-based hand hygiene preparations

Risk	Mitigation
Fire – general	• Do not produce in quantities exceeding 50 litres locally. If producing in excess of 50 litres, produce only in central pharmacies with specialized air conditioning and ventilation. • Since undiluted ethanol is highly flammable production facilities should directly dilute it to the concentrations outlined in this Guide. • Involve fire officers, fire safety advisers, risk managers, and health and safety and infection control professionals in risk assessments prior to embarking on system change • Risk assessment should take into account: – The location of dispensers – The storage of stock – The disposal of used containers/ dispensers and expired stock. • Store away from high temperatures or flames • Water or aqueous (water) film-forming foam (AFFF) should be used in case of fire; other types of extinguishers may be ineffective and may spread the fire over a larger area rather than put it out. • Health-care workers should be advised to rub hands until dry (once dry – hands are safe).
Fire – production and storage (central)	• Local and central (bulk) storage must comply with fire regulations regarding the type of cabinet and store, respectively. • Production and storage facilities should ideally be air-conditioned or cool rooms. • No naked flames or smoking should be permitted in these areas. • National safety guidelines and local legal requirements must be adhered to for the storage of ingredients and the final product. • Containers/dispensers should be stored in a cool place and care should be taken regarding the securing of tops/lids. • A designated 'highly flammables' store will be required for situations where it is necessary to store more than 50 litres. • Containers and dispenser cartridges containing handrub should be stored in a cool place away from sources of ignition. This applies also to used containers that have not been rinsed with water.

Risk	Mitigation
Fire – storage (local)	• The quantity of handrub kept in a ward or department should be as small as is reasonably practicable for day-to-day purposes.
Fire – disposal	• Rinse out used containers with copious amounts of cold water to reduce the risk of fire (the containers may then be recycled or disposed of in general waste).
Fire – location of dispensers	• Handrub dispensers should not be placed above or close to potential sources of ignition, such as light switches and electrical outlets, or next to oxygen or other medical gas outlets (because of the increased risk of vapours igniting).
Fire – spillage	• Significant spillages should be dealt with immediately by removing all sources of ignition, ventilating the area, and diluting the spillage with water (to at least 10-times the volume). • The fluid should then be absorbed by an inert material such as dry sand (not a combustible material such as sawdust), which should be disposed of in a chemical waste container. • Vapours should be dispersed by ventilating the room (or vehicle), and the contaminated item should be put in a plastic bag until it can be washed and/or dried safely.
Ingestion	• In areas where there is thought to be a high risk of ingestion, a staff-carried product is advised. • If a wall-mounted product is used, consideration should be given to small bottles. • If bottles with a greater capacity than 500 ml are used, consideration should be given to providing them in secured containers. • Product containers may be labelled simply as "antimicrobial handrubs" with a warning of dangers associated with ingestion. • National and local toxicology specialists should be involved in developing and issuing national/ local guidance on how to deal with ingestion (based on products available within a country).
Other	• Consideration should be given to the risks associated with spillage onto floor coverings, including the risk of pedestrian slips – it is important to deal with spillages immediately. • The siting of handrub dispensers above carpets is not recommended, because of the risk of damage and lifting/warping of carpets.