

Key Considerations for Procurers of 7.1% Chlorhexidine Digluconate for Umbilical Cord Care

When procuring 7.1% chlorhexidine digluconate for umbilical cord care, it is important to ensure that the chlorhexidine product is produced and packaged according to standard specifications. Product specifications include various product attributes (see Box 1 below). Well-written and complete specifications help ensure that purchased products are made with high-quality raw materials, produced under current good manufacturing practices (cGMP), tested according to international standards, packaged in compliance with national requirements, stored under conditions that do not compromise quality, and delivered to end users in good condition. This guidance document has been created to offer some key information to consider when procuring 7.1% chlorhexidine digluconate.

Box 1: Attributes to be included in product specifications

- **Description:** Generic name; Type of product; Intended use
- **Formulation (drug content):** active ingredients; excipients
- **Presentation:** Dosage form; Dosage size
- **Filling Volume** (as applicable)
- **Identification (markings):** Marking of product and labeling information required by regulatory authority in the country of origin and destination country, including a batch number.
 - Primary Packaging: Materials and description; Markings; Special labeling/logo (if desired)
 - Over packing (cartons): Materials and description; Markings
 - Exterior Packing (for shipping): Materials and description; Markings
- **Shelf Life:** In months or years; Stability/storage temperature; Months remaining upon receipt in-country; remaining number of months in the shelf life at the time of procurement
- **Printed Materials:** Language; Patient inserts; Physician inserts; Special instructions
- **Regulatory Requirements:** Any requirements for use in destination country, including required safety warnings that need to appear on the primary and secondary packaging.
- **Quality Assurance Requirements:** Pharmacopoeia standard (if applicable)
- **Shipment Documentation:** Test data; Certificate of Analysis; Regulatory certificates
- **Quality Compliance Provisions:** Pre-shipment inspection (of physical attributes); Pre-shipment sampling and testing (for analysis of suspect products)

It is good practice to consult with the national regulatory authority to ensure that the labeling information, patient information leaflet, and instructions for use are consistent with the requirements of the national regulatory authority. Such instructions should warn users to avoid putting 7.1% chlorhexidine digluconate product in the eyes or ears and to discard any remaining product after the specified period of use. Product packaging and labeling should be designed accordingly. Depending on the context, this may entail use of pictorial messages or icons on the primary packaging (e.g. tube or nozzle bottle) as well as including appropriate wording on instructions accompanying the product. In some settings, it may be appropriate to avoid forms of primary packaging that could easily be mistaken for eye or ear care products.

1

Select between the only two available dosage forms of 7.1% chlorhexidine digluconate: liquid or gel

Three randomized controlled trials in Nepal¹, Bangladesh², and Pakistan³ proved that applying liquid 7.1% chlorhexidine digluconate for umbilical cord significantly reduced neonatal mortality.⁴ The gel form of 7.1% chlorhexidine digluconate was proven to be just as effective as the liquid dosage form based on a non-inferiority study performed in Nepal.⁵ No other forms were included in the randomized controlled clinical studies or in subsequent bridging studies.

7.1% chlorhexidine digluconate may be available in other dosage forms such as cream or lotion. However, the human body might absorb chlorhexidine gluconate from these dosage forms differently than from the gel or liquid form. In addition, the shelf life and compatibility with other ingredients could be adversely affected when dosage forms are changed. For these reasons, drug regulatory agencies consider medicines in these non-tested dosage forms to be substantially different medical products, and thus they require additional clinical trials or bridging studies as well as stability and compatibility tests to prove that the new dosage form is equally as safe and efficacious as the original dosage form.

What can you do to make sure that you are buying a proven dosage form of 7.1% chlorhexidine digluconate?

- **Make sure that your tender documents specify that either liquid or gel is the dosage form for 7.1% chlorhexidine digluconate.**
- **If suppliers offer 7.1% chlorhexidine digluconate to you in a dosage form that is not gel or liquid:**
 - **Ask them what clinical evidence they have to prove that this different form is as safe and effective as the liquid or gel forms that were used in the randomized clinical trials or non-inferiority test.**
 - **Ask them if this dosage form (different from gel or liquid) has obtained market authorization in other countries and, if yes, where. Ask them to show you the documentation that states another country has registered this product for use for umbilical cord care.**

2

Make sure that the 7.1% chlorhexidine digluconate you are buying does not contain alcohol

The liquid and gel forms of 7.1% chlorhexidine digluconate in the three randomized clinical trials and in the non-inferiority study are water-based and do not contain any alcohol. Water-based product was used in these studies due to concern that use of alcohol might cause pain or a burning sensation in newborns. Further, topically applied products containing ethanol alcohol may cause percutaneous toxicity in the newborn.⁶ Because of this, it is recommended that 7.1% chlorhexidine digluconate for umbilical cord care not contain any alcohol.

What can you do to make sure that you are buying 7.1% chlorhexidine digluconate that does not contain alcohol?

- Check with suppliers to ascertain what inactive ingredients are contained in the 7.1% chlorhexidine digluconate solution being supplied to you. Drug regulations typically require pharmaceutical manufacturers to list names of inactive ingredients. However, if this information does not accompany the drug, ask the supplier to document that no alcohol is included in their product.

3

Make sure that the 7.1% chlorhexidine digluconate you intend to procure is produced by pharmaceutical manufacturers certified as compliant to WHO cGMP

Poor quality medicines are hazardous to health. It is therefore critical that medicines are consistently produced and that their quality is properly controlled according to appropriate quality standards. cGMP is a part of the quality assurance system. It covers all aspects of production—including raw materials, manufacturing facility and equipment, and ensuring the training and personal hygiene of staff—in order to guarantee the production and quality control of medicines in a consistent manner. Pharmaceutical manufacturers are required to comply with this practice by the drug regulatory authorities in both developed and developing countries. If 7.1% chlorhexidine digluconate is not manufactured by pharmaceutical companies that are compliant with WHO cGMP, infants could be exposed to the following risks:

1. Health hazards due to contamination of either active or inactive ingredients, or both.
2. Using the medicine in the wrong way due to incorrect or lack of information on the label.
3. Ineffective treatment or adverse effects due to either insufficient or excessive active ingredients.

What can you do to mitigate risks?

- Ask suppliers if they are certified with WHO cGMP. You might also want to consider whether the product is manufactured in facilities inspected and certified by internationally recognized organizations.
- Ensure the product is accompanied by a certificate of analysis (COA).
- If suppliers are providing the liquid form ask them if they have tested the product using monographs of the United States Pharmacopeial Convention before they released the product. If suppliers are providing the gel form, ask them if they have a validation method and have it checked by your national regulatory authority.
- Test the product at a WHO-prequalified quality control laboratory (http://apps.who.int/prequal/lists/PQ_QCLabsList.pdf) or laboratory accredited by your country's national regulatory agencies at the time of receipt against the COA.

The Chlorhexidine Working Group

This material represents a collaborative effort of the Chlorhexidine Working Group (CWG). The CWG is a group of organizations committed to advancing chlorhexidine for umbilical cord care.

For more information about chlorhexidine for umbilical cord care, please visit the chlorhexidine technical resource page on the Healthy Newborn Network site:

<http://www.healthynewbornnetwork.org/issue/chlorhexidine-for-umbilical-cord-care/>

¹ Mullany L, Darmstadt G, Khatri SK, et al. Topical applications of chlorhexidine to the umbilical cord for prevention of omphalitis and neonatal mortality in southern Nepal: a community-based, cluster-randomised trial. *The Lancet*. 2006; 367(9514): 910-918.

² El Arifeen S, Mullany L, Shah R, et al. The effect of cord cleansing with chlorhexidine on neonatal mortality in rural Bangladesh: a community-based, cluster-randomised trial. *The Lancet*. 2012; 379(9820): 1022-1028.

³ Soofi S, Cousens S, Imdad A, Bhutto N, Ali N, Bhutta Z. Topical application of chlorhexidine to neonatal umbilical cord for prevention of omphalitis and neonatal mortality in rural district of Pakistan: a community-based, cluster-randomized trial. *The Lancet*. 2012; 379(9820): 1029-1036.

⁴ Imdad A, Mullany L, Baqui A, et al. The effect of umbilical cord cleansing with chlorhexidine on omphalitis and neonatal mortality in community settings in developing countries: a meta-analysis. *BMC Public Health*. 2013; 13(suppl 3): S15

⁵ Hodgins S, Thapa K, Khanal L, Aryal S, Suveda BK, Baidya U, Mullany L. Chlorhexidine gel versus aqueous for preventative use on umbilical stump: a randomized noninferiority trial. *Pediatric Infectious Disease Journal*. 2010; 29(11): 999-1003.

⁶ Lachenmeier, Dirk W. Safety evaluation of topical applications of ethanol on the skin and inside the oral cavity. *J Occup Med Toxicol*. 2008; 3.1: 26-41.

