

Production Strategy: 7.1% Chlorhexidine Digluconate for Umbilical Cord Care

Selecting the right strategy to increase the availability of a quality, affordable medicine to reduce neonatal mortality

Key Facts and Background

- In January 2014, the World Health Organization (WHO) issued a new guideline for umbilical cord care:
“Daily chlorhexidine (7.1% chlorhexidine digluconate aqueous solution or gel, delivering 4% chlorhexidine) application to the umbilical cord stump during the first week of life is recommended for newborns who are born at home in settings with high neonatal mortality (30 or more neonatal deaths per 1000 live births). Clean, dry cord care is recommended for newborns born in health facilities and at home in low neonatal mortality settings. Use of chlorhexidine in these situations may be considered only to replace application of a harmful traditional substance, such as cow dung, to the cord stump.”
- 7.1% chlorhexidine digluconate aqueous solution (liquid) was proven to be sufficiently potent as an antiseptic based on three randomized controlled trials in South Asia.^{1,2,3} A gel form of 7.1% chlorhexidine digluconate was proven to be as effective as the liquid form based on a non-inferiority study performed in Nepal.⁴
- In July 2013, 7.1% chlorhexidine digluconate (delivering 4% chlorhexidine) for umbilical cord care, in both gel and liquid formats, was included in the WHO Model List of Essential Medicines for Children (EMLc) under Specific Medicines for Neonatal Care. This is a higher concentration than the 5% chlorhexidine digluconate (delivering 2.8% chlorhexidine) which is listed on the EMLc as an antiseptic.
- 7.1% chlorhexidine digluconate is specifically formulated for cord care and is different from other pharmaceutical and non-pharmaceutical products containing chlorhexidine digluconate, such as presurgical and oral antiseptics, surface disinfectants, and hand sanitizers.
- 7.1% chlorhexidine digluconate is a topical medicine for newborns. It should conform to the US Pharmacopeial Convention (USP) standards and be manufactured and marketed by pharmaceutical companies in compliance with good manufacturing practices (GMP) and according to applicable local regulations.

Local Production to Increase Availability

There are multiple strategies to establish the supply of product. Local production is one of them. Local production is defined as production in low- and middle-income countries (LMICs) by locally owned companies or subsidiaries of multinational companies. The potential benefits of local production include improvement in reliability of supply, foreign import savings, development of further innovation capacity, creation of enhanced export capacity, and development of human capital. Local production of high-quality medicines could also lead to cost savings and improvement in product quality, depending on the product to be produced and regular surveillance of LMICs' quality control issues.⁵ Furthermore, local production allows products to be better adapted to local cultural preferences. The product profile of 7.1% chlorhexidine digluconate is conducive to local production because 7.1% chlorhexidine digluconate for cord care does not require proprietary active pharmaceutical ingredients (API), equipment, or process for manufacturing.

Choosing the Right Strategy

Several factors must be taken into account when considering whether local production of 7.1% chlorhexidine digluconate would be an optimal option for LMICs to increase availability of the quality product at affordable prices (see Checklist, page 5). In certain situations, local production may not be the right choice. These situations include:

1. The pharmaceutical industry in the country is weak and pharmaceutical manufacturers in the country are not capable of:
 - a. Producing 7.1% chlorhexidine digluconate in GMP-compliant manufacturing facilities.
 - b. Performing quality control tests on the finished product in an adequately equipped laboratory.
2. The regulatory system in the country is inadequate and is unable to provide market authorization (known as product registration or regulatory approval) on the finished products based on proper dossier reviews and product testing.
3. Policy and regulations are not supportive of local production. The pharmaceutical industry heavily relies on imported raw materials, including API, excipients, and materials for primary and secondary packaging. Without supportive import regulations for raw materials, for example, locally produced 7.1% chlorhexidine digluconate will be more expensive than importing it.
4. The market size for 7.1% chlorhexidine digluconate in the country is too small to justify local production (either the cost to purchase and deliver the API to the country becomes too high and/or the price of the finished product becomes too high when the production quantity is too small).

Under one or more of these circumstances, the alternative would be to import 7.1% chlorhexidine digluconate from a country in the region or elsewhere.

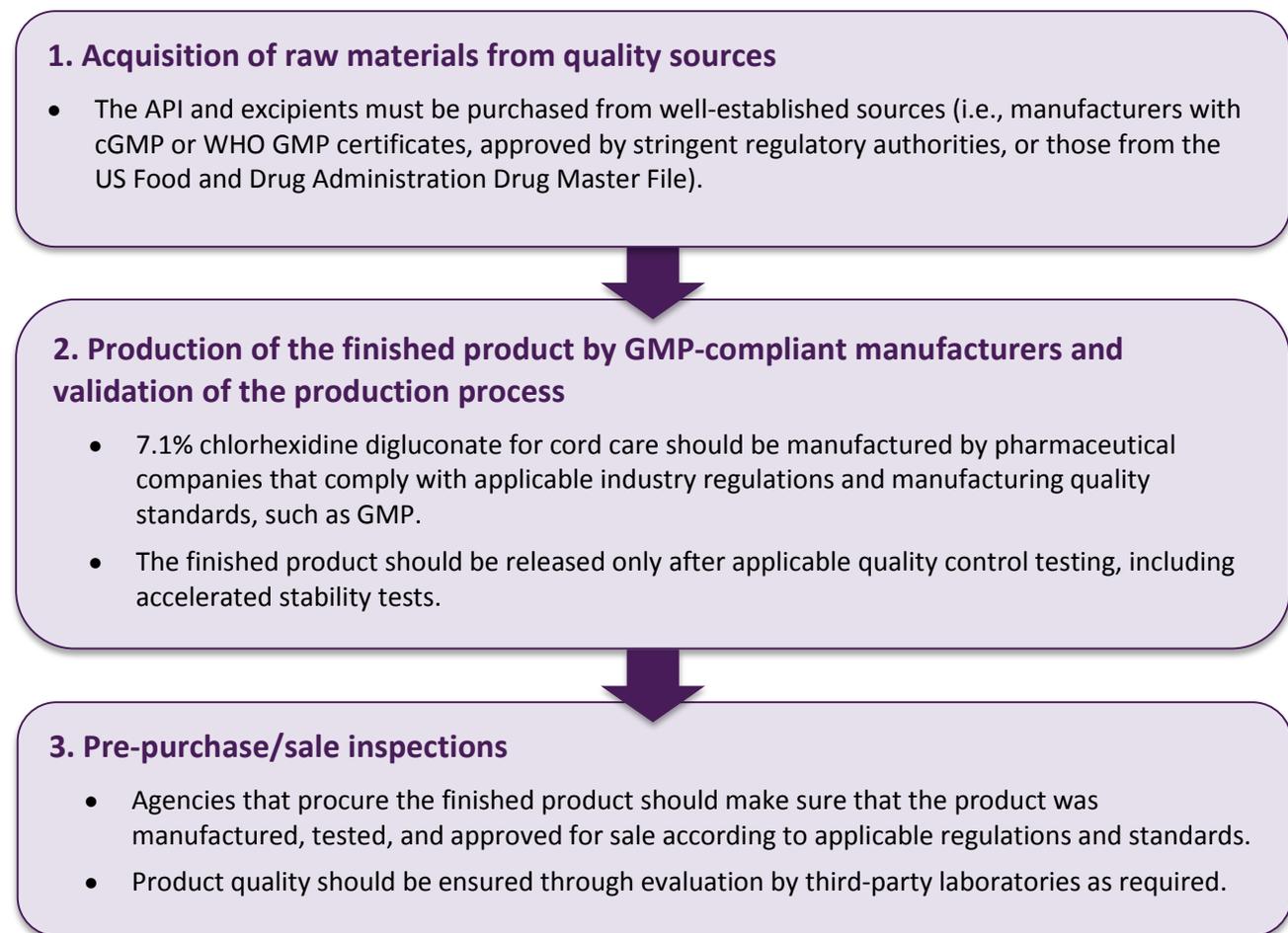
Currently there are these sources for purchasing 7.1% chlorhexidine digluconate for cord care:

- A gel product, branded Chlorxy-G, can be purchased from [Drugfield Pharmaceuticals Ltd.](#) in Nigeria.
- A gel product, branded Kawach, can be purchased from [Lomus Pharmaceutical Pvt. Ltd.](#) in Nepal.
- A gel product can be purchased from [Universal Corporation Ltd.](#) in Kenya.
- A liquid product, branded Hexicord, can be purchased from [ACI Limited](#) in Bangladesh.
- A liquid product can be purchased from the United Nations Children's Fund [Supply Division Catalogue](#), product number S1531515.

Ensuring Product Quality

Whichever strategy is chosen, the goal is to achieve an increased availability of the “quality” product at affordable pricing. The United Nations Commission on Life-Saving Commodities for Women and Children⁶ calls for pharmaceutical companies that manufacture 7.1% chlorhexidine digluconate for cord care to (1) have GMP certificates and (2) purchase the API from quality manufacturers, especially those compliant with the most current GMP (cGMP). In line with this, the quality of 7.1% chlorhexidine digluconate for cord care would be ensured through three layers: (1) acquisition of raw materials from quality sources, (2) production of the finished product by GMP-compliant manufacturing facilities, and (3) pre-purchase/sales inspections by third-party laboratories when required (see Figure 1).

Figure 1: Quality assurance through three stages.



Resources

For more information about chlorhexidine for umbilical cord care

Please visit the chlorhexidine for umbilical cord care technical resource page on the Healthy Newborn Network site at: <http://www.healthynewbornnetwork.org/page/chlorhexidine-umbilical-cord-care-resource-page>

The Chlorhexidine Working Group

The Chlorhexidine Working Group (CWG) is an international collaboration of organizations committed to advancing the use of 7.1% chlorhexidine digluconate (delivering 4% chlorhexidine) for umbilical cord care through advocacy and technical assistance.

Members include individuals representing:

- PATH [CWG Secretariat]
- ayzh
- Bill & Melinda Gates Foundation
- Boston University
- Burnet Institute
- Centre for Infectious Disease Research in Zambia
- Clinton Health Access Initiative
- Drugfield Pharmaceuticals Ltd. (Nigeria)
- Duke University:
 - o Global Health Institute
 - o Center on Globalization, Governance & Competiveness
- GSK (UK)
- Global Health Action
- Jhpiego
- John Snow, Inc.
- Johns Hopkins Bloomberg School of Public Health
- Lomus Pharmaceuticals Pvt. Ltd. (Nepal)
- Maternal Child Survival Program
- PSI
- Promoting the Quality of Medicines/ United States Pharmacopeia
- Save the Children/Saving Newborn Lives
- Systems for Improved Access to Pharmaceuticals and Services/Management Sciences for Health
- United Nations Children’s Fund
 - o Programme Division
 - o Supply Division
- United States Agency for International Development
- Universal Corporation Ltd. (Kenya)
- University of Illinois at Chicago School of Nursing
- World Health Organization

¹ Mullany LC, Darmstadt GL, 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-randomized trial. *Lancet*. 2006; 367(9514):910–918.

² Arifeen SE, Mullany LC, Shah R, et al. The effect of cord cleansing with chlorhexidine on neonatal mortality in rural Bangladesh: A community-based, cluster-randomized trial. *Lancet*. 2012;379(9820):1022–1028.

³ Soofi S, Cousens S, Imdad A, et al. Topical application of chlorhexidine to neonatal umbilical cords for prevention of omphalitis and neonatal mortality in a rural district of Pakistan: a community-based, cluster-randomized trial. *Lancet*. 2012; 379(9820):1029–1036.

⁴ Hodgins S, Thapa K, Khanal L, et al. Chlorhexidine gel versus aqueous for preventive use on umbilical stump: A randomized noninferiority trial. *Pediatric Infectious Disease Journal*. 2010; 29(11):999–1003.

⁵ Kaplan W, Ritz L, Vitello M. Local production of medical technologies and its effect on access in low and middle income countries: a systematic review of the literature. *Southern Med Review*. 2011; 4(2):4–14.

⁶ Every Woman Every Child. *UN Commission on Life-Saving Commodities for Women and Children Implementation Plan*. 2012. Available at: http://www.everywomaneverychild.org/images/Implementation_plan_Sept_2012.pdf.

Checklist for Production Decision-Making

Questions	Yes/No	Resources available from the Chlorhexidine Working Group
Capability and capacity of pharmaceutical companies		
Are there any pharmaceutical manufacturers in your country that have a good manufacturing practices (GMP) certificate issued by the local regulatory authority and have a manufacturing license for their current products?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Are there any pharmaceutical manufacturers in your country that already produce topical medicines in liquid or gel form?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Is the existing capability of pharmaceutical manufacturers adequate for manufacturing 7.1% chlorhexidine digluconate for cord care? <i>[Note: The adequacy of manufacturing capability should be assessed by trained GMP auditors].</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<ul style="list-style-type: none"> • US Pharmacopeia monographs for the finished products (liquid and gel forms) • Manufacturers' Guide • List of laboratories that can test the quality of the finished product
Are pharmaceutical manufacturers knowledgeable about where to obtain quality active pharmaceutical ingredients (API), excipients, and other raw materials?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<ul style="list-style-type: none"> • List of quality sources for the API
Do these pharmaceutical manufacturers have a good record of financial stability over time? <i>[Note: Financial statements over the past 3 to 5 years could be used as verification.]</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Given the domestic market size for 7.1% chlorhexidine digluconate, are there pharmaceutical companies willing to sell the product to public-sector purchasers at affordable prices?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<ul style="list-style-type: none"> • Market sizing estimation tool
Affordability		
Given the domestic market size for 7.1% chlorhexidine digluconate for cord care, can the API, excipients, and other materials be obtained from quality sources at reasonable costs?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
(If the API is imported) Do the tax and import duties for the API significantly affect the price of the finished product?	<input type="checkbox"/> Yes <input type="checkbox"/> No	

Questions	Yes/No	Resources available from the Chlorhexidine Working Group
Can 7.1% chlorhexidine digluconate for cord care be produced more inexpensively locally than importing a 7.1% chlorhexidine digluconate product? [Note: Price and cost associated with importing a product from Lomus Pharmaceuticals or purchasing from United Nations Children’s Fund Supply Division Catalogue can be used as a bench mark].	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Sustainability		
Are pharmaceutical manufacturers able to sustain the supply of 7.1% chlorhexidine digluconate given the domestic market size, product pricing, and cost of production of the product?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<ul style="list-style-type: none"> Market sizing estimation tool
<i>If the domestic market size is too small to sustain the supply:</i>		
Are there viable markets in neighboring countries into which the 7.1% chlorhexidine digluconate could be exported?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Are there any trade zones or regulations that could facilitate the export of 7.1% chlorhexidine digluconate for cord care while maintaining affordable end-user pricing?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Are pharmaceutical manufacturers in your country able to meet any larger regional demand?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Are pharmaceutical companies in your country capable of exporting and marketing medicines to neighboring countries?	<input type="checkbox"/> Yes <input type="checkbox"/> No	

The Checklist for Production Decision-Making was developed based on information obtained from the following sources:

Guimier J, Lee E, Grupper M. *Process and Issues for Improving Access to Medicine: The evidence base for domestic production and greater access to medicines*. London: DIFID Health Systems Resources Center; 2004. Available at: [http://www.who.int/3by5/capacity/4\)processes_issues_improvingaccess.pdf](http://www.who.int/3by5/capacity/4)processes_issues_improvingaccess.pdf).

Kaplan W. *Local Production and Access to Medicines in Low and Middle Income Countries: A literature review and critical analysis*. Geneva: World Health Organization; 2011. Available at: <http://apps.who.int/medicinedocs/documents/s19061en/s19061en.pdf>.

Bate R. *Local Pharmaceutical Production in Developing Countries: How economic protectionism undermines access to quality medicine*. London: International Policy Network; 2008. Available at: http://www.policynetwork.net/sites/default/files/local_drug_production.pdf.

Kaplan W, Laing R. *Local Production of Pharmaceuticals: Industrial Policy and Access to Medicines*. Washington, DC: The International Bank for Reconstruction and Development/The World Bank; 2005. Available at: http://www.who.int/medicines/technical_briefing/tbs/KaplanLocalProductionFinal5b15d.pdf.