Promoting the
QUALITY OF MEDICINES Plus

Importance of controlling the 4-Chloroaniline impurity in Chlorhexidine active pharmaceutical ingredient and gel product

Technical Brief

September 2022

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This document is made possible by the generous support of the American people through the U.S. Agency for International Development (USAID) Cooperative Agreement No. AID-7200AA19CA00025. The contents are the responsibility of U.S. Pharmacopeial Convention (USP) and do not necessarily reflect the views of USAID or the United States Government.

About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a five-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

Suggested Citation

PQM+.2022. Technical Briefing: Controlling Impurity in Chlorhexidine Gluconate (7.1%) Gel. Submitted to the U.S. Agency for International Development by the PQM+ Program. Rockville, MD: U.S. Pharmacopeial Convention.

Contents

Acronyms

4CA	4-chloroaniline
API	active pharmaceutical ingredient
CAPA	corrective and preventive action
CHMP	Committee for Medicinal Products for Human Use
CHX	chlorhexidine
CQA	critical quality attribute
EPAR	European Public Assessment Report
FPP	finished pharmaceutical product
GMP	good manufacturing practice
GSK	GlaxoSmithKline
LMICs	low- and middle-income countries
NMRA	national medicines regulatory authority
NMT	not more than
PQM	Promoting the Quality of Medicines
PQS	pharmaceutical quality system
UN	United Nations
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Introduction

About three-quarters (75 percent) of all neonatal deaths occurs during the first week of life, contributing to the approximately 6,700 newborn deaths every day globally. Infections are a key cause. One source of infection is the newly cut umbilical cord, as it becomes an entry point for bacteria that can lead to newborn infection, sepsis, and death.[1] Umbilical cord infections are more likely to occur in lower- and middle-income countries (LMICs) across Africa and South Asia, where a high proportion of births take place at home without a skilled birth attendant.

In response to the 2012 Commissioner's Report from the U.N. Commission on Life-Saving Commodities for Women and Children,[2] GlaxoSmithKline (GSK) reformulated Corsodyl mouthwash into chlorhexidine (CHX) antiseptic gel to prevent bacterial infection.[3] The drug substance has an antimicrobial activity that is widely used in pharmaceutical and cosmetic products. Its salt form, chlorhexidine digluconate (7.1%), is formulated and marketed by GSK as a CHX gel under the trade name Umbipro. The product is for prophylaxis against omphalitis, an infection of the umbilical cord stump in communities where health care resources are limited. The product is used on the umbilical cord stump to prevent neonatal infections in accordance with the World Health Organization (WHO) guidance which recommends the daily application of 4% chlorhexidine (7.1% chlorhexidine digluconate aqueous solution or gel, delivering 4% chlorhexidine) to the umbilical cord stump in the first week after birth only in settings where harmful traditional substances (e.g., animal dung) are commonly used on the umbilical cord.[4]

The Promoting the Quality of Medicines Plus (PQM+) program (and its predecessor, PQM), funded by the U.S. Agency for International Development (USAID) and implemented by the U.S. Pharmacopeial Convention (USP), contributes technical support to local manufacturers and national medicines regulatory authorities (NMRAs) in LMICs. One goal is to increase access to quality-assured CHX products to reduce preventable deaths in resource-limited communities using non-hygienic traditional practices that may result in neonatal infections.

USP has been in discussion with GSK about plans to discontinue production of Umbipro and ways to secure a supply of generic CHX. In collaboration with GSK, USP published the Chlorhexidine Digluconate (7.1%) Gel Technology Transfer report in 2019[5] to support the local production of CHX in LMICs and chlorhexidine 7.1% gel. In addition, a CHX job aid[6] to help laboratory testing and CHX gel monograph to control product specifications were published in USP's Global Public Health Monograph.

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[1] WHO. Newborns: improving survival and well-being: A new, low-cost intervention to reduce newborn mortality. PATH for the Chlorhexidine Working Group. https://www.who.int/news-room/fact-sheets/detail/newborns-reducing-mortality#:~:text=In%202019%2C%2047%25%20of%20all,the%20first%20week%20of%20life.

[2] U.N. Commission on Life-Saving Commodities for Women and Children. Commissioners' Report. September 2012. https://www.unfpa.org/sites/default/files/pub-pdf/Final%20UN%20Commission%20Report_14sept2012.pdf

[3] Surviving the first day: State of the world's mothers 2013. Save the Children. May 2013. https://www.savethechildren.org/content/dam/usa/reports/advocacy/sowm/sowm-2013.pdf

[4] World Health Organization. *WHO recommendations on postnatal care of the mother and newborn.* Geneva: World Health Organization (2022).

[5] PQM. GSK Chlorhexidine Digluconate (7.1%) Gel Technology Transfer Report. 2018. U.S. Pharmacopeial Convention. The Promoting the Quality of Medicines Program. Rockville, MD. https://www.usp-pqm.org/sites/default/files/pqms/article/gsk-chx-gel-tech-transfer-report-6-20-2019.pdf

[6] PQM+. 2020. Chlorhexidine Gel 7.1% gel job aid to assist with laboratory testing. Submitted to the U.S. Agency for International Development by the PQM+ Program. Rockville, MD: U.S. Pharmacopeial Convention.

The purpose of this technical briefing report is to increase awareness and understanding of the existing available quality resources of CHX and provide recommendations to address gaps for future technical support for a sustainable supply of quality-assured CHX products.

Chlorhexidine Quality Assurance

Technical Support

For quality assurance of locally produced CHX to be sustainable, local manufacturers and regulators must be aware of ongoing updates on critical quality attributes (CQAs) to ensure product quality. In collaboration with manufacturers and implementing partners, PQM provided technical support to manufacturers and regulators on the quality assurance of 7.1% chlorhexidine gluconate. These activities included publication of a technology transfer report that helped improve product quality and contributed to subsequent approval of the product from manufacturers in Nigeria, Ethiopia, Bangladesh, and Pakistan, where newborn deaths from infections constitute a major public health challenge.

The 4CA Impurity Concern

The lack of proper quality control of CHX active pharmaceutical ingredient (API) and product safety in resource-limited countries is a growing concern. The primary safety considerations are associated with the impurity profile, specifically 4CA, which has shown genotoxic and carcinogenic effects in nonclinical studies. Hydrolysis is believed to be a primary contributing factor for the generation of 4CA during production of the finished pharmaceutical product (FPP).[7] During hydrolysis, chlorhexidine digluconate experiences multiple degradation pathways and generates a range of impurities. The 4CA impurity increases with time, temperature, and product pH.

Control of 4CA Impurity

In addition to controlling the level of impurity in the drug substance, it is important to monitor the level of 4CA during manufacturing of the FPP to ensure that it remains within the monograph limits. Based on the intrinsic CHX drug substance's propensity to degrade, FPP manufacturers need to take the following measures: monitor the API pH; control and monitor in-process pH; select neutral excipients to protect API from hydrolysis; monitor storage conditions (temperature and humidity) during production operation as per good manufacturing practice (GMP) requirements; tighten the limit of 4CA at release; and maintain the product within monograph limits throughout its shelf-life. In addition to testing, it is recommended that manufacturers conduct comprehensive risk assessments from the perspective of personnel operation, premises, equipment, environment, and any materials used during manufacturing operation that impact 4CA generation. According to the European Public Assessment Report (EPAR) for Umbipro approval for use, the specification limits for 4CA were considered justified, but the Committee for Medicinal Products for Human Use (CHMP) recommended reviewing the limit once 30 commercial batches of the product were manufactured and released by GSK. However, GSK discontinued Umbipro before marketing 30 batches.

[7] PQM. GSK Chlorhexidine Digluconate (7.1%) Gel Technology Transfer Report. 2018. U.S. Pharmacopeial Convention. The Promoting the Quality of Medicines Program. Rockville, Maryland

Recommendations

It is important to increase awareness and build the capacity of manufacturers and regulators to control 4CA in the product to safeguard the public from the risks of this carcinogenic impurity. Recommended steps include:

- Increase awareness to understand the need and approach to minimize and control 4CA impurity in CHX product.
- Work with manufacturers to improve manufacturing premises, quality systems, air handling, purified water, major production equipment, and the validation of manufacturing process, all of which play a critical role in reducing the generation of 4CA.
- Provide technical support toward qualification/validation of analytical methods for the control of 4CA.
- Continue to work with local manufactures and NMRAs on implementing corrective and preventive actions (CAPA) and the CHX monograph to improve product quality and bring local manufacturers in compliance with GMP requirements.

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