

WHO/UNICEF/UNFPA JOINT STATEMENT

Appropriate Storage and Management of Oxytocin – a Key Commodity for Maternal Health

The World Health Organization (WHO), United Nations Children’s Fund (UNICEF) and United Nations Population Fund (UNFPA), in consultation with international experts and stakeholders, underscore the importance of ensuring the availability of quality-assured oxytocin at all assisted births to save women’s lives. This recommendation results from an exhaustive review of current evidence around oxytocin, particularly the finding that poor quality oxytocin is in circulation in many countries.

These partners strongly urge the following actions:

1. Ensure that oxytocin is managed in a cold chain of 2-8 °C (35-46 °F) for distribution and storage;
2. Procure oxytocin that meets the quality requirements established by WHO or a regulatory authority recognized by WHO;
3. Label oxytocin to clearly indicate storage and transport requirements at 2-8 °C (35-46 °F).

OVERVIEW

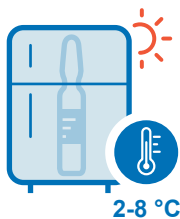
Postpartum haemorrhage is an emergency medical condition that affects approximately 5% of women who give birth each year, accounting for more than 70,000 maternal deaths annually. The highest proportion of these deaths occur in low- and middle-income countries (LMIC).¹ Postpartum haemorrhage-related deaths could be avoided through the use of prophylactic uterotonics during the third stage of labour, as well as by timely and appropriate management.²

According to *WHO Recommendations for the prevention and treatment of postpartum haemorrhage*, oxytocin is the first choice uterotonic for preventing and treating postpartum haemorrhage.² Oxytocin is an inexpensive, generic drug that is included in the WHO Model List of Essential Medicines.³

Several studies confirm that oxytocin currently circulating in many LMICs frequently fails to meet acceptable quality standards.^{4,5} Like vaccines, when oxytocin is not of sufficient quality or when it is not managed in cold chain, the medicine will rapidly degrade and become ineffective.⁶

Three urgent actions

Building upon the work of the United Nations Commission on Life-Saving Commodities for Women and Children, WHO, UNICEF and UNFPA agreed to issue this statement, including a request for three specific actions to ensure effective management of and access to good quality oxytocin.



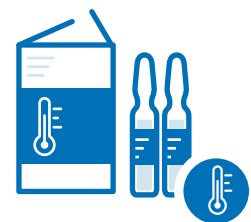
2-8 °C

1. Supply chains managers should ensure that oxytocin is maintained at 2-8 °C (35-46 °F)



Quality assured

2. Procurers and distributors of oxytocin should ensure that specifications clearly reference appropriate quality standards and requirements, including appropriate labelling for storage at 2-8 °C (35-46 °F)



2-8 °C

3. Medicine regulators should support and enforce labelling and marketing to reflect appropriate cold chain maintenance at 2-8 °C (35-46 °F)

Three urgent actions

1. Supply chains managers should ensure that oxytocin is maintained at 2-8 °C (35-46 °F)

While some manufacturer labelling continues to indicate that oxytocin is stable at ambient temperatures, the data supporting these claims may not be sufficiently conclusive or applicable to some climates. Consistent product management is critical and the general practice for all oxytocin products should be to store and transport at 2-8 °C (35-46 °F). Further WHO guidance on storage and transport of time- and temperature-sensitive pharmaceutical products can be found in the WHO Technical Report Series, No.961, 2011, Annex 9.^{12,13}

2. Procurers and distributors of oxytocin should ensure that specifications clearly reference appropriate quality standards and requirements, including appropriate labelling for storage at 2-8 °C (35-46 °F)

Procurers should ensure oxytocin is specified according to a recognized pharmacopeia and that appropriate labelling is a condition for procurement.

Where feasible, oxytocin should be from sources that are either WHO prequalified or approved by a recognized regulatory authority.⁷ If these sources are not available, at a minimum, the product should be manufactured in compliance with Good Manufacturing Practices as well as internationally recognized pharmacopoeial standards. Examples include: British Pharmacopeia, International Pharmacopeia, US Pharmacopeia, and Japanese Pharmacopeia.

3. Medicine regulators should support and enforce appropriate labelling and marketing to reflect correct cold chain maintenance at 2-8 °C (35-46 °F)

To promote improved and consistent management of oxytocin, as discussed above, it is essential that labels specify that oxytocin be maintained throughout transport and storage at 2-8 °C (35-46 °F) and that medicine regulatory authorities enforce this.

Manufacturers must label oxytocin products in a manner that reflects long-term stability studies covering storage, shipment and subsequent use in varying climates. To avoid confusion within the supply chain, WHO recommends that the results of accelerated stability studies permitting excursions for limited time periods are NOT included on oxytocin product labels. WHO Prequalification only accepts submissions for products with appropriate cold chain labels.¹⁴

EFFORTS TO DATE

Prequalification of oxytocin

To support national and global efforts to increase access to quality oxytocin, WHO, together with UNFPA, accepts submissions from manufacturers for WHO Prequalification of oxytocin.

A list of prequalified oxytocin sources is available online and updated regularly. Guidelines from WHO Prequalification on acceptable oxytocin products are also available.⁷

Research and evidence

Oxytocin has been shown to be a heat-sensitive product that requires refrigeration during transport, distribution, and storage at all points in the supply chain.⁸ While short excursions beyond 2-8 °C (35-46 °F) may not compromise the quality of the product, longer-term storage and distribution at a wide variety of ambient temperatures (e.g. warehouses without temperature control) are likely to result in product degradation and ineffective treatment.^{6,9} Countries with tropical climates, where the average daily temperature is above 30 °C (86 °F), are at particular risk for oxytocin failures if it is not maintained in an appropriate cold chain. One study showed that oxytocin can tolerate freeze-thaw cycles, however, data on long-term exposure to freezing temperatures were not found and freezing oxytocin should therefore be avoided.¹⁰

Joint Statement of 2015: Temperature-sensitive health products in the Expanded Programme on Immunization cold chain

Whether oxytocin is integrated into the cold chain of the Expanded Programme on Immunization (EPI) or other cold chains, a prior WHO/UNICEF joint statement in 2015 on the integration of cold chain products into the immunization cold chain remains an important reference. The 2015 joint statement featured integration of oxytocin as the main case study and provides important information for developing an integration plan that addresses good storage practices and other technical details, such as clear labelling and separation of non-vaccine products from vaccines and diluents.¹¹ A careful review of cold chain capacities may be needed in some countries, recognizing that increased need for cold chain capacity may actually include a more extensive list of products, such as daily-use insulin.

Conclusion

These recommendations will require intensified stewardship and accountability among national governments, global stakeholders, manufacturers, procurement agencies, supply chain managers (including those responsible for the EPI cold chain), maternal health programmes and health providers. The current evidence on compromised oxytocin quality will need to be widely disseminated. The implications of operationalizing the actions will also need to be considered, including increased investments in policy change, capacity building, information systems, infrastructure and other areas.

Heat-stable uterotonic alternatives to oxytocin are under exploration. Until these products are ready to be taken to scale, and even then, the quality of oxytocin currently in circulation must be assured to reduce the number of women who die while giving birth.

This joint statement urges stakeholders to implement these three specific actions. As with any guidance, its implementation will need to be supported and will need to accommodate and manage any unintended effects.

To ensure effective implementation, the way forward should also encourage:

stakeholders to work together to implement and monitor progress towards the three actions, especially supporting countries that have limited capacity to ensure the quality of oxytocin and its effective management;

oxytocin manufacturers to submit their products through the WHO Prequalification Process, leveraging WHO support to national governments to access quality oxytocin;

pharmaceutical managers to support studies on cold-chain expansion strategies to accommodate oxytocin as well as increased demand for other cold chain products;

technical agencies to align across technical resources, such as pharmacopoeia, to ensure that standards for quality oxytocin are clear and consistent; and

international agencies to support National Medicines Regulatory Authorities to assess oxytocin dossiers and manufacturing sites and to monitor the quality of oxytocin in circulation.

References

1. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health* 2014; 2(6): e323-33.
2. WHO recommendations: Uterotonics for the prevention of postpartum haemorrhage. Geneva: World Health Organization, 2018.
3. WHO Model List of Essential Medicines. Geneva, 2017.
4. WHO/PQ. Survey of the Quality of Medicines Identified by the UN Commission on Life-Saving Commodities for Women and Children. Geneva: World Health Organization, 2015.
5. Tortoni M, Gomes Freitas C, Kartoglu U, Metin Gülmezoglu A, Widmer M. Quality of oxytocin available in low- and middle-income countries: A systematic review of the literature. *BJOG: An International Journal of Obstetrics and Gynaecology* 2016.
6. Hogerzeil HV, Walker GJA, de Goeje MJ. Stability of injectable oxytocins in tropical climates: results of field surveys and simulation studies on ergometrine, methylethergometrine and oxytocin. Geneva: World Health Organization, 1993.
7. WHO. Essential Medicines and Health Products: Prequalification of medicines. 2018. <https://extranet.who.int/prequal/information/manufacturers>.
8. WHO. The International Pharmacopoeia, Eight Edition, 2018. 2018. <http://apps.who.int/phint/en/p/about/>.
9. Kartoglu U, Widmer M, Gulmezoglu M. Stability of oxytocin along the supply chain: A WHO observational study. *Biologicals: journal of the International Association of Biological Standardization* 2017.
10. Nassta GC, Pranker RJ, McIntosh MP. Effect of freezing on oxytocin ampules. *N Engl J Med* 2013; 368(22): 2145-6.
11. WHO/UNICEF Joint statement. Temperature-sensitive health products in the Expanded Programme on Immunization cold chain. Available at [https://www.unicef.org/health/files/EPI_cold_chain_WHO_UNICEF_joint_statement_A4_rev2_5-14-15_\(3\).pdf](https://www.unicef.org/health/files/EPI_cold_chain_WHO_UNICEF_joint_statement_A4_rev2_5-14-15_(3).pdf), 2015.
12. WHO. Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products.
13. WHO. Technical supplements to model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. Annex 5.
14. WHO/PQT. Oxytocin injection. Clarification of stability data and storage statement requirements. Guidance document. 31 October 2018.

For additional information

For additional information, please contact:

- Mariana Widmer, WHO, Geneva, widmerm@who.int
- Seloi Mogatle, UNFPA, Copenhagen, mogatle@unfpa.org
- Akthem Fourati, UNICEF, Copenhagen, afourati@unicef.org

WHO/RHR/19.5 © World Health Organization 2019 Some rights reserved. This work is available under the CC BY-NC-SA 3.0 IGO licence.

World Health Organization
20 Avenue Appia, 1211 Geneva 27
Switzerland
www.who.int

United Nations Children's Fund
Oceanvej 10-12, Copenhagen
Denmark
www.unicef.org

United Nations Population Fund
Marmovej 51, Copenhagen
Denmark
www.unfpa.org