

BMJ Open Temperature stability of oxytocin ampoules labelled for storage at 2°C–8°C and below 25°C: an observational assessment under controlled accelerated and temperature cycling conditions

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ABSTRACT

Introduction Oxytocin, administered via injection, is recommended by WHO for the prevention and treatment of postpartum haemorrhage. However, the susceptibility of oxytocin injection to thermal degradation has led WHO and UNICEF to recommend cold-chain storage of all oxytocin products. Nevertheless, some oxytocin products supplied to the global market are labelled for storage at ≤25°C, often with a shorter shelf-life relative to products labelled for refrigeration. Differences in labelled storage requirements can lead to uncertainties among stakeholders around the relative stability of oxytocin products and specifically whether ≤25°C products are more resistant to degradation. Such confusion can potentially influence policies associated with procurement, distribution, storage and the use of oxytocin in resource-poor settings.

Objectives To compare the stability of oxytocin injection ampoules formulated for storage at ≤25°C with those labelled for refrigerated storage.

Design Accelerated and temperature cycling stability studies were performed with oxytocin ampoules procured by the United Nations Population Fund (UNFPA) from four manufacturers.

Method Using oxytocin ampoules procured by UNFPA, accelerated stability (up to 120 days) and temperature cycling (up to 135 days between elevated and refrigerated temperatures) studies were performed at 30°C, 40°C and 50°C. Oxytocin content was quantified using a validated HPLC-UV method.

Results All ampoules evaluated exhibited similar stability profiles under accelerated degradation conditions with the exception of one product formulated for ≤25°C storage, where the rate of degradation increased at 50°C relative to other formulations. Similar degradation trends at elevated temperatures were observed during temperature cycling, while no significant degradation was observed during refrigerated periods of the study.

Conclusion Oxytocin ampoules formulated for non-refrigerated storage demonstrated comparable stability

Strengths and limitations of this study

- This is the first controlled study to evaluate the effect of cycling oxytocin injection products between refrigerated and elevated temperature storage conditions (simulating excursions outside of the cold chain).
- Stability comparisons between oxytocin injection products labelled for storage at 2°C–8°C and ≤25°C provide some clarity over uncertainties around whether oxytocin designated for ≤25°C storage provides any stability benefit over those labelled for refrigerated storage.
- Although a range of oxytocin products were assessed in this study, globally there are reported to be over one hundred manufacturers of oxytocin injection products. Therefore, the results should only be considered representative of those products with similar formulation constituents.

to those labelled for refrigerated storage and should not be interpreted by stakeholders as offering a more stable alternative. Furthermore, these products should not be procured for use in territories with high ambient temperatures, where all oxytocin injection products should be supplied and stored under refrigerated conditions.

INTRODUCTION

Postpartum haemorrhage (PPH) is a leading cause of maternal morbidity and mortality worldwide,^{1,2} with the majority of cases occurring in low-income and middle-income countries (LMICs).³ Oxytocin, administered via intravenous or intramuscular injection, is recommended by WHO for the prevention and treatment of PPH.⁴ However, oxytocin injection degradation is increased at elevated

temperatures, leading to deamidation and formation of inactive dimers/trimers.^{5 6} This is particularly problematic in resource-poor settings where cold-chain infrastructure can be lacking or unreliable and high ambient temperatures are common, undermining efforts to maintain controlled conditions during supply and storage of pharmaceuticals. Studies of sea shipments of essential medicines in tropical regions have detected within-pack temperatures as high as 42.4°C.⁷ Similarly, a WHO observational study reported storage temperatures as high as 30.1°C during distribution of oxytocin ampoules from the central store to regional facilities in Ghana.⁸ In addition, limited resources can contribute to extended distribution times, increasing the risk of periods of uncontrolled storage. United Nations Population Fund (UNFPA) records in 2014 indicated that shipments from manufacturers to destination ports took up to 35 days and were held for 6–30 days before transport to facilities. Under these circumstances, where there is a failure to maintain cold-chain conditions, oxytocin quality can be compromised at the point of use.⁹ A systematic review reported 57.5% of oxytocin ampoules collected in Africa had a low drug content, falling below International and US Pharmacopeial (USP) specifications of 90%–110% of labelled claim.^{10–12} The studies evaluated in the review did not determine the cause of the low oxytocin content, however, a subsequent exploratory study in the Democratic Republic of Congo analysed samples for both oxytocin content and known heat-related degradation products of oxytocin. The study found that 80% of ampoules collected from 15 facilities contained less than the specified content of oxytocin and in all of these ‘failed’ samples, there was a commensurate quantity of degradation products (relative to the labelled oxytocin content). This suggests the product contained the appropriate amount of oxytocin initially, however, degradation had occurred subsequent to manufacture, likely due to uncontrolled (elevated) temperatures during storage.¹³

The susceptibility of oxytocin injection to degradation has led WHO and UNICEF to recommend cold-chain storage and transport of all oxytocin injection products.¹⁴ Nevertheless, some oxytocin products supplied to the global market are labelled for storage at $\leq 25^{\circ}\text{C}$ or ‘in a cool place’, often with a shorter shelf-life (24 months) relative to products labelled for refrigeration (36–48 months). This difference in labelled storage conditions can lead to uncertainties among stakeholders around the relative stability of oxytocin products and whether $\leq 25^{\circ}\text{C}$ products are more resistant to degradation than refrigerated products. This was reflected in a qualitative study of key stakeholders in Ethiopia, India and Myanmar, which demonstrated that the storage of oxytocin ampoules varied widely between countries and facilities.¹⁵ In addition, anecdotal evidence, obtained from groups working in the field (including the UNFPA), indicates that there is a perception that products labelled for storage at $\leq 25^{\circ}\text{C}$ or outside the refrigerator (such as ‘in a cool, dark place’) have been formulated to be more stable

and can better withstand storage at ambient temperatures. Of greater concern, some public procurers have policies to purchase oxytocin injection products labelled for storage outside of the refrigerator on the basis of a perception that these products offer greater stability and can overcome problems associated with incomplete cold chain (19th General Membership, Reproductive Health Supplies Coalition, personal communications, Nepal, 25–28 March 2019). Controlled temperature studies have reported no oxytocin degradation in ampoules stored at 4°C–8°C for 12 months, but 3%–7% and 9%–19% reductions in oxytocin content when stored at 21°C–25°C and 30°C, respectively, for a similar period.¹⁶ However, there are currently no comparisons of the stability of oxytocin ampoules labelled for different storage conditions. Therefore, in collaboration with UNFPA, this study compares the stability of oxytocin ampoules, designated for storage either at 2°C–8°C or $\leq 25^{\circ}\text{C}$, under accelerated conditions and during temperature cycling storage protocols simulating excursions from cold-chain storage conditions.

METHODS

Samples of three oxytocin products labelled for storage at 2°C–8°C were procured by UNFPA from AS Grindeks, Biologicici and RotexMedia (10 IU/mL solution, online supplementary file 1) with three batches obtained from each manufacturer and were representative of what the UNFPA would typically procure. Samples formulated for storage at $\leq 25^{\circ}\text{C}$ were procured from AS Grindeks and Biol (10 IU/mL, online supplementary file 2) with three and two batches obtained from each manufacturer, respectively. While, ampoules procured from Biol were formulated for $\leq 25^{\circ}\text{C}$ storage and, for the purposes of this study, will be designated as a $\leq 25^{\circ}\text{C}$ labelled product, it should be noted that local regulatory authorities approved the product only for storage at 2°C–8°C, recognising storage challenges in hot climates. The product was, therefore, relabelled accordingly prior to supply. However, as the product was originally formulated for $\leq 25^{\circ}\text{C}$ storage, it remains representative of the products currently available that are labelled for non-refrigerated storage. In all cases, all oxytocin products were obtained from stringent regulatory authority approved manufacturers.

International air freight was used to transport ampoules either from the UNFPA liaison offices in Copenhagen, Denmark immediately after procurement or directly from manufacturers to our facility for stability assessment. Internal monitors confirmed temperature conditions were maintained within required limits (2°C–8°C) in all shipments. On arrival, all ampoules, whether labelled for storage at 2°C–8°C or $\leq 25^{\circ}\text{C}$, were stored under refrigerated conditions until study commencement. The temperature of the refrigerators and stability storage cabinets used were monitored weekly prior to and throughout the study. All ampoules used remained within their expiration date during the entire duration of the study.

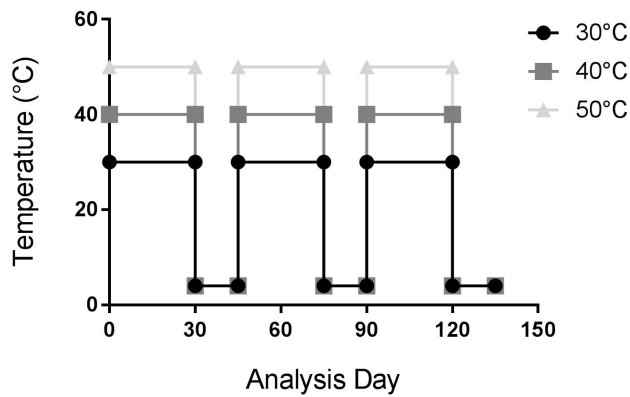


Figure 1 Visualisation of the oxytocin temperature cycling study. One cycle consisted of ampoule storage at either 30°C, 40°C or 50°C for a 30-day period then a refrigeration period for 15 days. This cycle was undertaken three times, for a total study duration of 135 days.

Accelerated stability study

An accelerated degradation study was undertaken to investigate the effects of constant storage at three temperatures (30°C, 40°C and 50°C) for up to 120 days. The 30°C and 40°C storage conditions were selected based on WHO recommendations for assessing stability of products used in hot climates (climatic zones III and IV).¹⁷ The 50°C condition was selected as an extreme limit, reflecting high-temperature excursions previously reported for essential medicines shipped in tropical regions.⁷ Ampoules from all batches were stored in calibrated temperature controlled cabinets (Humiditherm, Thermoline).

Sampling was performed on days 0, 15, 30, 60, 90 and 120 for all samples. At each time point, three ampoules (two ampoules at 120 days due to limited sample numbers) were sampled from each batch. Due to each individual ampoule being fully sealed during storage and opened only when sampled no evaporation or loss of volume was anticipated. Each ampoule was tested for oxytocin content with the solution pH also measured.

Temperature cycling study

The study assessed the effects on stability of cycling samples between storage at either 30°C, 40°C or 50°C for a 30-day period and refrigerated conditions for 15 days (figure 1). Rationale for the 30-day excursion out of the fridge came from UNFPA information that shipments could sometimes be held up outside of the cold chain for this period in their supply chains. The cycle was undertaken three times, with sample collection undertaken on days 30, 45, 75, 90, 120 and 135. At each collection time point, three ampoules per batch and per temperature condition were assayed for oxytocin content. Similar to the accelerated temperature study, no evaporation or change in volume was anticipated due to ampoules remaining sealed prior to sampling for each collection time point. The pH was measured for ampoules collected

under each condition. Due to limited sample numbers of 2°C–8°C-labelled ampoules at the 135-day time point, ampoules were tested in duplicate rather than triplicate.

Oxytocin assay

A validated high performance liquid chromatography-ultraviolet (HPLC-UV, Shimadzu Nexera X2 Ultra high performance liquid chromatography system (UHPLC)) assay method was developed to quantify the oxytocin content of each ampoule. Chromatographic separation was achieved on a Kinetex C₁₈XB column (50×2.1 mm, 2.6µm, Phenomenex, USA). The injection volume was 10µL. The mobile phase comprised A: 0.1% trifluoroacetic acid (TFA) in H₂O and B: 0.1% TFA in 90:10 acetonitrile:H₂O, which was delivered at a flow rate of 0.5 mL/min. Elution was performed by a linear gradient from 10% to 40% B in 3 min, 40% B for 0.1 min and then returned to 10% B and equilibrated for 2 min. The UV detection was assessed over a wavelength range of 210–300 nm. The column oven was set at 40°C (to aid chromatographic resolution) and the autosampler was set at 10°C (to maintain sample stability). External standards were prepared over a concentration range of 4–24µg/mL using oxytocin active pharmaceutical ingredient (API) powder (Grindeks, Latvia). Data acquisition and processing were performed using LabSolutions software V.5.82 (Shimadzu).

Ampoules of oxytocin were allowed to equilibrate at room temperature for around 30 min before opening to ensure no temperature related effects, for example, volatility and/or volume change that would influence sampling for analysis. Ampoule contents were transferred to HPLC vials and analysed. After the initial oxytocin analysis, vials were stored at –80°C prior to degradant analysis. A validated liquid chromatography–mass spectrometry (LCMS) (Shimadzu Nexera-LCMS 8030) assay was used to quantitate oxytocin degradation products. Chromatographic separation was achieved on an XSelect charged surface hybrid (CSH) C₁₈ column (3 mm X 150 mm, 5µm, Waters, USA) maintained at 60°C. Mobile phase comprising A: 10 mM ammonium formate in H₂O and B: 100% acetonitrile was delivered at a flow rate of 1.5 mL/min and followed a linear gradient of 15%–30% B in 30 min then 30%–50% B in 5 min and from 50% to 90% B in 3 min after which starting conditions were resumed. The autosampler was set at 4°C. The Nexera UHPLC system was coupled to an LCMS-8030 triple quadrupole mass spectrometer (Shimadzu) and ionisation was performed by electrospray in positive ion mode. Nebulising gas flow was set at 3 L/min and the Q3 scan spectra recorded from m/z 250–1500. Data acquisition and processing was performed using LabSolutions software V.5.82 (Shimadzu). The assay was validated and met set criteria for accuracy and precision prior to the commencement of the analysis.

Results from both the accelerated stability and temperature cycling studies were analysed in consultation with the Statistical Consulting Platform, Monash University, using

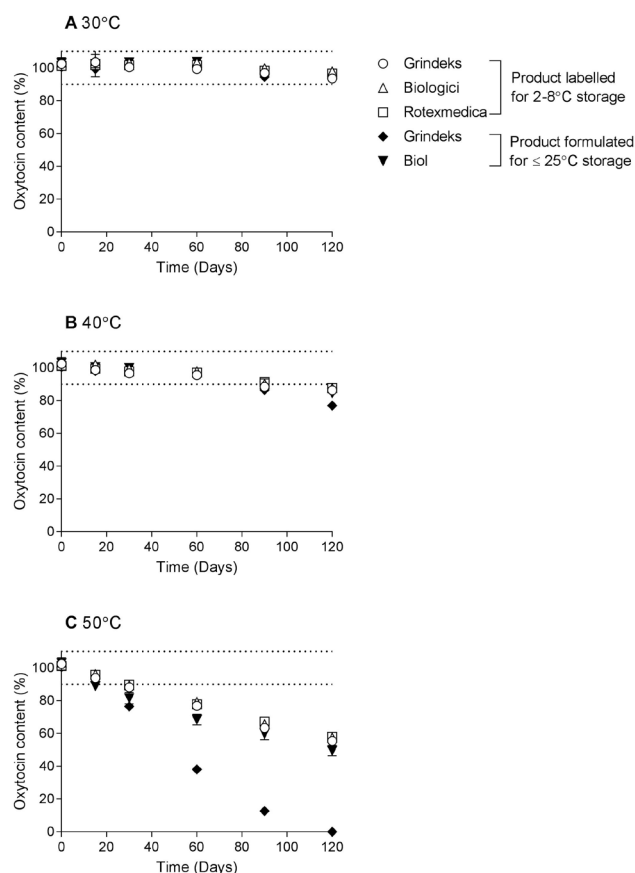


Figure 2 Accelerated stability study summarising percentage oxytocin content versus time profiles of products labelled for refrigerated storage (white symbols) compared with those formulated for storage outside the cold chain (black symbols) when stored at 30°C (A), 40°C (B) and 50°C (C). Each symbol represents the mean of all batches of oxytocin injection product (each batch analysed in triplicate with 120-day ampoules analysed in duplicate) supplied by each manufacturer with errors expressed as \pm SD. The dotted line represents the acceptable upper (110%) and lower (90%) limit of oxytocin content specified by international pharmacopoeias.

a general linear model, specifically, a univariate analysis of variance (IBM SPSS Statistics V.22). Statistical differences were considered significant when $p \leq 0.05$.

Patient and public involvement

No patients or the public were involved in this study.

RESULTS

Accelerated stability study

Ampoules stored at 30°C showed a similar decrease in oxytocin content over the 120-day assessment period (102% at day 0 vs 96% at day 120), irrespective of manufacturer or temperature storage labelling (figure 2). All ampoules remained within USP and International Pharmacopoeia specifications of 90%–110% of stated nominal oxytocin concentration ($16.7 \mu\text{g}/\text{mL} = 100\%$).^{10 12}

Conversely, ampoules from all manufacturers fell below the pharmacopoeial minimum content specification of 90% after 120 days storage at 40°C and 30 days at 50°C. When compared with previously reported data by Hogerzeil *et al*,¹⁶ only one condition and duration used (30°C for 2 months) was aligned to allow for direct comparison. In our accelerated temperature study, a mean of $102\% \pm 1.7\%$ of oxytocin was measured when ampoules were exposed to these conditions compared with $97\% \pm 1.0\%$. In both cases, the oxytocin concentrations remained within USP specifications of 90%–110%.

For AS Grindeks ampoules labelled for storage at $\leq 25^\circ\text{C}$, a more rapid degradation of oxytocin occurred during storage at 50°C compared with the other ampoules. After 120 days storage at this temperature, $<2\%$ of the labelled oxytocin content remained compared with $>50\%$ in all other products tested at the same time point, with statistically significant differences ($p \leq 0.05$) observed at time points beyond 60 days. The pH of AS Grindeks ampoules labelled for storage at $\leq 25^\circ\text{C}$ also differed from the other products with a decrease in pH occurring as the study progressed, which was most pronounced during storage at 50°C, where a $\text{pH} \leq 3$ was recorded after 30 days. The pH of all other ampoules remained between $\text{pH} 3.5$ – 4.5 throughout the study. Degradant analysis indicated an increasing concentration of known degradation products (such as deamidated species and oxytocin disulphide-linked dimers and trimers) in all samples over the course of the study. For all ampoules analysed, the total content of degradation products in a sample at a given time point was commensurate with the loss of oxytocin measured in that same sample.

Temperature cycling study

The stability profiles of ampoules exposed to temperature cycling conditions are shown in figure 3. During the periods of storage at elevated temperatures, the degradation profiles of oxytocin ampoules from each manufacturer were not significantly different to the profiles observed for the accelerated stability study. Specifically, all ampoules cycled between temperatures of 30°C and 2°C–8°C remained within USP quality specifications over the duration of the study. Whereas ampoules from all manufacturers reached at or below the minimum 90% specification after a total of 135 days of cycling between 40°C and 2°C–8°C (where ampoules were exposed to a total of 90 days at 40°C in three 30-day cycles). When cycled between 50°C and 2°C–8°C, ampoules from all manufacturers were below the minimum 90% specification after the second cycle (a total of 60 days at 50°C in two 30-day cycles).

During periods of storage at 2°C–8°C, there was no significant loss of oxytocin content, and in some cases, a small increase was observed. It is hypothesised that this increase may be attributed to reversible formation of succinimide intermediates in the deamidation degradation pathway, (detailed in online supplementary file 3). However, this process only pertains to oxytocin molecules

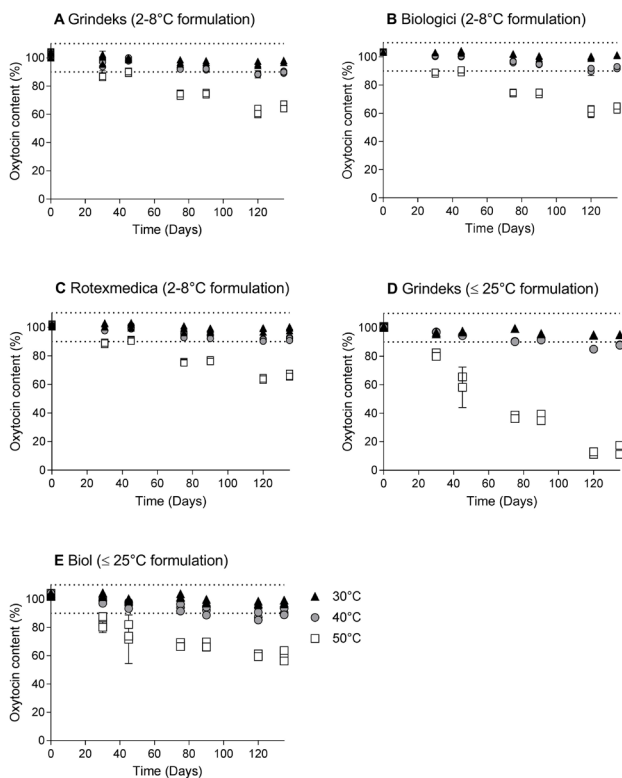


Figure 3 Percentage oxytocin content versus time profiles for (A) AS Grindeks, (B) Biologici Italia and (C) RotexMedica, and for ampoules labelled for storage at $\leq 25^{\circ}\text{C}$, (D) AS Grindeks, (E) Biol exposed to a temperature cycling protocol at 30°C (black triangle), 40°C (grey circles) and 50°C (white squares) with the total number of days exposed to elevated temperatures was equivalent to 90 days. Reference lines show 90%–110% of nominal oxytocin concentration ($16.7\ \mu\text{g}/\text{mL}=100\%$). Each symbol represents the mean of triplicate analysis one of each of three batches of oxytocin supplied by each manufacturer with errors expressed as $\pm\text{SD}$ (with the exception of the 135-day samples which were $\pm\text{range}$).

in the process of deamidation and does not indicate any reversal of already formed oxytocin degradants back to the active parent compound and therefore would not meaningfully impact stability considerations in the field.

In all cases, the pH profiles of the ampoules exposed to temperature cycling conditions were consistent with those recorded for the accelerated stability assessment. Total degradant assays also indicated a mass balance, with the mass of total degradants increasing in proportion to the decrease in oxytocin over time.

DISCUSSION

This is the first study to compare the stability of oxytocin injection products labelled for storage at 2°C – 8°C with those labelled for storage at $\leq 25^{\circ}\text{C}$. The results demonstrated that, of the products tested, those designated for storage at $\leq 25^{\circ}\text{C}$ provide no stability benefit over those labelled for refrigerated storage, and in one example, demonstrated poorer stability characteristics.

The stability of all products tested, when stored at 30°C and 40°C , was similar in both the accelerated and temperature cycling studies irrespective of formulation or labelling. When intermittent periods of refrigerated storage were subtracted from the temperature cycling profiles, leaving only the cumulative days at elevated temperature, the degradation profiles were observed to be comparable to the relative accelerated data across all temperatures assessed. However, at 50°C , the AS Grindeks $\leq 25^{\circ}\text{C}$ labelled oxytocin product was observed to degrade at a higher rate than the 2°C – 8°C labelled and Biol products. It is proposed that this more rapid degradation can be attributed to the formulation composition of the AS Grindeks $\leq 25^{\circ}\text{C}$ labelled product (table 1). Specifically, the Grindeks $\leq 25^{\circ}\text{C}$ labelled product contains the preservative chlorobutanol, which is known to hydrolyse at high temperatures to form acidic degradation products.¹⁸ This likely explains the reduction in pH observed for this product during storage at 50°C and, given that degradation of oxytocin is catalysed in acidic conditions, the increased rate of degradation.⁵ The Biol $\leq 25^{\circ}\text{C}$ labelled ampoules similarly contain chlorobutanol, however, this formulation also includes a buffering agent (sodium acetate trihydrate) that maintains a higher pH to mitigate against this mechanism. The 2°C – 8°C labelled ampoules

Table 1 Comparison of the formulations of AS Grindeks oxytocin injection product labelled for refrigerated storage with AS Grindeks and Biol products labelled for storage outside the cold chain

		Grindeks (2°C – 8°C)	Grindeks ($\leq 25^{\circ}\text{C}$)	Biol ($\leq 25^{\circ}\text{C}$)
Oxytocin ($16.7\ \mu\text{g}/\text{mL}$)	Active	Yes	Yes	Yes
Glacial acetic acid	pH modifier	Yes	Yes	Yes
Sodium acetate trihydrate	Buffer salt	Yes	No	Yes
Sodium chloride	Tonicity	Yes	No	Yes
Sodium hydroxide	pH modifier	Yes	No	No
Chlorobutanol hemihydrate	Preservative/stabiliser	No	Yes	Yes
Water for injection	Diluent	Yes	Yes	Yes
Shelf-life		4 years (2°C – 8°C) 3 months (up to 30°C)	2 years	2 years

do not contain chlorobutanol and, therefore, are not liable to this acidification mechanism.

The results demonstrate that the stability profiles of the oxytocin products labelled for $\leq 25^{\circ}\text{C}$ storage offer no stability advantage over those labelled for 2°C – 8°C storage over the time frame assessed for this study.

The incidence of oxytocin injection products with less than the specified content of active ingredient is high across Africa and Asia,¹¹ likely due, in large part, to uncontrolled storage and exposure to high temperatures. Consequently, WHO and UNICEF have jointly recommended that all oxytocin products are supplied and stored under refrigerated conditions to avoid product deterioration in countries where ambient temperatures exceed 25°C .¹⁴ Compliance with this recommendation can be undermined by the availability of oxytocin injection products labelled for storage outside of the cold chain (ie, $\leq 25^{\circ}\text{C}$ or similar), and can lead to a perception among stakeholders in these countries that these products overcome the requirement for cold-chain storage and supply (even if manufacturers are not purporting enhanced stability).

The results of this study demonstrate that, at the temperatures assessed, all oxytocin injection products were subject to degradation, and while products stored at 30°C remained within USP specification after 120 days, they still exhibited a statistically significant decrease ($p < 0.05$) in content relative to day 0. Furthermore, WHO guidelines on stability testing of pharmaceutical products require that manufacturers of products to be stored outside of the refrigerator and intended for sale in hot climatic regions (ie, climatic zones III and IV) demonstrate adequate stability at 30°C (not 25°C) over the intended shelf-life of the product.¹⁷ The majority of LMICs fall into this category, and therefore, these data (1) demonstrate that products labelled for storage at $\leq 25^{\circ}\text{C}$ are not suitable for use in these countries and (2) support WHO/UNICEF recommendation that all oxytocin products, irrespective of formulation and labelling, should be stored under refrigerated conditions to ensure maintenance of quality. These conclusions are supported by previously reported WHO data where oxytocin content in ampoules stored for 12 months in the dark at 30°C was below the USP minimal specification of 90% of labelled content¹⁶ (84%–87%). Products labelled for storage at $\leq 25^{\circ}\text{C}$ (or similar labelling equating to non-refrigerated storage) are, therefore, not suitable for most LMICs. In contrast, products labelled for storage at 2°C – 8°C specifically require refrigerated storage that cannot be misinterpreted and will ensure the product does not degrade excessively. However, it should be acknowledged that both types of product would be equally susceptible to degradation outside of the refrigerator.

The temperature cycling study results simulated high-temperature excursions when the product moves in and out of the cold chain. These results show the inherent stability of the oxytocin injection products to be relatively unchanged by the cycling process and that returning

products to refrigerated conditions after a high-temperature excursion will halt product degradation. Therefore, high-temperature excursions should be minimised and refrigerated storage maintained wherever possible.

CONCLUSION

The stability of oxytocin injection products formulated and labelled for storage outside the cold chain afford no greater stability than those formulated for refrigerated storage. Indeed, at high temperatures ($>40^{\circ}\text{C}$), the stability of the ‘store at $\leq 25^{\circ}\text{C}$ ’ products may be reduced, depending on formulation composition. The outcomes of this study indicate that oxytocin injection products labelled for storage at $\leq 25^{\circ}\text{C}$ should not be procured for use in territories with hot climates, which include most LMICs. Therefore, these results are supportive of the joint WHO/UNICEF recommendation that all oxytocin injection products, irrespective of labelling, should be supplied and stored in the cold chain to maintain quality.

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Contributors PL, SM and MPM devised the study concept. T-HN, PL, MPM and RSM designed the study. Non-pharmacopeial methods were developed by KD, while sample analysis was conducted by RSM, CM and PW. Interpretation of results was conducted by PL, MPM, RJP, RSM and T-HN. T-HN drafted the publication with review and significant contribution by all other authors.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data relevant to the study are included in the article or uploaded as online supplementary information.

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