Quality of reproductive health supplies – is it getting any better?



Reproductive health supplies: a question of availability, quality and affordability

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8 November 2017, Brussels



Where do we get our data (evidence)?



- Refer to other studies "Data Mining"
- Conduct own studies
- Collaborate with partners for studies

Systematic Review Study – Oxytocin quality



BJOG	n International Journal of bstetrics and Gynaecology
DOI: 10.1111/1471-0528.13998 www.bjog.org	Systematic review
Quality of o middle-incor of the litera	vtocin available in low- and e countries: a systematic review

MR Torloni," C Gomes Freitas," UH Kartoglu," A Metin Gülmezoglu, M Widmer^c

Objective: To identify, critically appraise and synthesize the findings of studies on the quality of oxytocin available in LMIC

Search: 7 databases, from inception until March 2015

Inclusion criteria: injectable oxytocin - API or sterility

Mariana Widmer - Reproductive Health and Research Department, WHO



Systematic Review - study selection



Systematic Review Conclusions



- 1 in every 3 women would receive less oxytocin than expected
- No prequalified products (currently 2)
- Non-registered manufacturers
- Sampling at service level cannot identify cause of low quality: manufacturer or supply chain?



WHO – Quality Monitoring Projects



Objectives for Prequalification Related Surveys

- Monitor quality of medicines procured by UN agencies/ prequalified products
- Contribute to quality control of medicines
- Contribute to capacity building by cooperation with Medicine Regulatory Authorities (strengthening of health systems)

Survey of the quality of medicines identified by the UNCoLSC for Women and Children



UN Commission strategy

 Increasing access to and appropriate use of medicines and medical devices that effectively address major avoidable causes of death during pregnancy, childbirth and childhood – 13 neglected commodities defined

Objectives of the survey

- Identify products of good quality or the quality of which can be improved in short period of time
- Evaluate quality of products currently available at the first level of distribution chain

10 from 22 countries selected for sampling

Burkina Faso, Kenya, Madagascar, Nepal, Nigeria, Tajikistan, Tanzania, Uganda, Vietnam, Zimbabwe



Criteria

- Majority of selected medicines in country registers
- · Several products from various manufacturers per medicine
- Longer experience in medicines regulation
- Representation of countries from various geographic regions
- Willingness of NMRAs to cooperate





Selection of medicines for sampling & testing



To optimize use of resources a benefit/risk analysis was performed

- Medicines of assured quality not included e.g. Production in stringent regulatory systems
- Low-risk medicines not included
- Samples of innovator products were not collected



Medicines included in the survey



- Oxytocin injection
- Magnesium sulfate injection
- Gentamycin injection
- Procaine benzylpenicillin injection (Procaine penicillin, Procaine penicillin G)
- Ampicillin injection
- Ceftriaxone injection
- Betamethasone injection (as sodium phosphate and/or acetate)
- Dexamethasone injection
- Amoxicillin dispersible tablet
- Zinc sulfate dispersible tablet or syrup
- Levonorgestrel tablet
- 11 Mifepristone tablet





Compliance with survey specifications



Compliant Non-compliant



The Oxytocin Injection Case



- Collected only from central Stores
- Temperature at collection site recorded at time of sampling
- Product Label Information evaluated
- Manufacturer details collected









Oxytocin Sample Failures by country



	# of samples					
Total samples	14/8 (Fail/Pass) and Source for failing samples					
Burkina Faso	1/2 (China)					
Kenya	1/1 (India)					
Madagascar	1/1 (China)					
Nepal	3/3 (India)					
Nigeria	2/3 (India, China)					
Tajikistan	1/3 (India)					
Tanzania	2/3 (India)					
Uganda	3/3 (China)					
Viet Nam	0/1					
Zimbabwe	0/2					
Overall failure rate	64%					

Oxytocin Test Results: WHO/UNCoLSC study

- Tested according to the International Pharmacopiea for this survey
- For 13 of non-compliant samples (10 manufacturers) content of oxytocin was found below the lower acceptance limit of 90.0%;
- Content failures ranged from 52% 89.8% of the labelled amount.
- Assay test failures accompanied by the presence of significant levels of related substances or potential impurities that were over the acceptance limits.
- Visible particles found in 1 sample.
- In the remaining six samples (6 manufacturers) the oxytocin content was within the acceptance limits, however, related substances were found above the acceptance limits.

Registration of oxytocin



- Individual products registered according to different pharmacopeia or manufacturers' specifications. Impact on the interpretation of results and contradicting local opinions on product quality.
- In house methods accepted for local registration. No demonstration of equivalency with the pharmacopoeial method requested.
- Single-dose/use injections containing antimicrobial preservatives. No evidence of justification or authorisation.
- Evidence of formulation and manufacturing process development not requested.
- Storage conditions and shelf life based on actual stability data submitted in registration dossier.

Survey Conclusion for Oxytocin



- Quality of oxytocin in LMIC (Africa-Asia) is questionable
- Cause of low quality:
 - Supply chain storage conditions?
 - Manufacturer?
 - Regulators?



Why would samples not comply? What could be wrong?



- Storage conditions leading to deterioration.
- Reference pharmacopoeia not declared and tests conducted using "wrong" monograph.
- Manufacturer using pharmacopoeia that does not have comprehensive requirements
- Poor manufacturing practice (Poor GMP) and manufacturing process not adequately protecting product.
- Poor formulation inclusion of excipients/ingredients that affect stability of the product. Copying the innovator is not always the best option!
- Container closure system should be kept protected from light. Use coloured glass.

Regulation and procurement of life-saving commodities for women and children in EWEC Countries – WHO, 2015



- Survey to evaluate the performance of the national medicines authorities of the ten countries
- 8 countries with failing samples, 3 answered the survey with favourable scores.

How is it possible to have pharmaceutical products of low quality in the market while the performance of the NMRA is adequate. Where does the system fail?

The survey evaluated registration status of collected samples: 3/22 samples were not registered in the country of collection. 2/3 had deviations from the specifications. All were imported and placed on the market legally. Other mechanisms used to control the supply of needed medicines need to be controlled in the same way as registered products.



Stability of oxytocin along the supply chain

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Biologicals Available online 25 May 2017 In Press, Corrected Proof



Stability of oxytocin along the supply chain: A WHO observational study

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https://doi.org/10.1016/j.biologicals.2017.05.004

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Abstract

Postpartum haemorrhage is the leading cause of maternal mortality in low-income countries and oxytocin is the drug recommended by WHO for preventing and treating it. There are concerns about the quality of oxytocin available at the service level provider. The study aimed to document how temperature variations along the supply chain affect quality of oxytocin. The study was run from March to June 2015 in four regions of Ghana. 130 ampoules of oxytocin were shipped from the manufacturer to service level following Ghanaian public sector supply chain. Along the supply chain, temperatures were recorded continuously. After one month storage at central, regional and service level, ampoules were sent to laboratory for testing. Quality of the initial oxytocin sample from the manufacturer and the 130 oxytocin samples received from study points were tested according to International Pharmacopeia monograph, Samples fully complied with specifications. Temperature profile showed that the lowest and highest temperatures experienced were -9.9 °C and +30.1 °C. The results of this study indicate that the activity of oxytocin was not affected by these temperature excursions which occurred along the supply chain. The quality of the oxytocin from the manufacturer as well as from the service level was within the required specifications.

Keywords

Postpartum haemorrhage; Oxytocin; Quality; Supply chain; Temperature monitoring

Kartoglu, Widmer, Gülmezoglu. Biologicals 2017 http://dx.doi.org/10.1016/j.biologicals.2017.05.004

Figures (6)

References

Outline

Abstract

Keywords

Results

Funding Acknowledgements

1. Introduction 2. Material and methods

Ethics approval

4 Discussion and conclusion

Disclosure of interests















Stability of oxytocin along the supply chain

This is the first study that evaluates the extent of temperature exposure impact along the supply chain on the quality of oxytocin from the manufacturer until the service level.



In-country storage and transport



Temperature (°C)





Results and Conclusions

- Temperature profile showed that the lowest and highest temperatures experienced were -9.9 °C and +30.1 °C.
- The results of this study indicate that the activity of oxytocin was not affected by temperature excursions along the supply chain.
- Study highlights the need for routine oxytocin surveillance and monitored storage conditions along the supply chain.

Recommendations (1)



National Procurement systems

- 71% of respondent countries had national coordination mechanisms for medicines procurement.
 - Coordinate demand aggregation, establish/share market information and market controls.
 - ✓ Align national and partner organizations' procurement policies.
 - Improve Logistics management information systems (LMIS). Many are electronic at central but still paper-based at peripheral level.
- Only 35% of countries granted tax reductions or exemptions on imported raw materials for manufacturing medicines (76% provided incentives for importation of medicines)
 - \checkmark Review tax incentives for local production.

Recommendations (2)



- Manufacturers
 - ✓ use quality standards that meet the best attributes rather than restrict to only certain pharmacopoeial requirements e.g. should include acceptance criteria for degradants and/or related substances (Impurities).
- Researchers
 - Generate reliable data on stability, quality and other attributes (e.g. biowaiver) for RH products.
- Publishers of pharmacopoeia
 - ✓ Review and update quality acceptance criteria

Recommendations (3)



Regulatory systems

Only 56% of national regulatory authorities had regulatory environment enabling "*favourable*" regulation of the life-saving commodities - *registration processes, post-market surveillance, quality control, importation controls, and monitoring activities.*

- Capacity building e.g. training on dossier review (cf oxytocin scenario vs pharmacopoeia limits).
- ✓ joint inspections and dossier reviews to share resources and reduce costs (including building on existing initiatives currently coordinated by WHO).

Recommendations (4)



Regulatory systems Cont'd

- ✓ Reliance and recognition of other marketing authorisations from reference authorities e.g. use of WHO Collaborative processes.
- investments in joint monitoring capacity including information-sharing systems (existing or new) on quality complaints, laboratory results and PMS data.
- Countries without either ISO-certified or WHO-prequalified laboratories to be encouraged to consider additional development of local laboratory services.

Recommendations (5)



Development Partners

- Support WHO efforts directly
 - Prequalification of RH products there is currently limited support for prequalification and collaborative support for reproductive health products.
 - \checkmark reliance and recognition.
 - ✓ Harmonisation activities joint worksharing initiatives.
- Join WHO and other partners in support for local production in current recipient and regulatory support for producing countries.

https://extranet.who.int/prequal/content/quality-monitoring-0



Essential Medicines and Health Products: Prequalification of medicines						Information for	r ✔ Glossary Contact us Website feedback
	â	About Us 👻	Key Resources 👻	Events	News	FAQ	٩
	Quality I	Monitoring					Do You Need Assistance?
Documents A-Z Prequalified Lists Prequalification Pipeline FPPs and APIs Eligible for Prequalification ("EOIs") Key Performance Indicators Procedures & Fees for WHO Prequalification Procedures Amendments to APIMFs Variations to FPPs	 Field sampling and testing projects are carried out by WHO in order to: monitor the quality of medicines (both WHO-prequalified and non-WHO prequalified medicines) procured by UN agencies contribute to national quality control of medicines and contribute to strengthening of health systems and capacity building by cooperation with national medicines regulatory authorities (NMRAs). Projects are managed according to a pre-established protocol with defined study objectives. Samples are collected by NMRA staff and tested by WHO-prequalified laboratories, if available, or by laboratories whose test results have been proven to be reliable. Results obtained are discussed with the NMRAs of the participating countries before publication. Quality monitoring reports Three reports summarizing the findings of quality monitoring projects carried out under the auspices of WHO prequalification are available, relating to: anti-tuberculosis medicines circulating in selected newly independent states of the 						For assistance regarding prequalification please refer to the Support to Manufacturers, CROs and QCLs section of this website where we provide technical advice and information about assistance.
Requalification of FPPs Cauality monitoring Notices of concern/suspension	 selected a antiretrov 	antimalarial medici					
Monitoring QCL performance	RELATE	ED DOCUMENTS				^	
Prequalification Reports Guidance Documents	Survey of the quality of medicines identified by the United Nations Commission on Life Saving Commodities for Women and Children (2015) Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union (2011)						
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