

Impact of temperature excursions on oxytocin ampoule stability

A UNFPA and Monash University collaboration

A/Prof Michelle McIntosh

Wednesday Oct 12th 2016



GENERAL MEMBERSHIP MEETING
— of the —

**REPRODUCTIVE HEALTH
SUPPLIES COALITION**

10-14 OCTOBER 2016

#RHSUPPLIES2016



Reproductive Health
SUPPLIES COALITION

Content

Accelerated stability studies of UNFPA procured oxytocin ampoules
Temperature cycling studies of UNFPA procured oxytocin ampoules
Analysis of oxytocin ampoule quality in DRC

Accelerated Stability Study

UNFPA Supplier #1	Batch A	Triplicate
	Batch B	Triplicate
	Batch C	Triplicate
UNFPA Supplier #2	Batch A	Triplicate
	Batch B	Triplicate
	Batch C	Triplicate
UNFPA Supplier #3	Batch A	Triplicate
	Batch B	Triplicate
	Batch C	Triplicate

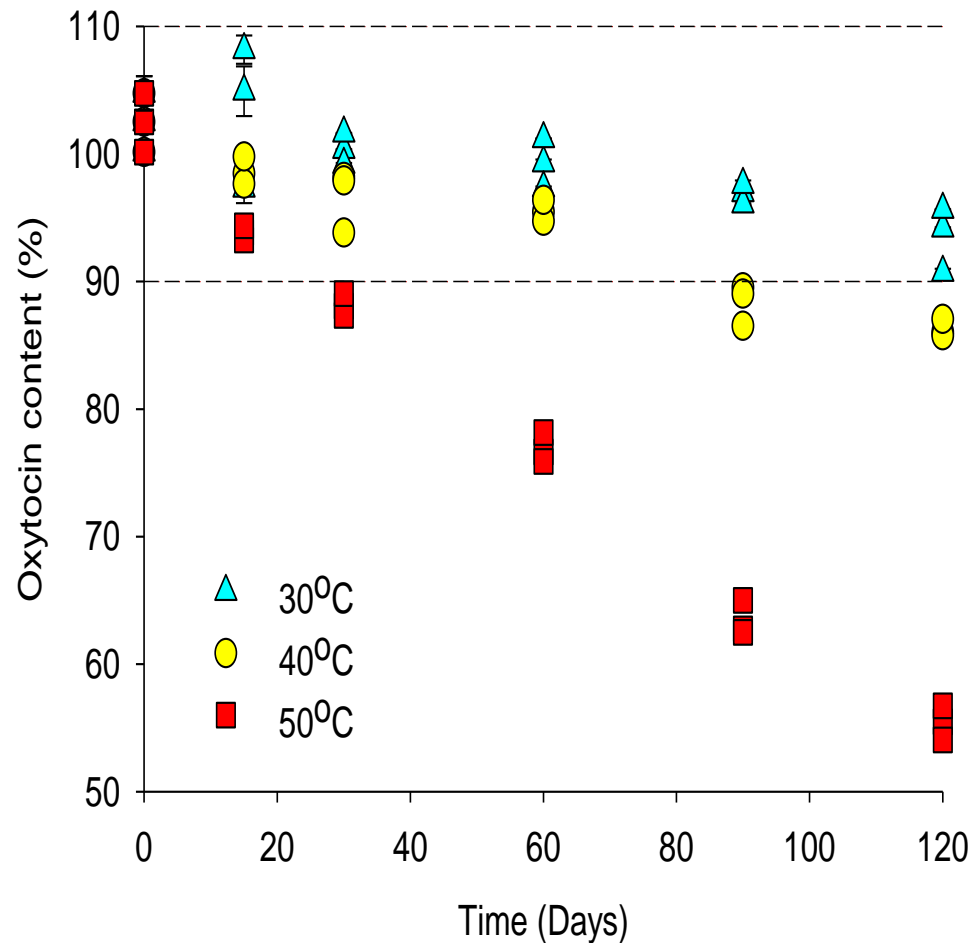
Samples stored at 30, 40 and 50 degrees for 120 days

Analysis on day 0, 15, 30, 60, 90 and 120

Accelerated stability study

(as percentage of nominal conc. 16.7ug/mL)

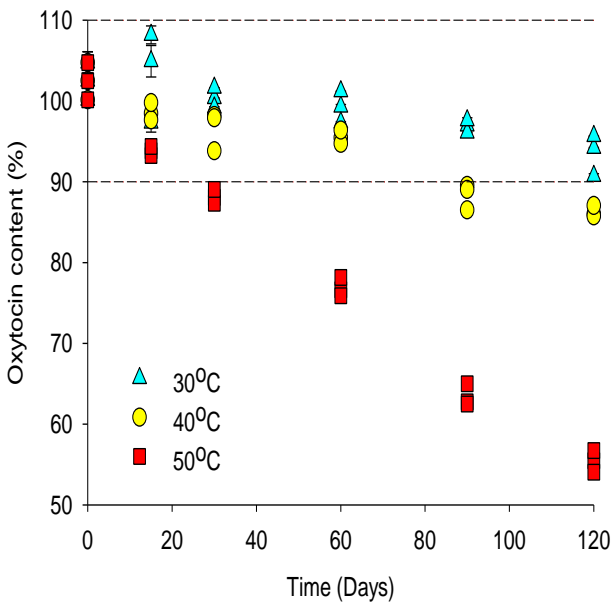
UNFPA supplier #1



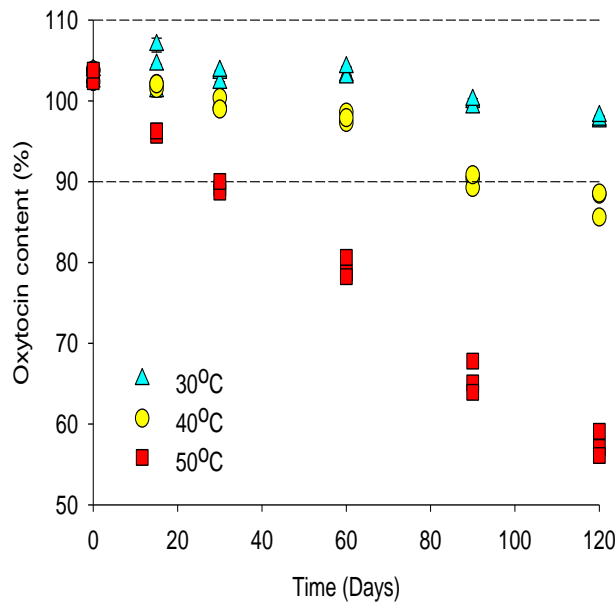
Accelerated stability study

(as percentage of nominal conc. 16.7ug/mL)

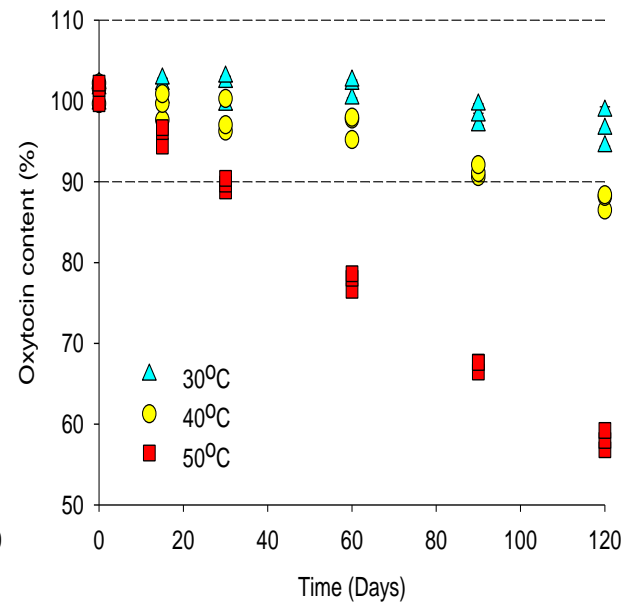
UNFPA supplier #1



UNFPA supplier #2



UNFPA supplier #3



Accelerated Stability Study

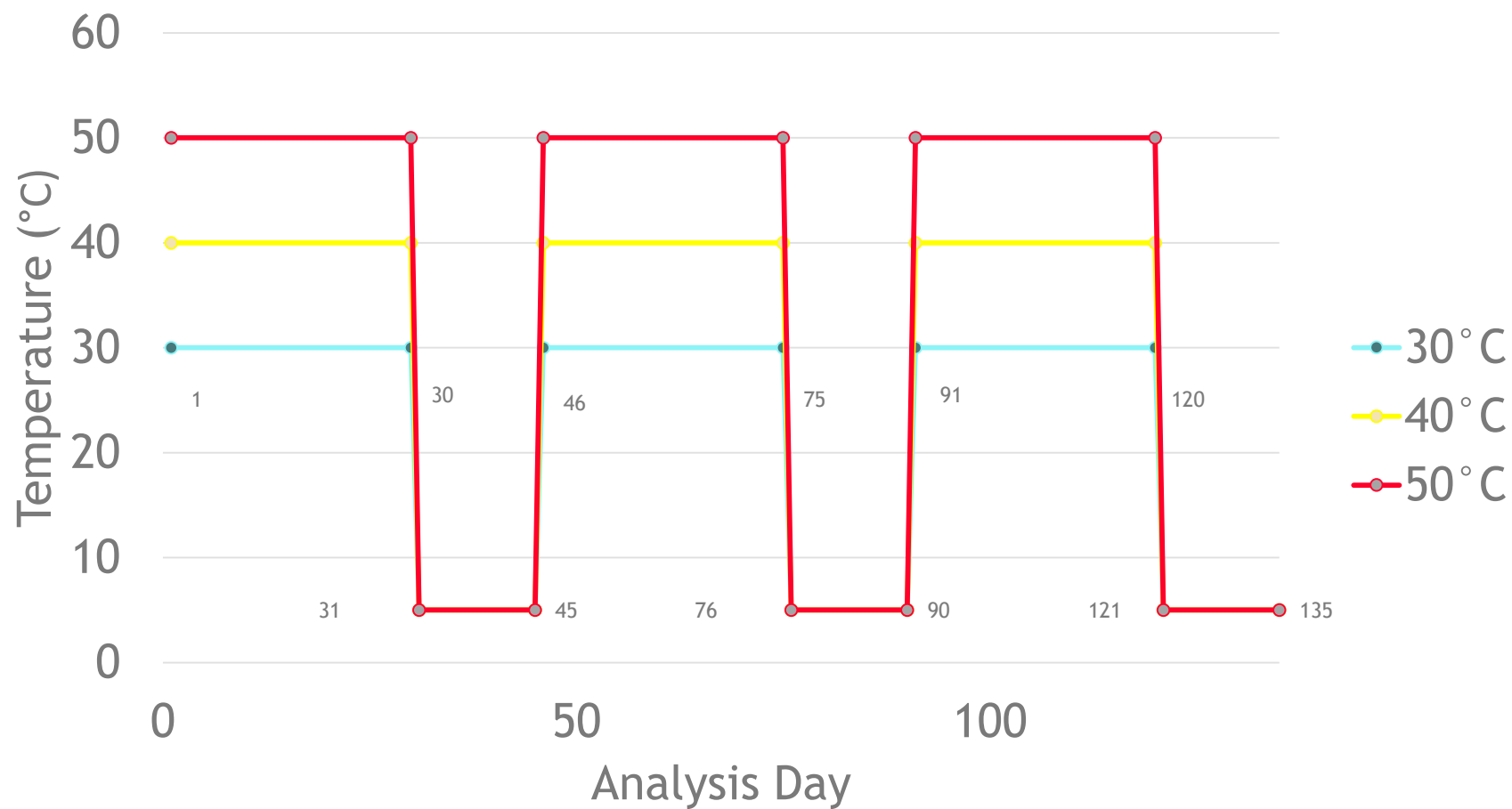
UNFPA Supplier – labelled as store between 2-8 degrees

- Product specification for content of oxytocin injection is 90-110% nominal/label concentration (16.7 µg/mL)
- Real-time data required for product registration
- Accelerated stability studies can be used to predict % degradation at elevated temperatures
- Arrhenius equation: $k=Ae^{-Ea/RT}$
- Approximate shelf-life (i.e. duration content remains > 90% nominal concentration):
 - 30 deg: 200 ± 58 days
 - 40 deg: 80 ± 9 days
 - 50 deg: 22 ± 2 days
 - 55 deg: 14 ± 1 day
 - 60 deg: 9 ± 1 day

Temperature Cycling Study

UNFPA Supplier #1	Batch A	Triplicate
	Batch B	Triplicate
	Batch C	Triplicate
UNFPA Supplier #2	Batch A	Triplicate
	Batch B	Triplicate
	Batch C	Triplicate
UNFPA Supplier #3	Batch A	Triplicate
	Batch B	Triplicate
	Batch C	Triplicate

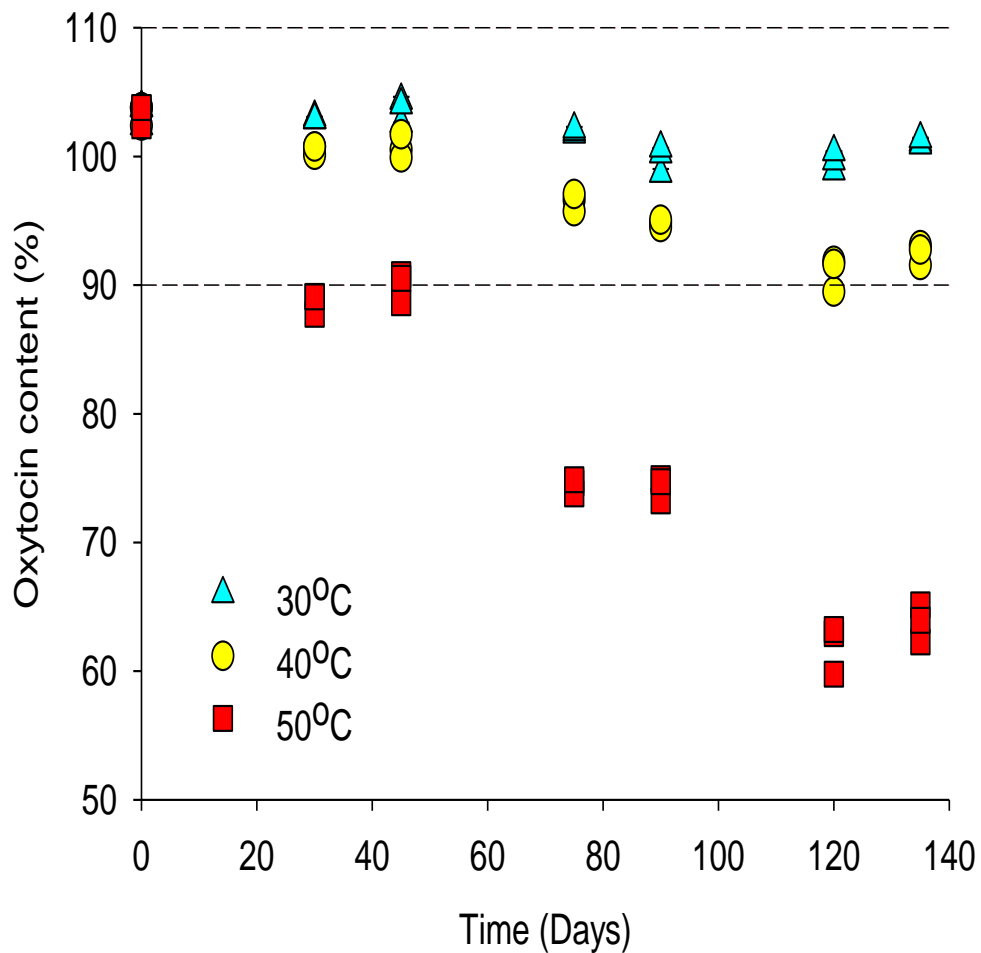
Temperature Cycling Protocol



Temperature cycling study

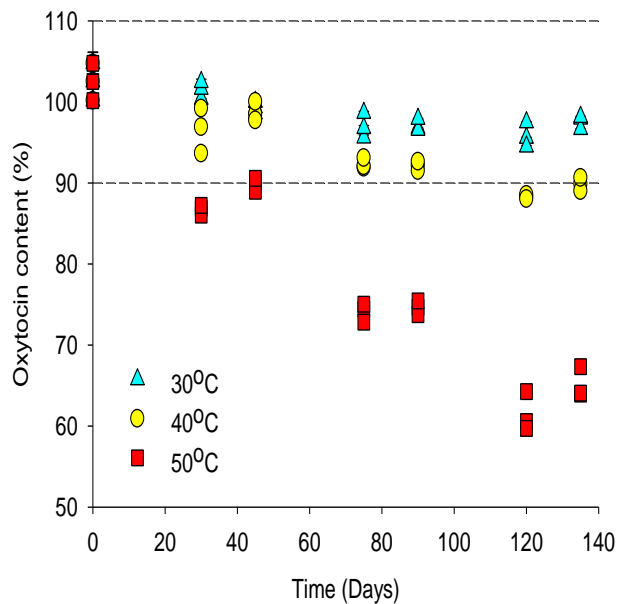
(as percentage of nominal conc. 16.7ug/mL)

UNFPA supplier #2

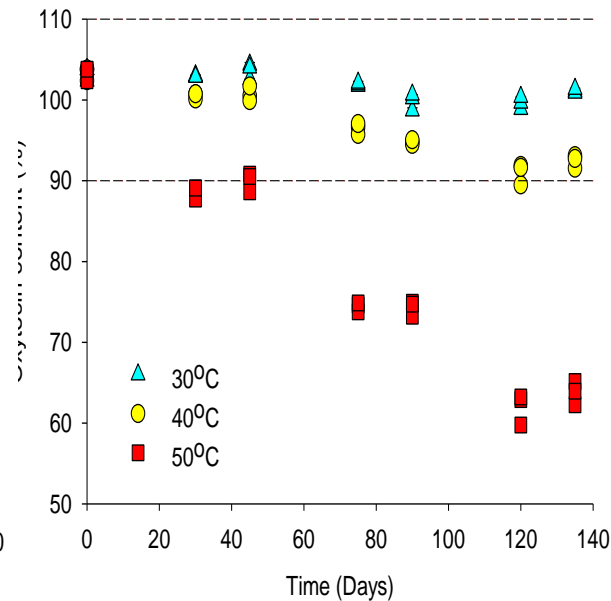


Temperature cycling study (as percentage of nominal conc. 16.7ug/mL)

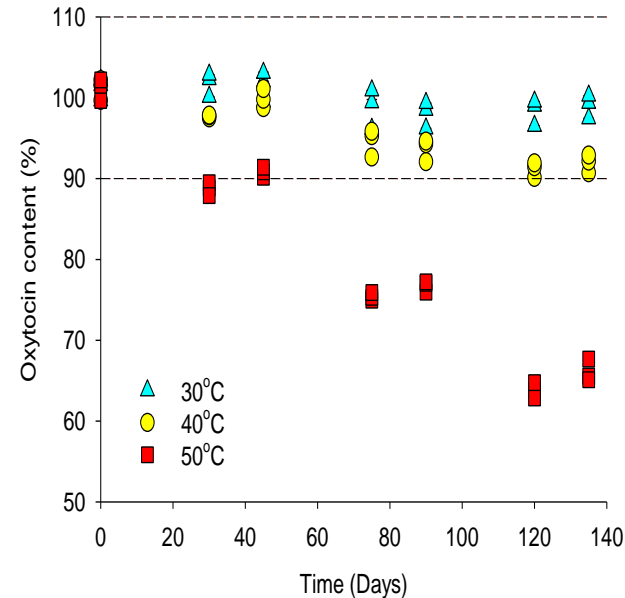
UNFPA supplier #1



UNFPA supplier #2



UNFPA supplier #3



Temperature cycling study conclusions

Samples stored at 30°C were within spec at study conclusion (135 days)

Samples stored at 40°C were out of spec beyond 120 days

Samples stored at 50°C were out of spec at first sampling point (30 days)

Unexpectedly, oxytocin concentrations increased slightly after every refrigeration period...

Currently investigating the possibility that a temperature-dependent, reversible aspartic residue forms via a succinimide intermediate occurring during asparagine degradation

Oxytocin ampoule quality within Democratic Republic of Congo

A collaboration between MHCD
and Monash University

Dr Luc Mulimbalimba MP (MHCD)
Pete Lambert (Monash)

DRC Ampoule Collection

- 15 collection sites including:
 - Rural
 - Urban
 - Hospital
 - Clinic
 - Pharmacy
- 20 ampoules per site (where possible)
- Storage condition and instructions, manufacturer, batch details and expiry date recorded (where possible)
- Couriered to Monash, non-temperature controlled
- Oxytocin content assayed via validated HPLC method
- Degradants determined via validated LC/MS method
- Sterility tested via USP <71>

DRC Ampoule Samples - collected July 2016

Four manufacturers, eight different batches and a range of expiry dates (April 17 - Nov 2018)

- Bandundu $82.0 \pm 1.4\%$
- Bas Congo $95.9 \pm 11.7\%$
- Bukavu $69.0 \pm 8.8\%$
- Goma $79.7 \pm 4.3\%$
- Luvungi $75.8 \pm 2.5\%$
- Kinshasa $80.2 \pm 16.3\%$

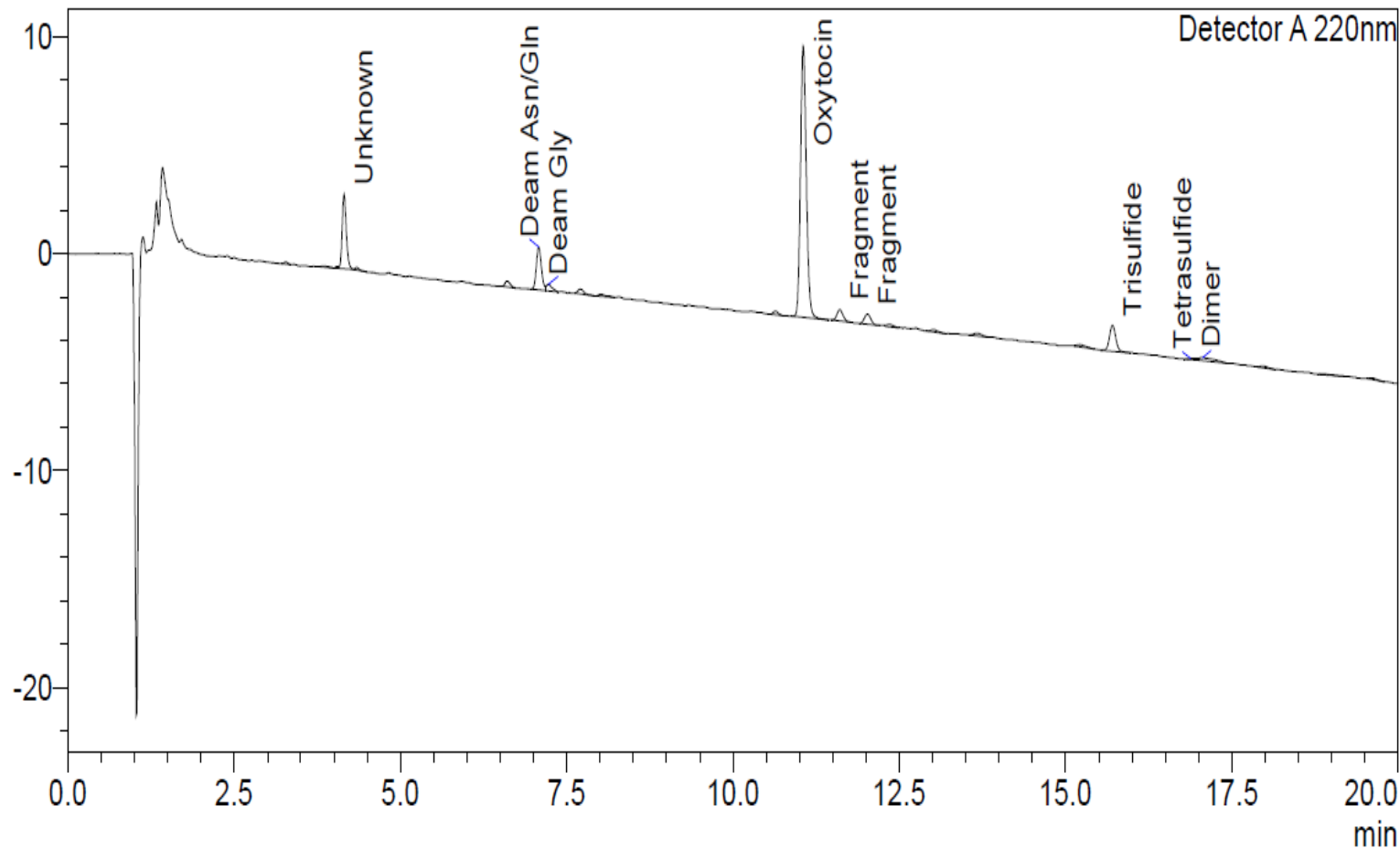
DRC Ampoule Samples

Manufacturer #1 - same batch number; expiry date Nov 2018

- Kinshasa hospital 99.1 ± 0.9%
- Kinshasa pharmacy 80.7 ± 2.0%
- Bandundu hospital 81.4 ± 1.0%
- Bandundu health clinic 82.8 ± 0.9%
- Bandundu rural pharmacy 1 82.0 ± 1.3%
- Bandundu rural pharmacy 2 81.8 ± 2.1%

Example UV Chromatogram

mV



Summary and Future Work

No ampoules were stored under refrigerated conditions

All ampoules supplied by Chinese manufacturers

79.5% of ampoules do not contain specified content of oxytocin

Unknown impurity (~10%) in all samples (not present in European samples)

All ampoules tested passed sterility testing

Further investigation into unknown impurity

Presentation of data to DRC MoH prior to publication of data

More comprehensive study planned in Ethiopia in partnership with FMHACA, MoH and MERQ Consultancy (in-country partner)