Quality of misoprostol and oxytocin products

Peter Hall

Concept Foundation, Bangkok and Geneva

- Quality of misoprostol products
- Factors influencing quality
- Working for quality
- Implications for procurement
- Quality of oxytocin products
- Storage and stability, use of cold chain
- Implications for procurement and supply chain

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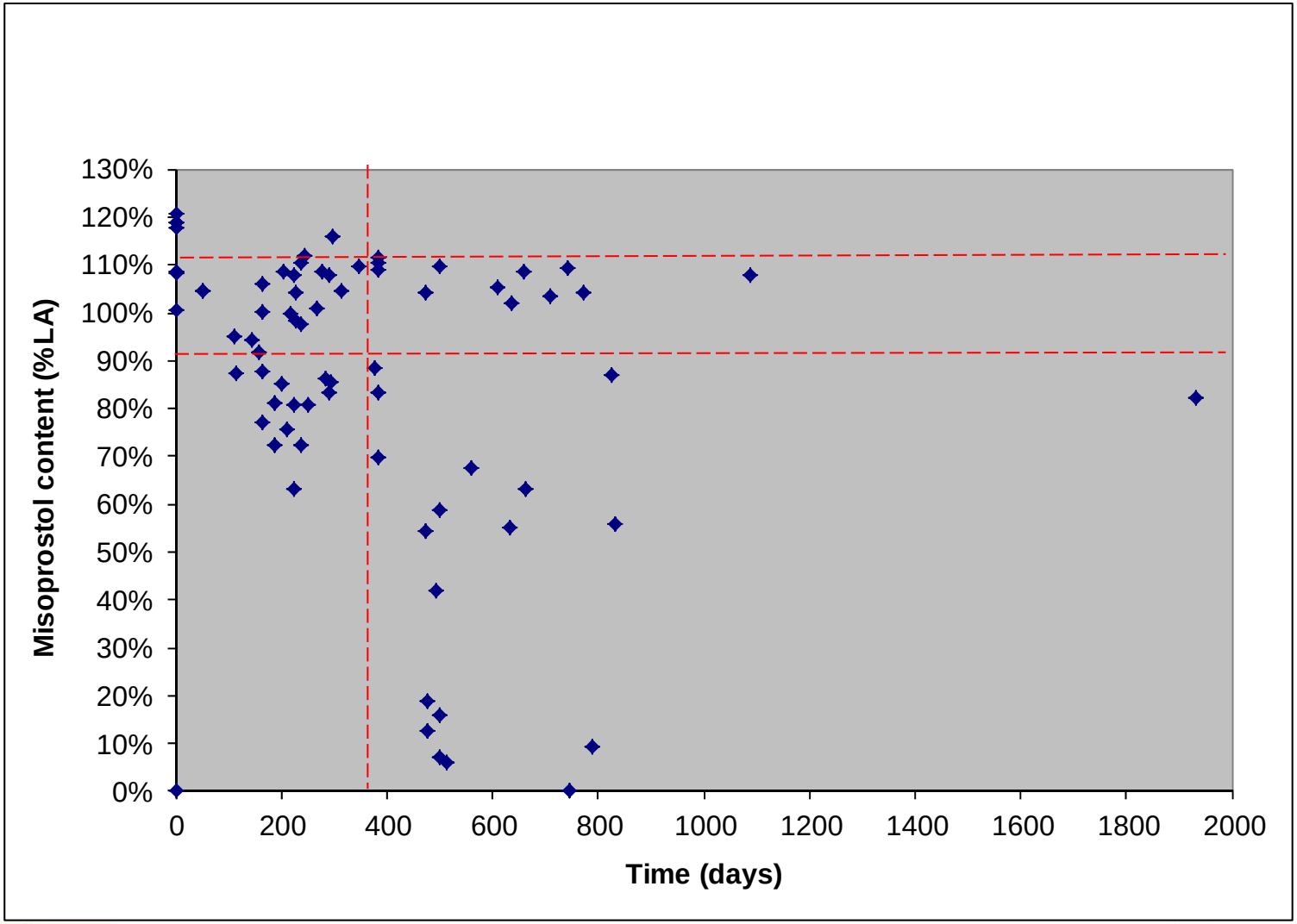
Misoprostol content by age



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Misoprostol study - overall conclusions

- Results showed significant problems with certain misoprostol finished products when analyzed for content and purity.
- With some products, misoprostol appeared to degrade rapidly between 3 months and one year (these would not have been detected by preshipment QC!).

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Misoprostol – working for quality

Concept discussed results with several of the principal manufacturers of misoprostol FPPs

Evidence that appropriate environmental control at all stages of manufacturing process and use of a double aluminium blister pack will prevent degradation of the finished product.

Together with API of proven quality and establishment of appropriate quality assurance procedures, manufacturers can make quality FPPs.

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Misoprostol – working for quality

Concept has visited 14 companies and concluded:

PQ by end of 2014	Potential for PQ in 2015	Not interested	Unlikely to achieve PQ
1 (1 PQd, Dec 13)	4	5	4

Worked with two API manufacturers to get misoprostol dispersion prequalified by WHO. One accepted and one under review.

Provided technical assistance to one manufacturer, now prequalified and to five additional manufacturers to meet GMP and submit appropriate documentation to the ERP/RHM and WHO PQP

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Misoprostol – working for quality

- Worked with Jhpiego on “Misoprostol business case”
- Developed clinical module for registration of dedicated product for prevention of PPH and incomplete abortion. Licensing, on non-exclusive basis, to all FPP manufacturers reaching WHO PQ.
- Concept’s ISO 17025 accredited laboratory (HCI) has developed and validated assay for misoprostol + A-type misoprostol (principal degradation product). Services provided to IPPF and MSI and for product assessment in Nepal and Nigeria in collaboration with UNFPA.

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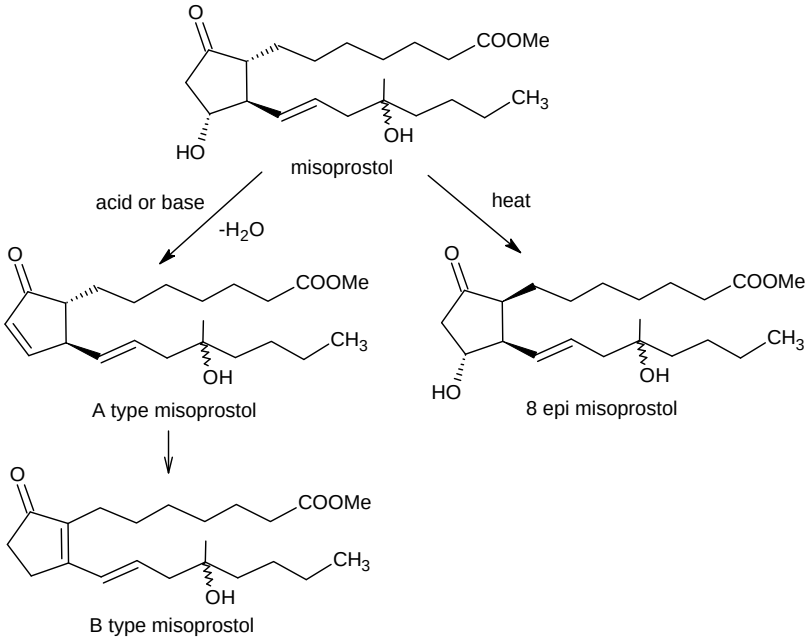
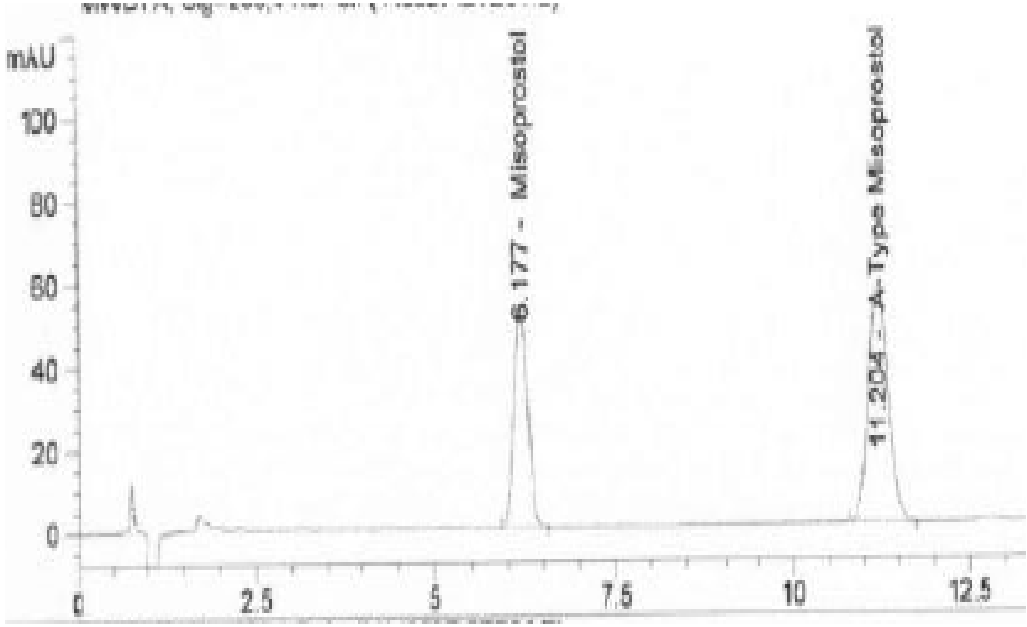
What happens to misoprostol





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What happens to misoprostol

No.	Packaging	Age at analysis - days	Misoprostol - %LC	A-type Misoprostol (µg/tablet)	Comment
1	Plastic/alu	483	52.7	56.93	Significant degradation
2	Plastic/alu	452	42.2	77.44	Significant degradation
3	Plastic/alu	150	104	16.7	Degradation observed, expect to begin losing potency.
4	Alu/alu	N/A	ND	ND	Likely to be counterfeit
5	Alu/alu	452	106.9	ND	Innovator
6	Alu-alu	181	100.2	6.06	Likely to lose some potency but in alu/alu, probably limited.
7	Alu-alu	181	109.4	ND	Satisfactory
8	Alu-alu	181	111.2	ND	Overage, no problem for use

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Implications for procurement

- Preshipment testing of little value for inappropriately manufactured and packaged product. Within 6 months, the product may only have 20% content!
- **Never** purchase product in plastic/aluminium blister packs.
- As quality-assured products (PQd by WHO or approved by a SRA) become available, national and international procurers must ensure that they purchase misoprostol from these manufacturers. The dangers of distributing poor quality product remain too great to ignore.

Oxytocin

- Some 300 brands, manufacturers likely to be more than 100, in all regions of the world.
- Studies by PATH and USP in Ghana, India and Indonesia have shown major problems of quality of oxytocin as well as in the sterility of products.
- In Ghana, 55.6% of the samples failed BP specifications (but actual content not reported). Out of 40 samples (all Chinese) tested for sterility, 35 failed! Of the 14 manufacturers, 11 were Chinese; only 2 products registered with the Ghana FDA.

UNColSC study by WHO

- Samples collected in 10 countries
  - Kenya, Madagascar, Nigeria, Uganda, Zimbabwe,
  - Burkina Faso, Nepal, Tajikistan, Tanzania, Vietnam only 5IU (10IU not available)
- 22 samples from 15 manufacturers in India, China, Germany, Hungary, Italy, Russia
- Problems with content (8 samples, <90.0%, although 5, 85.2-89.8%), impurities (14 samples, IP) and visible particles (3 samples)

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Storage conditions and stability data

A study undertaken for Concept in India identified 68 potential FPP manufacturers, 12 provided labelling on storage conditions and supporting stability data:

6, 2-8ºC; 2, "in a cold place"; 1, <25ºC;

2, <30ºC; and 1, "good and well storage".

Adequate stability data to support storage labelling claimed by 8/12 companies, including 2 stating either <25ºC or <30ºC.

In WHO study, labelling on storage conditions gave:

3, 2-8^{0}C; 1, 2-15^{0}C; 7, <20/25/30^{0}C;

1, above 0^{0}C; and 3 were not available

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UNCoLSC and oxytocin in the cold chain

- **High-level advocacy.** Aim for a joint WHO/ UNICEF statement to dispel the misconception that nothing but vaccines should go in the cold chain and recommend operations research (OR) on feasibility and challenges.
- **Country-level advocacy and targeted pilot operations research projects.** Selection of a few Pathfinder Countries for OR and provision of information and data generated to national decision-makers. at higher levels. UNCoLSC study by PATH ongoing in Mali and Ghana + briefing document "Placing Oxytocin in the Immunization Cold Chain" available.

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Implications for procurement and supply chain

- Major problem relates to heat-related degradation – inappropriate storage in the supply chain to and at health facilities.
- 20 years ago, WHO recommended that oxytocin should be kept refrigerated but that it could be kept for up to one month at 30°C or two weeks at 40°C
- Purchase of quality product + use of cold chain would be most effective risk mitigation strategy.