Quality Testing of Levonorgestrel Emergency Contraceptives

David Jenkins
FHI 360
September 26th, 2014

Emergency Contraceptives – Market Sampling

PSIA (Prosalud Inter Americana)

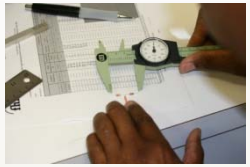
- **Interested in quality of ECs (0.75 mg / 1.5 mg Levonorgestrel tablets) available within South American market**
- **Large number of brands available**
- **Peru has ~20 brands registered that are manufactured in approximately 10 different countries**
- **contacted FHI 360's (www.fhi360.org) Product Quality and Compliance (PQC) Laboratory (c/o David Jenkins)**

Emergency Contraceptives – Market Sampling

FHI 360's Laboratory

- **Experience in quality assurance testing for public health commodities for USAID, PSI, MSI, and others…**

Medical devices




Pharmaceuticals


- **US laboratory is ISO 17025 accredited by A2LA (American Association of Laboratory Accreditation)**

Emergency Contraceptives – Market Sampling

- **PQC contracted an independent organization within Peru to purchase samples at pharmacies**

- **Each sample comprised of >60 tablets from the same brand and batch, where the following was recorded:**
  - **Brand**
  - **Manufacturer**
  - **Lot Number**
  - **Number of tablets / blister packs purchased**
  - **Manufacturing Date**
  - **Expiration Date**
  - **Date Purchased**
  - **Purchaser**
  - **Address of Purchase**

Emergency Contraceptives – Market Sampling

- **Samples from 20 different EC brands were obtained**
  - **13 lots of 1.5 mg Levonorgestrel tablets**
  - **12 lots of 0.75 mg Levonorgestrel tablets**
- **Due to the nature of the results, product brand names and manufacturers will not be revealed**
- **Pictures of product / packaging were taken upon arrival at the laboratory**

Emergency Contraceptives – Market Sampling

Tested to the Ph. Int. (Levonorgestrel Tablets)

http://www.who.int/medicines/publications/pharmacopoeia/Levonorgestrel-tabs_QAS10-371FINAL.pdf

- **ID – based on TLC (A) and HPLC (B)**
- **Dissolution – in-vitro measure of release of API from the product (Q=75%)**
- **Limit of dextronorgestrel – HPLC method that can quantify the two types of norgestrel…dextro (bio-inactive) and levo (bio-active)**
- **Related Substances – impurity quantification**
- **Assay / Content Uniformity – measure of the amount and variance of the levonorgestrel**

Emergency Contraceptives – Market Sampling

API Level	Product Code - Expiration Date (a)	Dissolution (Stage; AVG)	Related Substances	Assay-CU (Min. – Max.)
1.5 mg	1 - Feb 2016	S2; 80.1	S-0.1%, T-0.6%	100.0; 97.7 - 102.4
	2a - May 2015	NC	NC	NC
	2b - Aug 2016	S2; 77.4	S-0.3%, T-1.0%	95.1; 82.2 - 103.4
	2c – Dec 2016	S3; 58.5	S-0.4%, T-1.3%	96.2; 85.4 – 136.6
	3a - Oct 2015	S1; 94.3	S-0.4%, T-1.1%	101.3; 100.5 - 102.6
	3b - Dec 2016	S3; 73.0	S-0.6%, T-1.8%	97.6; 90.0 - 105.7
	4 - Oct 2014	S1; 59.6 (b)	S-0.9%, T-1.5%	96.7; 93.3 - 98.0
	5a - Dec 2013	S1; 93.8	S-0.4%, T-1.4%	97.3; 96.5 - 98.6
	5b - Nov 2013	S1; 98.2	S-0.3%, T-1.4%	97.0; 88.2 - 99.5
	6 - Apr 2014	S3; 57.8	S-0.3%, T-1.3%	99.0; 92.9 - 102.6
	7 - Oct 2013	S1; 95.2	S-0.3%, T-1.1%	91.4; 86.3 -93.8
	8 - Apr 2013	S1; 95.7	S-0.4%, T-1.8%	96.0; 93.6-97.7
	9 - May 2014	S2; 76.7	S-0.5%, T-1.4%	98.3; 94.8-101.0

(a) With exception of 2a, all samples yielded compliant results for ID (TLC and confirmation of levonorgestrel through the HPLC evaluation for dextronorgestrel). No sample showed evidence of dextronorgestrel.
(b) Only Stage 1 was conducted because 3 tablets were found to be below 60%.

Emergency Contraceptives – Market Sampling

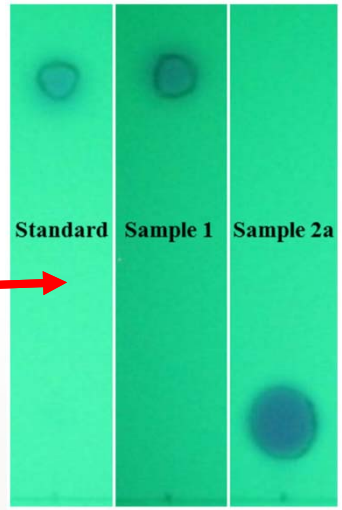
API Level	Product Code - Expiration Date (a)	Dissolution (Stage; AVG)	Related Substances	Assay-CU (Min. – Max.)
0.75 mg	10 – Oct 2014	S1; 0.0 (b)	S-62.3%, T-72.9%	92.3; 72.9 - 126.5
	11 - Dec 2014	S2; 77.0	S-0.2%, T-0.4%	100.4; 97.7 - 103.7
	12 - Jul 2013	S1; 83.6	S-0.4%, T-1.2%	99.9; 95.0 - 105.6
	13 - Sept 2015	S2; 77.8	S-0.2%, T-0.6%	99.3; 98.3 - 100.7
	14a - June 2014	S1; 90.6	S-0.5%, T-1.6%	101.9; 100.1 - 104.7
	14b - June 2014	S1; 88.3	S-0.5%, T-1.5%	102.0; 100.8 - 103.6
	15 - Nov 2013	S1; 92.5	S-0.3%, T-1.3%	99.8; 93.2 - 105.3
	16 - Sept 2013	S1; 89.5	S-0.4%, T-0.5%	102.5; 100.3 - 105.6
	17 - Oct 2013	S1; 95.2	S-0.4%, T-2.0%	96.4; 71.5 – 115.1
	18 - Aug 2013	S1; 92.9	10 - Oct 2014	98.3; 94.2 - 103.3
	19 - Nov 2013	S2; 79.8	S-0.3%, T-1.6%	101.7; 94.8 - 106.2
	20 - Mar 2015	S1; 101.5	S-0.4%, T-1.5%	104.2; 99.8 - 116.4

(a) With exception of 2a, all samples yielded compliant results for ID (TLC and confirmation of levonorgestrel through the HPLC evaluation for dextronorgestrel). No sample showed evidence of dextronorgestrel.
(b) No active release was observed on the 6 tablets tested. Additional tablets were tested for longer periods of release (1 hour) and observed ~2-5% release of active.

Emergency Contraceptives – Market Sampling

Major Finding

- Product 2a – did not show any evidence for levonorgestrel, but for another compound
- TLC was first evidence (confirmed with HPLC)



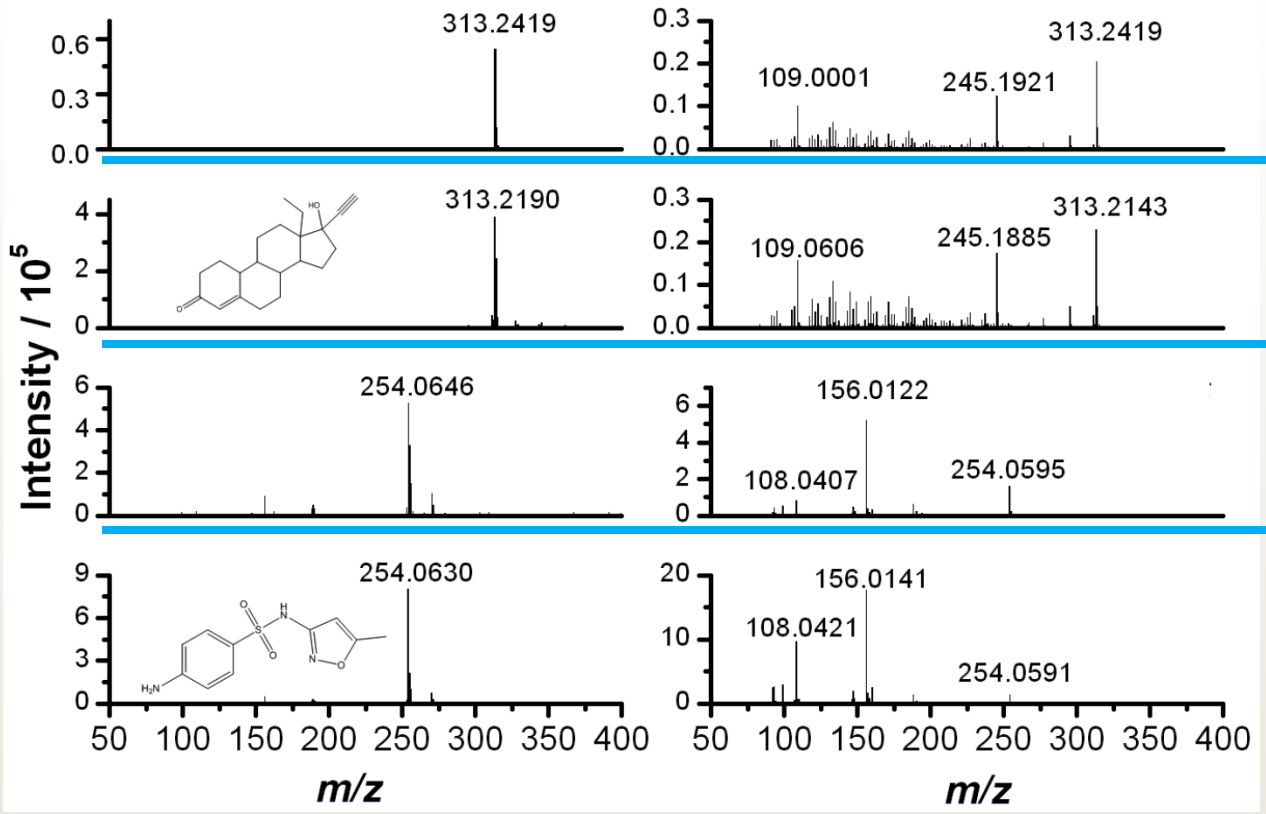
Need to identify unknown compound

- Additional analysis requested from Professor Facundo Fernández's research group – School of Chemistry and Biochemistry of the Georgia Institute of Technology
- Prof. Fernández's group - Experienced in the analysis of falsified / substandard pharmaceuticals using various techniques (based primarily on mass spectrometry)

Emergency Contraceptives – Market Sampling

Major Finding

Mass Spec confirmed the absence of levonorgestrel in 2a, but presence of sulfamethoxazole (common antibiotic)



Tablet with Levonorgestrel

Levonorgestrel Standard

Sample 2a

Sulfamethoxazole Standard

Emergency Contraceptives – Market Sampling

Overall Summary

- 25 samples in total; 18 fully compliant (72%)
- One sample (2a) showed no evidence of levonorgestrel but contained sulfamethoxazole and another (10) did not release active (8% ineffective)
- Lower levels of release (2c, 3b, 4, 6) and high range of API (17) may yield questionable therapeutic effect (20%)
- Peruvian authorities contacted regarding results

Emergency Contraceptives – Market Sampling

Overall Summary

- **PLoS ONE publication**
- "A Tiered Analytical Approach for Investigating Poor Quality Emergency Contraceptives", MEMonge, PDwivedi, MZhou, MPayne, CHarris, BHouse, YJuggins, PCizmarik, PNNewton, FMFernández, DJenkins, *PLOS One,* **2014,** *9(4)*, e95353. http://dx.doi.org/10.1371/journal.pone.0095353

- **Press Attention…**
- **DIGEMID halted activity with a major distributor in Peru**
- **Testing from Venezuela (completed)**
- **Samples from Bolivia and Ecuador in process**

Emergency Contraceptives – Market Sampling

Working Towards Solutions to the Problem

- **Sources for Poor Quality Medications**
  - **Substandard Manufacturing**
  - **Deterioration**
  - **Falsification**
- **Results could have occurred from any of these sources**
- **Need increased Resources**
  - **Regulatory Oversight for Product Registration**
  - **Monitoring of Manufacturers / Distribution Mechanisms**
  - **Further monitoring of field samples - continue pharmacopeia analysis, utilize Mass Spec, NIR, Raman techniques…expand scope of GPHF Minilab for hormonal contraceptives**

Emergency Contraceptives – Market Sampling

Acknowledgements

None of the authors have any competing interests

Michael Payne – TLC, Limit of Dextronorgestrel

Chris Harris – Assay/CU, Related Substances

Blaine House – Dissolution

Yvonne Juggins – Data Analysis / Report Prep.

Peter Cizmarik – Data Analysis / Report Prep.

Dr. Maria Eugenia Monge – Mass Spec Analysis

Dr. Prabha Dwivedi – Mass Spec Analysis

Dr. Manshui Zhou – Mass Spec Analysis

Prof. Facundo Fernandez – Mass Spec Analysis

Dr. Paul Newton – Additional Sample / Data Analysis