Quality Testing of Levonorgestrel Emergency Contraceptives

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FHI 360
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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](http://www.fhi360.org) Product Quality and Compliance (PQC) Laboratory (c/o David Jenkins)
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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)
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• 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
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- 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
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Tested to the Ph. Int. (Levonorgestrel Tablets)


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

(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%.

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**fhi360**
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</tr>
</thead>
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<tr>
<td>0.75 mg</td>
<td>10 – Oct 2014</td>
<td>S1; 0.0 (b)</td>
<td>S-62.3%, T-72.9%</td>
<td>92.3; 72.9 - 126.5</td>
</tr>
<tr>
<td></td>
<td>11 - Dec 2014</td>
<td>S2; 77.0</td>
<td>S-0.2%, T-0.4%</td>
<td>100.4; 97.7 - 103.7</td>
</tr>
<tr>
<td></td>
<td>12 - Jul 2013</td>
<td>S1; 83.6</td>
<td>S-0.4%, T-1.2%</td>
<td>99.9; 95.0 - 105.6</td>
</tr>
<tr>
<td></td>
<td>13 - Sept 2015</td>
<td>S2; 77.8</td>
<td>S-0.2%, T-0.6%</td>
<td>99.3; 98.3 - 100.7</td>
</tr>
<tr>
<td></td>
<td>14a - June 2014</td>
<td>S1; 90.6</td>
<td>S-0.5%, T-1.6%</td>
<td>101.9; 100.1 - 104.7</td>
</tr>
<tr>
<td></td>
<td>14b - June 2014</td>
<td>S1; 88.3</td>
<td>S-0.5%, T-1.5%</td>
<td>102.0; 100.8 - 103.6</td>
</tr>
<tr>
<td></td>
<td>15 - Nov 2013</td>
<td>S1; 92.5</td>
<td>S-0.3%, T-1.3%</td>
<td>99.8; 93.2 - 105.3</td>
</tr>
<tr>
<td></td>
<td>16 - Sept 2013</td>
<td>S1; 89.5</td>
<td>S-0.4%, T-0.5%</td>
<td>102.5; 100.3 - 105.6</td>
</tr>
<tr>
<td></td>
<td>17 - Oct 2013</td>
<td>S1; 95.2</td>
<td>S-0.4%, T-2.0%</td>
<td>96.4; 71.5 – 115.1</td>
</tr>
<tr>
<td></td>
<td>18 - Aug 2013</td>
<td>S1; 92.9</td>
<td>10 - Oct 2014</td>
<td>98.3; 94.2 - 103.3</td>
</tr>
<tr>
<td></td>
<td>19 - Nov 2013</td>
<td>S2; 79.8</td>
<td>S-0.3%, T-1.6%</td>
<td>101.7; 94.8 - 106.2</td>
</tr>
<tr>
<td></td>
<td>20 - Mar 2015</td>
<td>S1; 101.5</td>
<td>S-0.4%, T-1.5%</td>
<td>104.2; 99.8 - 116.4</td>
</tr>
</tbody>
</table>

(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.
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**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)
Major Finding

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

- **PLoS ONE publication**

- **Press Attention…**
- DIGEMID halted activity with a major distributor in Peru
- Testing from Venezuela (completed)
- Samples from Bolivia and Ecuador in process
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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
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Prof. Facundo Fernandez – Mass Spec Analysis
Dr. Paul Newton – Additional Sample / Data Analysis