Product Recalls and Failure Modes – A Case Study with Phenytoin Sodium

Reference resource

Mansoor A. Khan, Ph.D.
Professor and Vice Dean
Interim Head, Department of Pharmaceutical Sciences
Presidential Impact Fellow
Texas A&M University, College Station
Outline

• Product Recalls
• Why Phenytoin Sodium?
• In-house formulations
• Commercial products
Total recalls - 10284

• Class 1 recalls - 1139
• Class 2 recalls – 8034
• Class 3 recalls – 1070
• Unclassified – 40
Type of submissions (only by word searches at this time)

- NDAs – 526
- ANDAs – 1186
- BLAs – 8
- OTC – 168
- Compounding 1580
Top reasons of recall

- cGMP issues – 905
- Microbial contamination – 741
- Stability – 606
- Degradation – 339
- Particulates – 302
- Data integrity – 266
- Dissolution – 198
- Superpotent – 116
- Potency failures – 106
Recall by dosage forms

- Tablets – 1697
- Injections - 1501
- Solutions – 1061
- Capsules – 746
- Creams – 214
- Suspensions – 115
- Ointment – 51
- Syrups – 45
<table>
<thead>
<tr>
<th>Route</th>
<th># recalls</th>
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<tbody>
<tr>
<td>[ORAL]</td>
<td>1459</td>
</tr>
<tr>
<td>[INTRAVENOUS]</td>
<td>308</td>
</tr>
<tr>
<td>[TOPICAL]</td>
<td>153</td>
</tr>
<tr>
<td>[INTRAMUSCULAR, INTRAVENOUS]</td>
<td>77</td>
</tr>
<tr>
<td>[TRANSDERMAL]</td>
<td>44</td>
</tr>
<tr>
<td>[OPHTHALMIC]</td>
<td>42</td>
</tr>
<tr>
<td>[RESPIRATORY (INHALATION)]</td>
<td>23</td>
</tr>
<tr>
<td>[NASAL]</td>
<td>18</td>
</tr>
<tr>
<td>[INTRACAUDAL, PERINEURAL, EPIDURAL, INFILTRATION]</td>
<td>16</td>
</tr>
<tr>
<td>[INTRAMUSCULAR, INTRAVENOUS, SUBCUTANEOUS]</td>
<td>13</td>
</tr>
<tr>
<td>[INTRAMUSCULAR]</td>
<td>13</td>
</tr>
<tr>
<td>[SUBCUTANEOUS]</td>
<td>12</td>
</tr>
<tr>
<td>[IRRIGATION]</td>
<td>8</td>
</tr>
<tr>
<td>[AURICULAR (OTIC)]</td>
<td>7</td>
</tr>
<tr>
<td>[PERINEURAL, INFILTRATION]</td>
<td>6</td>
</tr>
<tr>
<td>[RECTAL]</td>
<td>6</td>
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<tr>
<td>[INTRAVENOUS, SUBCUTANEOUS]</td>
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<td>[DENTAL]</td>
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<tr>
<td>[INTRAPERITONEAL]</td>
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</tbody>
</table>
History

• Synthesized by German chemist Heinrich Biltz in 1908 and sold to his discovery to Parke-Davis

• In 1938, outside scientists including H. Houston Merritt and Tracy Putnam discovered phenytoin's usefulness for controlling seizures

• FDA approved it for seizure in 1953

• Available dosage forms – prompt and extended release capsule, chewable tablets and injection

• Among Top 200 drugs – 158

• More than 4.1 million prescription written in 2015

• First-line drug in the management of seizures in emergency room

• One of the cheapest antiepileptic drug
History

• Narrow therapeutic drug
• Variability in clinical response – Pharmacokinetic, pharmacodynamics, pharmacogenomics
• Among top 10 drugs in the FAR
• Product recalls – Brand and generics
• $10 million fine for hiding quality issues of Dilantin
Lawsuits

Pfizer’s drug Dilantin causes Cerebellar Atrophy

May 7, 2018
Design Space for Phenytoin Capsules

Step 1: Create/Conduct Designed Expt

<table>
<thead>
<tr>
<th>Blend Time</th>
<th>Milling</th>
<th>None</th>
<th>Once</th>
<th>Twice</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>R01</td>
<td>R04</td>
<td>R07</td>
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<tr>
<td>45 min</td>
<td>R02</td>
<td>R05</td>
<td>R08</td>
<td></td>
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<tr>
<td>75 min</td>
<td>R03</td>
<td>R06</td>
<td>R09</td>
<td></td>
</tr>
</tbody>
</table>

additional centers: R10, R11

Step 2: Measure Product Performance

Step 3: Select Design Space

- 30 min: Q = 20-40%
- 60 min: Q' = 40-80%
- 120 min: Q'' > 75%

Step 4: Conrol the process

NIR Probe Spectrometer unit

FDA: Pfizer Crada
Phenytoin

Fig. 15-3. Phenytoin levels in blood at the time patients experienced certain adverse effects of the drug. (Data from Kutt, H., et al.70)

Table 15-4. Relationship Between Degree of Seizure Control and Plasma Phenytoin Concentration Interval*

<table>
<thead>
<tr>
<th>Phenytoin concentration (μg/ml)</th>
<th>No. of patients</th>
<th>No. of patients without seizures during 2 mo</th>
<th>Seizure-free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 9.9</td>
<td>95</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>10.0 to 19.9</td>
<td>33</td>
<td>24</td>
<td>72</td>
</tr>
<tr>
<td>above 20.0</td>
<td>20</td>
<td>19</td>
<td>95</td>
</tr>
</tbody>
</table>

*Data from Lund, L.69
Pharmaceutics Core

- High Shear granulator, Model KG5 (Key International Inc)
- 10-station tableting machine (Mini Press-1, Globe Pharma)
- Quadro Co-Mill
- 3D-Printer
- V-blender, Model VH2
- Niro Fluid Bed Processor, Model Strea-1
- Microfluidizer M-110L (Microfluidcs)
- 8” Vector Hi Coater, Model HCT Mini
**Analytical testing capability**

- Analytical method development and validation
- Assay and impurities by HPLC
- (three systems, Agilent 1290)/UPLC-MS (Waters, Acquity H-Class)
- Dissolution (USP Apparatus 1 and 2) (three systems, Agilent and Distek)
- Differential scanning calorimetry (DSC) (Q2000, TA Instruments)
- Thermal gravimetric analysis (TGA) (Q5000, TA Instruments)
- Powder X-Ray diffractometry (PXRD) (D2 Phaser, Bruker)
- Particle Sizing (solid and liquid) (PSA 1190, Anton Paar)
- Texture Analyzer
  - Melting point
  - Infra-Red, FTIR and Raman (Model Nicolet IS50 FTIR GOLD SPEC, IS50 NIR Module INTG Sphere, IS50 SABIR Fiber Probe 2M, IS50 Raman Module and IS50 ATR Module Kit)
  - Ultra-Violet/Visible Spectroscopy
  - Chemical mapping (Raman confocal) (Horiba)
  - Chemical imaging (NIR hyperspectroscopy)
Pharmaceutics Core – Stability studies
In-house Formulations

• Capsules formulation composition
  • Phenytoin sodium - 52.63%
  • Lactose monohydrate -31.58%
  • Magnesium stearate - 5.26%
  • HPMC K4M - 10.53%
• Process variables
  • B1 – Dry mixing
  • B2 – Granulated with water
  • B3 – Granulated with ethanol
  • B4 – Granulated with water-ethanol mixture
• Characterized – Assay, dissolution, spectroscopic, X-ray powder and NIR hyperspectroscopic
• Stability - 40 ºC /75% RH and 30 ºC /65% RH for 4 weeks
## In-house Formulations

### Initial Samples

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Assay</th>
<th>Weight gain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>30 °C/65% RH</td>
</tr>
<tr>
<td>B1</td>
<td>105.85±3.62</td>
<td>84.08±4.56</td>
</tr>
<tr>
<td>B2</td>
<td>97.07±5.00</td>
<td>85.09±0.95</td>
</tr>
<tr>
<td>B3</td>
<td>100.07±1.15</td>
<td>94.05±3.38</td>
</tr>
<tr>
<td>B4</td>
<td>105.95±5.37</td>
<td>95.23±4.62</td>
</tr>
</tbody>
</table>

### After 4 Weeks at 40°C/75%RH

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Assay</th>
<th>Weight gain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>40 °C/75% RH</td>
</tr>
<tr>
<td>B1</td>
<td>99.54±2.58</td>
<td>8.55±1.76</td>
</tr>
<tr>
<td>B2</td>
<td>98.78±1.62</td>
<td>9.92±1.66</td>
</tr>
<tr>
<td>B3</td>
<td>103.29±2.48</td>
<td>4.02±0.89</td>
</tr>
<tr>
<td>B4</td>
<td>105.49±3.33</td>
<td>3.31±2.32</td>
</tr>
</tbody>
</table>
In-house Formulations

- Initial—All the formulations exhibited similar FTIR spectra except formulation B4. Doublet peaks of PS at 1572 and 1592 cm⁻¹ and 1674 and 1687 cm⁻¹ were not well defined in the case of formulation B4 that was granulated with water-ethanol mixture. It indicated low-level conversion of PS into PHT and/or interactions.

- Stability
  - Two doublets and hump peaks at 1592 and 1574 cm⁻¹, and 1674 and 1687 cm⁻¹ and 3318 cm⁻¹ disappeared.
  - Peaks of PHT appeared at 1712, 1738, 1770, 3202 and 3263 cm⁻¹ that indicated complete conversion of PS into PHT in those formulations.
In-house Formulations

- Initial—All the formulations exhibited similar NIR spectra except formulation B4 where peaks due to PS and LM were less sharp and of low intensity, and exhibited low intensity peak of PHT at 4798 cm\(^{-1}\)
- Stability
  - LM peak at 5192 cm\(^{-1}\) disappeared indicating either its degradation or interaction of with formulation components
  - Triplet peaks of PS at 4516, 4574 and 4624 cm\(^{-1}\) appeared as singlet peak at 4584 cm\(^{-1}\) of PHT
  - sharp peak of PHT at 4798 cm\(^{-1}\) was also present, and valley due to PS at 5218 cm\(^{-1}\) disappeared
  - NIR data suggested complete conversion of PS into PHT in the formulations stored at 40 °C/75% RH
In-house Formulations

- Peaks of PS at 9.40, 9.90, 11.05, 13.04, 14.10, 15.02, 21.87, 22.33 and 23.00° disappeared, appeared as a notch or significant reduction in intensity in the formulation B4. Thus, differently processed formulations might have different ratio of amorphous and crystalline forms, even new polymorphic forms or interaction between among components of formulations.

- Stability
  - The major changes observed were appearance of PHT peaks, disappearance of PST peaks and disappearance and/or distortion of LM peaks and appearance of new peaks.
  - Peaks of PS at 9.40, 11.02, 11.75, 13.04, 14.10, 15.02 and 23.00° disappeared.
  - PHT peaks at 10.95, 12.60, 16.20, 16.85, 17.80, 25.55 and 26.52° appeared.
  - Peaks intensity of LM at 12.41, 16.29, 19.04, 19.47, 19.87 and 20.74 decreased or peaks were distorted.
In-house Formulations

- Indicated conversion of PS into PHT
In-house Formulations

Phenytoin sodium disproportionation

Lactose

Maillard reaction

Colored products
In-house Formulations

- USP basket method in 900 mL water at 100 rpm
- USP dissolution specification - 75% in 120 min
- Only B1 meeting USP specification at initial time point
- Products failed in stability
In-house Formulations

Effect of processing parameters and controlled environment storage on the disproportionation and dissolution of extended-release capsule of phenytoin sodium


Quantitative estimation of phenytoin sodium disproportionation in the formulations using vibration spectroscopies and multivariate methodologies

Sathish Dharani, Ziyaur Rahman, Sogra F. Barakhi Ali, Hamideh Afrooz, Mansoor A. Khan
## Commercial formulations

- Three commercial products
- In-use stability testing at 30 °C/75% RH for 12 weeks
- Tests- Assay, impurity, dissolution, XRD, FTIR and NIR chemical imaging and SEM

<table>
<thead>
<tr>
<th>Product</th>
<th>Product-A</th>
<th>Product-B</th>
<th>Product-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDC code</td>
<td>00071-0369-32</td>
<td>65162-0212-10</td>
<td>62756-0402-01</td>
</tr>
<tr>
<td>Lot number</td>
<td>R78275</td>
<td>HK13117</td>
<td>JKR7571A</td>
</tr>
<tr>
<td>Expiration date</td>
<td>Nov 2018</td>
<td>Oct 2019</td>
<td>Nov 2018</td>
</tr>
<tr>
<td>Inactive ingredients</td>
<td>Lactose monohydrate, NF; confectioner's sugar, NF; talc, USP; and magnesium stearate, NF</td>
<td>D&amp;C Red #28, D&amp;C Red #33, FD&amp;C Blue #1, gelatin, hydroxypropyl cellulose, mannitol, magnesium stearate, talc and titanium dioxide</td>
<td>Lactitol monohydrate, sodium lauryl sulfate, talc and magnesium stearate.</td>
</tr>
<tr>
<td>Component of capsule shell</td>
<td>FD&amp;C red No. 28; FD&amp;C yellow No. 6; and gelatin NF</td>
<td>Not described</td>
<td>gelatin, and black printing ink, which contains black iron oxide, FD&amp;C Blue No. 2, FD&amp;C Red No. 40, FD&amp;C Blue No. 1, D&amp;C Yellow No. 10, shellac glaze and SDA 3A alcohol or N-butyl alcohol and propylene glycol</td>
</tr>
</tbody>
</table>
Commercial formulations

Initial

Product-A

Product-B

Product-C

After 4 weeks at 30 °C/75% RH
No changes in Product B and C
Notable peaks of PHT appeared were 3263, 3202, 1770, 1738 and 1712 cm\(^{-1}\). Peaks of PS at 3318, 1688 and 1674 cm\(^{-1}\) disappeared while doublet peaks at 1592 and 1574 cm\(^{-1}\) appeared as a single broad peak at 1579 cm\(^{-1}\) after 8 and 12 weeks exposure to in-use conditions.
Product-A, peaks of PS completely disappeared while prominent peaks of PH at 10.95, 12.60, 16.20, 16.85, 17.80, 19.97, 22.03 and 25.55° appeared. Moreover, triplet peaks of LMH become distorted and many new peaks appeared in 8 and 12 weeks stability samples. Product-B and Product-C indicated conversion of PS into PHT.
Commercial formulations

PS to PHT conversion
non-uniform in the case of Product-A
Commercial formulations

PS to PHT conversion in Product-B
Commercial formulations

PS to PHT conversion in Product-C
## Commercial Formulations

<table>
<thead>
<tr>
<th>Test method</th>
<th>Strength</th>
<th>Dissolution test conditions</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>30 mg Capsules</td>
<td>900 ml water, apparatus I, 50 rpm</td>
<td>30 min – 25-35% 60 min – 46-66% 120 min – NLT 70%</td>
</tr>
<tr>
<td></td>
<td>100 mg capsules</td>
<td></td>
<td>30 min – 20-40% 60 min – 40-80% 120 min – NLT 75%</td>
</tr>
<tr>
<td>Test 2</td>
<td>100 mg capsules</td>
<td>900 ml water, apparatus I, 75 rpm</td>
<td>30 min – 20-40% 60 min – 45-85% 120 min – NLT 75%</td>
</tr>
<tr>
<td>Test 3</td>
<td>200 mg and 300 mg capsules</td>
<td>900 ml water, apparatus I, 75 rpm</td>
<td>30 min – 10-35% 60 min – 30-85% 120 min – NLT 65%</td>
</tr>
<tr>
<td>Test 4</td>
<td>30 mg capsules</td>
<td>900 ml water, apparatus I, 50 rpm</td>
<td>30 min – 30-40% 60 min – 47-63% 120 min – NLT 70%</td>
</tr>
<tr>
<td>Test 5</td>
<td>100 mg capsules</td>
<td>900 ml water, apparatus I, 50 rpm</td>
<td>30 min – 20-40% 60 min – 50-85% 120 min – NLT 85%</td>
</tr>
</tbody>
</table>
Product-A failed in dissolution test in 4-weeks while Product-B and Product-C failed in 6-weeks
# Commercial Formulations

<table>
<thead>
<tr>
<th></th>
<th>Product-A</th>
<th>Product-B</th>
<th>Product-C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial</strong></td>
<td>Assay - 102.8±0.0</td>
<td>Assay - 96.3±0.1</td>
<td>Assay – 97.7±0.6</td>
</tr>
<tr>
<td>Assay - 96.1±0.2</td>
<td>Assay – 98.5±0.0</td>
<td>Assay - 96.0±3.2</td>
<td>Impurity A - 98.3±0.1</td>
</tr>
<tr>
<td>Assay – 96.0±0.1</td>
<td>Assay – 98.7±0.1</td>
<td>Assay – 98.7±0.1</td>
<td>Impurity A - 98.3±0.1</td>
</tr>
<tr>
<td><strong>4 weeks</strong></td>
<td>Assay- 96.1±0.2</td>
<td>Assay – 98.5±0.0</td>
<td>Assay – 97.7±0.6</td>
</tr>
<tr>
<td>Assay - 96.0±0.1</td>
<td>Assay – 98.7±0.1</td>
<td>Assay – 98.7±0.1</td>
<td>Impurity A - 98.3±0.1</td>
</tr>
<tr>
<td><strong>8 weeks</strong></td>
<td>Assay – 96.0±0.1</td>
<td>Assay – 98.7±0.1</td>
<td>Assay – 98.7±0.1</td>
</tr>
<tr>
<td>Assay – 96.0±0.1</td>
<td>Assay – 98.7±0.1</td>
<td>Assay – 98.7±0.1</td>
<td>Impurity A - 98.3±0.1</td>
</tr>
<tr>
<td><strong>12 weeks</strong></td>
<td>Assay 92.5±0.8</td>
<td>Assay 95.3±0.1</td>
<td>Assay – 97.7±0.6</td>
</tr>
<tr>
<td>Assay – 92.5±0.8</td>
<td>Assay – 95.3±0.1</td>
<td>Assay – 97.7±0.6</td>
<td>Impurity A - 98.3±0.1</td>
</tr>
</tbody>
</table>

**USP Assay limit** - 95-105%

Impurity A – 0.5%

Impurity B - 1%
Staff at DPQR and Texas A&M FDA PQFACT Team
Ziyaur Rahman, Ph.D
Sathish Dharani, Ph.D.
Hamideh Afrooz, Pharm.D.
Raktima Bhattacharya, Ph.D.
Sogra Fathima, Ph.D.