FDA Regulation of Promotion & Advertising

Part 4: FDA Enforcement

ComplianceOnline Seminar
January 24-25, 2013

Michael A. Swit, Esq.
# Statistical Record – OPDP/DDMAC

<table>
<thead>
<tr>
<th>Year</th>
<th>Warning Letters</th>
<th>Untitled</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>3</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>2011</td>
<td>5</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>2010</td>
<td>13</td>
<td>38</td>
<td>51</td>
</tr>
<tr>
<td>2009</td>
<td>11</td>
<td>30</td>
<td>41</td>
</tr>
<tr>
<td>2008</td>
<td>10</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>2007</td>
<td>9</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>2006</td>
<td>14</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>2005</td>
<td>15</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>2004</td>
<td>12</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>2003</td>
<td>5</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>2002</td>
<td>1</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>2001</td>
<td>7</td>
<td>66</td>
<td>73</td>
</tr>
<tr>
<td>2000</td>
<td>4</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td>1999</td>
<td>3</td>
<td>105</td>
<td>108</td>
</tr>
<tr>
<td>1998</td>
<td>10</td>
<td>157</td>
<td>167</td>
</tr>
<tr>
<td>1997</td>
<td>0</td>
<td>137</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td><strong>122</strong></td>
<td><strong>760</strong></td>
<td><strong>882</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Average/Yr:</strong></td>
<td><strong>7.6</strong></td>
<td><strong>55.1</strong></td>
</tr>
</tbody>
</table>

• Omission or minimization or risk information
• Misleading efficacy claims
• Misleading superiority claims
• Promotion of unapproved uses of drugs, including broadening the indication

Copaxone Warning Letter

• March 14, 2012 – Teva –
  – Hot Link – Warning Letter
  – Hot Link – Teva promotional materials

• 2011 AAN Exhibit Panels and “Team Copaxone” webpages relating to David Kyle and Karen Stewart

• General allegations – false or misleading – due to:
  – overstate efficacy
  – present unsubstantiated claims
  – broaden indication of drug
  – present unsubstantiated superiority claims
  – omit material facts
Copaxone -- Overstating Efficacy

- **AAN Panel Claims:**
  - “20 years of proven safety” … “up to 15 years continuous Copaxone therapy” … “Expanded Disability Status Scale (EDSS) scores remained stable after an average of 15 years on therapy”
  - **FDA:**
    - these overstate safety and efficacy by implying long-term data; however, the PI (package insert) only includes data for up to 3 years
    - you also cited an open-label extension study – that is not “substantial evidence”
      - only 100/231 patients remained
      - need adequate & well-controlled studies
Copaxone …

• **Unsupported comparative claim:**
  – **Claim:** “No other RRMS therapy can demonstrate the long-term results like Copaxone”
  – **FDA:** we are unaware of any adequate and well-controlled clinical trials that show that Copaxone is safer, more effective, or otherwise superior

» … continued …
Copaxone – David Kyle and Karen Stewart

- Overstating Efficacy/Broadening Indication
- Webpage: “Running, Swimming and Biking After Multiple Sclerosis” – Kyle …

Before Copaxone

- “It’s hard to believe that just a few years ago, this energetic and dynamic athlete had to use a cane for mobility and often could barely muster enough energy to work half a day. This was the case for David, who was diagnosed with multiple sclerosis (MS) in 2002. David awoke one morning experiencing numbness in his toes.”

- “Over the course of a few weeks, the numbness moved up his body and he eventually became partially paralyzed from the chest down. The symptoms subsided briefly only to return just six months later, this time advancing to his entire right side.”
Copaxone – David Kyle and Karen Stewart …

• **Kyle Website …**

  After Copaxone

  • “With the help of his doctor, David began COPAXONE® (glatiramer acetate injection) therapy in 2003”

  • “After a year and a half of hard work and determination, David was the USA Triathlon National Champion in the physically challenged category.”

  • David went on to compete and win numerous national and international triathlons from 2005-2008.

• **Karen Stewart Website …**

  Before Copaxone

  • “Karen was diagnosed with relapsing-remitting multiple sclerosis (RRMS) in 1996, after experiencing numbness in her leg and optic neuritis, an inflammation of the optic nerve causing an acute loss of vision.”

  • “In the years following her diagnosis, Karen’s health began to worsen. She could no longer walk unassisted, fatigue became a daily challenge and, eventually, the worsening of her symptoms forced her to leave her job.”
Copaxone – David Kyle and Karen Stewart ...

Karen Stewart ... after ...

After Copaxone

- “In 1998, after discussing therapy options with her neurologist, she began taking COPAXONE® ... to manage her MS.”

- “Although individual results may vary, over the past few years, Karen has made fitness a priority in her life. She exercises six days a week, added Pilates to her exercise regimen and continues to work as a registered nurse (RN). To date, Karen has walked 22 marathons ...”

FDA:

While these statements may be an accurate reflection of these patients' experiences, the patient testimonials misleadingly broaden the indication and overstate the efficacy of Copaxone. As described in the Background section, Copaxone has demonstrated efficacy in decreasing the frequency of relapses in patients with RRMS. However, Copaxone is not indicated for slowing, preventing or reversing physical disability associated with RRMS. Moreover, FDA is not aware of substantial evidence or substantial clinical experience supporting the implication that Copaxone treatment will result in the magnitude of effects as described in the above patient testimonials. We note that these patient testimonials, in part, state: “[a]lthough individual results may vary” (Karen Stewart webpage) or “[w]hile individual results may vary” (David Kyle webpage). However, these statements do not mitigate the misleading impression that Copaxone can prevent or reverse the physical disability caused by RRMS. The personal experiences of “Team Copaxone” patients such as “David Kyle” and “Karen Stewart,” do not constitute substantial evidence to support such claims and presentations. If you have data to support these claims, please submit them to FDA for review.
Copaxone – David Kyle and Karen Stewart …

• **Key lessons**
  
  – Testimonials – even if accurate, do not equal substantial evidence or “substantial clinical experience”
    
    ➢ inconsistent with approved labeling, which was:
      
      ▪ decreasing relapses of RRMS
      
      ▪ not indicated for slowing, preventing or reversing physical disability of the MS sufferer
  
  – Teva – needed data from A&WCCT to make these claims (and, theoretically, would have to submit to FDA as a supplement to approved application before making them)
Copaxone – David Kyle and Karen Stewart …

- **Key lessons …**
  - **Broadened indication – type of MS**
    - FDA – approval is for RRMS
    - Webpage claims talk about cycling “after Multiple Sclerosis”, but without qualification as to RRMS
  - **Broadened indication – length of therapy**
    - Kyle and Stewart, on website, are stated to have started Copaxone in 1998 and 2003; suggests long-term usage
    - FDA – this implies that Copaxone is effective over a long term, but your PI data is only for 3 years ..
Copaxone – David Kyle and Karen Stewart …

- **Key lessons**
  - **Omission of Risk Information**
    - **FDA** – webpage fails to include *any* discussion of risk information
      - references to approved labeling in website do not cure error
  - **Implied Superiority (based on alleged less risk)**
    - **FDA** -- AAN Panels – listed serious AEs that were not in the Warnings & Precautions part of Copaxone PI;
      - however, these are listed in the Adverse Event list on PI
    - **FDA** – AAN Panels – also failed to list a number of Warnings that are in Copaxone PI such as chest pain, skin necrosis, and potential impact on immune response
EpiPen WL – DTC Ad – May 2012

- **Overstatement of Efficacy** – [Hot Link to Letter]
  
  - **FDA:** “… particularly alarming from a public health perspective because the misleading presentation of the use of the EpiPen may result in serious consequences, including death.”
  
  - **TV ad:**
    
    - Mother: “Excited for Max’s birthday party? Should be pretty awesome.”
    - Son: “Yeah!”
    - Mother: “Even with your peanut allergy and a cake made of who-knows-what.”

    **SUPER (over visual):** EpiPen® (epinephrine) Auto-Injector can’t eliminate the risk of anaphylaxis. [frames 1 to 2]

    - Mother: “Because we’re prepared, right Jake?”
    - Son: “Yup!”
    - Mother: “With EpiPen.”

    **SUPER (over visual):** Be prepared. With EpiPen®. EpiPen® (epinephrine) Auto-Injector can’t eliminate the risk of anaphylaxis. [frame 3]
EpiPen WL – DTC Ad – May 2012 …

- **Overstatement of Efficacy – Hot Link to Promo**
  - **FDA**: Overwhelming impression is that the EpiPen *alone* can provide assurance that a child with history of anaphylaxis does not need to worry or take other precautions
    - gives impression don’t have to worry about the cake – “… a cake made of who-knows-what…”
    - **FDA** -- “The standard of care to prevent a potentially life-threatening anaphylactic reaction is to take precautionary measures to avoid the allergen.”

- **Logistics – came in via FDA’s “Bad Ad” website**
  - April 20 – conference call bet. FDA & Pfizer
    - agreed to pull materials
EpiPen WL – DTC Ad – May 2012 …

• Corrective Actions requested

Because the violation described above is serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated.

– “Corrective messages”
  ➢ Describe the violative promotional pieces/activity
  ➢ Summarize the violative messages
  ➢ Provide info to correct each message
  ➢ Use same media to correct and same duration of time and frequency as violative promotional mats.
  ➢ Be free of promotional material
Ista – Bromday WL – Omitted Risk Info

- **July 2011**
  - Hot Link – Warning Letter
  - Hot Link – Promotional Materials

- **FDA**
  - first, we sent you a WL on Xibrom last year, before you got approval of a supplement to change the labeling to once/day dosing – omitted risk information also
  - Flyer – fails to include **any** of the Warnings or Precautions, including:
    - omitted risk of sulfite anaphylaxis – life threatening
    - omitted risk not to use when wearing contacts
Ista – Bromday WL – Omitted Risk Info

- FDA – also omitted material facts on dosage
  - Xibrom (first generation) – dosing began 24 hours after surgery
  - Bromday – dosing begins 1 day before surgery
  - Problem –
    - because the flyer suggests that Bromday replaces Xibrom, erroneous conclusions on dosing are possible
    - also, the PI for Bromday has a precaution against using a topical NSAID more than 24 hours before surgery (issue: seems to be, but is not clear in WL, 1 day vs. 24 hours)

- Full PI – did not cure the defects in the flyer
Shire – Vyvanese – WL – May 2001

• Magnet promo – ADHD drug
  – Hot Link to Warning Letter
  – Hot Link to Magnet

• Bad Ad report – from a pediatric medical office

• FDA
  – violative because it makes representations regarding use of Vyvanse, but omits the full indication and risks associated with the use of the drug.
    ➢ implied the drug was safer and more effective
    ➢ Magnet – had a plastic sleeve for inserting the biz card of sales rep – when inserted, it blocked the risk info
Shire – Vyvanese – WL – May 2001 …

- **Omitted risk information**
  - Product has a Boxed Warning on potential for abuse
  - Other serious risks, including some that are fatal
  - Contraindications – many – omitted
  - FDA -- “Please see accompanying Full Prescribing Information, including Boxed Warning” – not adequate (also not clear where it was)

- **Omitted indication information** – all said was “First Prodrug Stimulant” – nothing about ADHD
  - fails to adequately communicate important information on ADHD indication regarding special diagnostic considerations, need for comprehensive treatment, and long-term use.
Shire – Vyvanese – WL – May 2001 …
Gelnique – Untitled Letter – Nov. 2010

• “Stall Cling” – not clear what it clung to
  – Hot Link -- U-Letter
  – Hot Link – Promo
  – Viewed at ACOG annual clinical meeting in S.F.

• Alleged violations
  – minimizes risk
  – overstates efficacy
  – broadens indication
  – omits important risk info
  – makes unsubstantiated claims
Gelnique – Untitled Letter – Nov. 2010 …

**Minimized risk**
- risk info in very small font at bottom of piece in single-spaced typed paragraphs
- not reasonably comparable to efficacy claims – which are large and easy to see graphically – as to prominence
- adverse events presented before more serious risks

**Overstated Efficacy**
- failed to disclose that the big “71%” was compared to a placebo reduction of 56% (or 2.0 vs. 2.7 episodes per day)
- disclaimer on placebo in very small print in bottom corner – does not mitigate this overstatement
Visit us at booth 1709

Gelnique®
(oxybutynin chloride) Gel 10%

Smart gel technology
is her weapon against wetting

Significant reduction in incontinence episodes
(P<0.0001)

71%

Fits into a woman's skin care routine

Excellent compliance rate

91%

Gelnique® is indicated for the treatment of overactive bladder with symptoms of urge incontinence, urgency, and frequency.

Important Safety Information

The most common adverse reactions reported were dry mouth, constipation, and bloating.

Please see full Prescribing Information before use.

Please see brief prescribing information below.

1. In a phase 3, 12-week, randomized, double-blind, placebo-controlled clinical trial comparing Gelnique® (brand name) vs. placebo (P = 0.0001). Study included women age 40-70 years with urge incontinence with symptoms of urgency, frequency, and incontinence. Women were randomized to Gelnique® or placebo for 12 weeks and were assessed for the primary outcome of incontinence episodes at the end of treatment. The study showed that Gelnique® significantly reduced the number of incontinence episodes compared to placebo. In addition, Gelnique® was well tolerated, with no serious adverse events reported.

2. Excellent compliance rate with Gelnique® was observed across all age groups. Compliance was defined as a patient taking the prescribed dose of Gelnique® as directed for at least 80% of the treatment period. The study demonstrated that Gelnique® was highly compliant, with an average compliance rate of 91% across all age groups.

3. Please see full prescribing information before use. Prescribing information is available from the manufacturer or your healthcare provider.
Gelnique – Untitled Letter – Nov. 2010 …

• **Broadened indication** –
  – Significant reduction in “incontinence episodes” – implies drug is for all types of incontinence
  – **Approved indication** – narrower – “overactive bladder with symptom of urinary incontinence, urgency and frequency”
  – FDA – fact that full indication is at bottom in Brief Summary does not cure the violation vs. size/prominence of violative statement

• **Omitted Risk Info** – failed to include Warning in P.I. on hypersensitivity and need to discontinue if develop hypersensitivity to drug -- in Brief Summary, but not in “Important Safety Info” (buried)
Gelnique – Untitled Letter – Nov. 2010 …

- **Unsubstantiated claims**
  - “Fits into a woman’s skin care routine”
    - not supported by “substantial evidence”
    - inconsistent with skin care warnings
    - inconsistent with detailed instructions on how gel is to be applied (e.g., keep dry for 1 hour; don’t cover until dry)
  - “Smart Gel Technology is her weapon against wetting”
    - no evidence suggests their technology is any better than other overactive bladder treatments
    - claim implies it is better
Trisenox – Untitled Letter – June 2011

• **Hot Link – Untitled Letter**

• **Hot Link – Promotional Materials**

• **Sent in via a 2253**

• **FDA:**
  – broadens indication
  – minimizes and omits risk info
  – misleading claims
  – unsubstantiated claims
  – overstates efficacy

  ➢ Result – promotes for broader population than proven by substantial evidence
Trisenox – Untitled Letter – June 2011 …

- **Broaden indication**
  - indication – very narrow

  TRISENOX is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha [promeyelocytic leukemia/retinoic acid receptor-alpha] gene expression.

  The response rate of other acute myelogenous leukemia subtypes to TRISENOX has not been examined.

- web claims – falsely imply good for any type of APL
  - “TRISENOX: Standard of Care in Relapsed and Refractory APL”
  - “Successful Therapy for Relapsed and Refractory APL”
  - “Initiating TRISENOX Therapy for your Relapsed or Refractory APL Patients”
Minimized Risk

- info on risk must be given same prominence as those relating to effectiveness
  - effectiveness info – “large, bold, and colorful font and graphics, on the top portion of page”
  - risk info -- including on Boxed Warning, appears in small type at bottom
  - also, when safety info was nearer to the top on the website, it related to minor safety issues and still downplayed major issues

» … continued …
• **Overstated Efficacy**
  
  – used data based on a new definition of “complete remission” (CR) that FDA had not recognized in the approved labeling; was essentially a retrospective re-calculation of response rates based on looser criteria (eliminated a bone marrow confirmation step)
  
  ➢ and because “molecular remission” (MR) was based on CR, the reanalysis skewed those numbers as well
Trisenox – Untitled Letter – June 2011 …

• **Unsubstantiated claims**
  
  • “APL cells are uniquely sensitive to TRISENOX (arsenic trioxide).”
  
  • “TRISENOX selectively targets and degrades the PML/RARα protein. This releases the maturation block to enable partial differentiation.”

  — **Contrast:**

  ➢ PI says that the mechanism of action of drug is not completely understood

  ➢ “Arsenic trioxide also causes damage or degradation of the fusion protein PML/RAR-alpha.”
Trisenox – Untitled Letter – June 2011 …

• Misleading claims – Dosing
  • “Manageable dosing, sensitive to patient needs”
  • “TRISENOX® (arsenic trioxide) injection offers manageable administration schedules for patients and healthcare providers[.]”

  – Contrast:
    ➢ Infusion – every day for up to 4 hours per day for up to 60 days
      – MANAGEABLE?
    ➢ Frequent lab and ECG testing required

• Omission of Risk – from WARNINGS and PRECAUTIONS section of P.I.
  – fetal harm and warning against nursing
  – human carcinogen
Infergen – Warning Letter – March 2011

• Three Rivers Pharmaceuticals – “Statgram”
  – Hot Link -- Warning Letter
  – Hot Link – Promotional Materials

• Came in both via 2253 and “Bad Ad” program

• FDA allegations
  – omits and minimizes important risk information
  – broadens and omits material facts about approved indication,
  – overstates efficacy
  – unsubstantiated claim
  – failure to provide adequate directions for use -- labeling
July 2, 2010

INFERGEN® is now approved for daily dosing with ribavirin for retreatment of HCV patients.

Dear __________:

Approximately 50% of patients with chronic hepatitis C fail to respond to their initial course of therapy. On July 2, 2010, Three Rivers Pharmaceuticals received approval for expanded labeling for INFERGEN® from the United States Food and Drug Administration. The new labeling allows INFERGEN to be given daily in combination with ribavirin (RBV) as a retreatment strategy to assist HCV patients.

The expanded labeling for INFERGEN was based on the results of the U.S., phase 3, multi-center, randomized, DIRECT (Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy) clinical trial under lead investigator Bruce R. Bacon, M.D. The primary endpoint of increased sustained virological response (SVR) was achieved demonstrating that INFERGEN provides a second chance for those HCV patients who require retreatment. The results of the DIRECT trial were published recently in Hepatology, June 2009.

No standard of care has yet emerged regarding retreating patients that fail initial therapy. The DIRECT study evaluated 487 difficult-to-treat non-responders, 80% of which did not achieve a 2-log_{10} drop in HCV RNA on prior therapy with pegylated-interferon plus ribavirin. Key findings in the 15 mcg arm of the DIRECT trial revealed the following:

- In patients maintaining full dose of INFERGEN/RBV therapy, SVRs were 17%
- Patients demonstrating partial response (>2-log_{10} drop in HCV RNA) with previous treatment and low fibrosis scores F0-F3 had SVRs of 31.6%
- In patients achieving viral negativity by Week 12 while on INFERGEN/RBV, SVRs were 63.6%

Providers can obtain additional prescribing information regarding INFERGEN, including the product's safety profile and the box warning for all interferon alphas regarding neuropsychiatric, autoimmune, ischemic and infectious disorders, and complete product information by visiting our product website at www.infergen.com.

Sincerely,

Jonathan Ieyoub, RN, MS, NP - C
Associate Director, Medical Affairs
Infergen – Warning Letter – March 2011 …

• Omits risk information
  – sent without the P.I.; only risk information was:
    “Providers can obtain additional prescribing information regarding INFERGEN, including the product’s safety profile and the box warning for all interferon alphas regarding neuropsychiatric, autoimmune, ischemic and infectious disorders, and complete product information by visiting our product website at www.infergen.com.”
  – Infergen – its labeling is packed full of warnings, precautions, contraindications, etc. – ranging from requiring close monitoring to suicidal and homicidal ideation, etc.

• Did not include full P.I. – because FDA regarded piece as “labeling,” the brief summary rule was n/a
  – “Highlights” Labeling – not enough
Infergen – Warning Letter – March 2011 …

• Broadens Indication
  – Statgram -- claimed approved for daily dosing with ribavirin for retreatment of HCV patients
  – But –
    ➢ Infergen is approved only for patients 18 or older with compensated liver disease
    ➢ omits fact that Infergen has not been proven in naïve patients or those with co-infections involved HIV or HBV

• Overstated Efficacy
  – number of claims made about sustained virological responses (SVRS), but were based on an underpowered, open label study; thus not substantial evidence

• Mutual Pharmaceutical – video and “sell sheet”
  – Untitled Letter [Hot Link]
  – Promotional Material [Hot Link]

• FDA Allegations
  – omit risk info
  – minimize risk info
  – overstates efficacy
  – unsubstantiated safety superiority claims
• Omitted risk info
  – Warning from PI on risk of rhabdomyolysis in patients with renal dysfunction or elderly
  – Sell sheet –
    ➢ “Tough but Gentle” – inconsistent with P.I., which includes fatal overdoses, life-threatening and fatal drug interactions, and neuromuscular toxicity
    ➢ “Tolerability is comparable to Placebo” – clearly not!

• Risk info not comparable to efficacy discussions
  – video spent 15 minutes on Colcrys and how it compares to unapproved colchicines; no verbal discussion on risk;
  – then goes, without any alert, into a “running telescript format” for risk info

• **Minimized Risk/Unsubstantiated Safety Superiority**
  
  • Audiovisual presentation: “NSAIDs, which have a black box, are not indicated nor have they ever been approved for the prophylaxis of gout flares. As with all medication, please remember that your gout patients suffer from many comorbid conditions and caution is needed in the concomitant medications you prescribe for your patients.”
  
  • Screen text: “REALITY NSAIDs have never been FDA-approved for gout flare prophylaxis. Many patients with gout have comorbid conditions that preclude the use of NSAIDs long term. COLCrys is approved for prophylaxis of gout flares as part of the management of gout.”

  – **FDA concerns:**
    
    ➢ erroneously suggests there are no issues with Colcrys in patients with comorbid conditions
    
    ➢ erroneously suggests that Colcrys is superior (safer) for patients with concomitant medications and comorbid conditions
    
    ➢ FDA – no A&WCCT on a head-to-head basis to support

• **Overstatement of Efficacy – video**

  • “In a randomized clinical trial, Colcrys showed significant separation from placebo when looking at pain in 16 hours and reached its primary outcome measure in 24 hours.”
  • “COLCRYST significantly reduces the pain associated with gout flares within 16 hours.”

  – **FDA – the P.I. states that the efficacy of Colcrys was assessed at 24 hours, not 16**
    ➢ study was not powered to evaluate outcomes at 16 hours

• **Merck** – [Hot Link to untitled letter](#)
  – complaint via “Bad Ad”
  – oral statements by Dr. Armando Favazza – at lunch – “on behalf of Merck” – no slides or materials
  ➢ “Merck Peer Discussion Group”
  ➢ Not a response to a question

• **FDA** – statements promote Saphris for an unapproved use, for which labeling lacks adequate directions for use
  – adjunctive therapy for major depressive disorder (MDD) “just as he might prescribe Abilify” and “it works just as well”
  – approved indications – schizophrenia and bipolar, but not MDD
Testopel – Warning Letter – March 2010

• Slate Pharmaceuticals – CIII -- testosterone therapy
  – WL is about 14 pages long [Hot Link]

• Unapproved uses – by reference to testimonials on:
  – Depression; erectile dysfunction, Type 2 diabetes, HIV
  – Increased muscle mass and bone strength

• Omitted Risk
  – video – 2 minutes on efficacy; 10 seconds on risk, none done verbally

• Minimized Risk – video – doctor said patient can come get treated and not have to “think about anything else”
Testopel – Warning Letter – March 2010 …

• **Broadened indication** – created impression could be used for any testosterone replacement, when there are limits to its approved use
  
  – “only approved implantable testosterone pellet”

• **Overstating Efficacy** – many statements that people “Reclaim their lives” or “feel normal again” – however, FDA:
  
  – no substantial evidence of this
  – understates the serious risks associated with the drug
Testopel – Warning Letter – March 2010 …

- **Unsupported Superiority**
  - Slate: claimed greater PD effect on gonadotrophin suppression and PK features are advantageous compared to other T preps
    - study they relied on was not even on their drug
    - study was not an A&WCCT done head-to-head; rather open label, single dose and non-randomized PK study
  - Slate – also contended men preferred their pellet product over others – but relied on same flawed study as above

[note – the violations in this letter were lengthy; I pulled some of the highlights]
Pexeva -- Untitled Letter – May 2011

• Noven Pharmaceuticals, Inc. – Flash Card
  – Untitled Letter [Hot Link]
  – Promotional Material [Hot Link]

• Drug – indicated for PD, MDD, OCD and GAD
  – boxed warning on suicidality

• Broadened indication
  – “Broad spectrum therapy” and linked MDD to anxiety
    ➢ FDA – implies Pexeva is effective in persons with MDD comorbid to anxiety, but not proven by substantial evidence
      ▪ Study cited did not even measure GAD
Pexeva -- Untitled Letter -- May 2011 …

• Overstated Efficacy –
  – Flash card – listed numerous individual symptoms that can be linked to MDD, PD, OCD, and GAD;
  – FDA -- claims that the manner in which the clinicals supporting approval were done did not specifically measure those symptoms; thus, these lack substantial evidence

• Omission of Risk Info
  – omits warning in P.I. about serotonin syndrome, which can be fatal
  – fails to state the Pexeva is not approved in pediatric pops.
Help your patients weather their storm...

Mood disorders can lead to overlapping symptoms—choose from the comprehensive coverage your patients need

- As many as 75% of patients with MDD also exhibit a range of anxiety symptoms or distinct disorders.

---

These selected symptoms of GAD, MDD, OCD, DCD, and PD are used here only as examples.

PEXeva is indicated for the treatment of MDD, GAD, Panic Disorder, and OCD.

Please see Important Safety Information, including Black Boxed WARNING.
Please see accompanying full Prescribing Information including WARNINGS—Clinical Worsening and Suicide Risk; Usage in Pregnancy: Teratogenic and Nonteratogenic Effects.
**Broad Patient Response**

**Significant improvement in total HAMD scores and HAMD anxiety subscales**

As many as **75%** of patients with Major Depressive Disorder (MDD) also exhibit a range of anxiety symptoms or distinct anxiety disorders.

- Patients receiving paroxetine achieved a **46%** reduction in HAMD total score vs **27%** in the placebo group.
- Improvement observed as early as Week 1 for psychic anxiety and agitation, and at Week 4 for somatic anxiety.

**Significant improvement in associated sleep disturbances**

- **50%** reduction in sleep disturbances at Week 6 (P<0.05 vs placebo)
- Improvement seen as early as Week 1

**PExEVA is indicated for the treatment of MDD, GAD, Panic Disorder, and OCD.**

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults.

All patients being treated for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior. Use with MAOIs, thioridazine, or pimozide is contraindicated. Most common adverse events include asthenia, infection, sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, dizziness, insomnia, decreased libido, tremor, nervousness, abnormal ejaculation, impotence, and female genital disorders.

Please see accompanying full Prescribing Information including Black Boxed WARNING.

References:

**Pexeva Tablets**
(paroxetine mesylate)

**BROAD-SPECTRUM THERAPY**

[www.duanemorris.com](http://www.duanemorris.com)

• Alcon Research, Ltd. – Rebate Card – via 2253
  – Untitled Letter [Hot Link]
  – Promotional Material [Hot Link]

• What kind of ad is it supposed to be?
• Can you find what’s wrong with the next ad?
Pay NO MORE THAN $25* with this Most Relief Rebate

*Offer restrictions: Offer not valid for prescriptions reimbursed under Medicaid, a Medicare drug benefit plan or other federal or state programs (such as medical assistance programs). If you are eligible for drug benefits under any such program, you cannot use this voucher. By using this voucher, you agree that you will not submit a claim for the prescription to a government payer.

To the Patient: You must present this voucher to the pharmacist along with your prescription to participate in this program. If you have any questions regarding your eligibility or benefits, or if you wish to discontinue your participation, call the PATADAY™ Solution program at 877-264-2440 (8:00 AM–8:00 PM EST, Monday–Friday). When you use this voucher, you are certifying that you understand the program rules, regulations, and terms and conditions. You are not eligible if prescriptions are paid by any state or other federally funded programs, including, but not limited to Medicaid or Medicare, Medicare, VA or DOD or TrICare, or where prohibited by law, and you will otherwise comply with the terms above.

- Patients are responsible for a $25 out-of-pocket expense. This instant savings voucher will then be applied toward any remaining out-of-pocket expense up to a maximum of $25.
- If you purchase PATADAY™ Solution, through mail order and they do not accept this voucher, call McKesson Corporation at 877-264-2440 and request a Direct Member Reimbursement (DMR) form.

To the Pharmacist: When you use this voucher, you are certifying that you have not submitted and will not submit a claim for reimbursement under any federal, state or other governmental programs for this prescription.

- Submit transaction to McKesson Corporation using BIN #610524.
- If primary coverage exists, input card information as secondary coverage and transmit using the COB segment of the NCPDP transaction. Applicable discounts will be displayed in the transaction response.
- Acceptance of this voucher and your submission of claims for the PATADAY™ Solution program are subject to the LoyaltyScript™ Program Terms and Conditions posted at www.mckesson.com/program.
- Patient is not eligible if prescriptions are paid in part or full by any state or federally funded programs, including but not limited to Medicare or Medicaid, Medicare, VA, DOD, or TrICare and where prohibited by law.
- For questions regarding setup, claim transmission, patient eligibility or other issues, call the LoyaltyScript™ for PATADAY™ Solution program at 877-264-2440 (8:00 AM–8:00 PM EST, Monday–Friday).

You are encouraged to report negative side effects to prescription drugs to the FDA. Visit www.fda.gov/report or call 1-800-FDA-1088.

For full prescribing information visit pataday.com.

FOR QUESTIONS CALL 877-264-2440

Alcon

2010 Alcon, Inc. 10/10 PAT10513RB

RxBIN: 610524
RxPCN: Loyalty
RxGRP: 50775558
ISSUER: (80840)
ID:

• Suggests indication
  – graphic of dandelion and the eye – which FDA says has a plant allergen superimposed over the iris

• Suggests dosage – logo -- “Once Daily”

• Superiority – “Most relief”

• Once falls out of reminder labeling, requires full labeling
Device Warning Letters
# FDA Device Advertising – Warning Letters

<table>
<thead>
<tr>
<th>Company</th>
<th>Date</th>
<th>Description</th>
<th>Close-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oratec Interventions, Incorporated</td>
<td>08/17/2001</td>
<td>Labeling/Premarket Notification Procedure/Adulterated/Misbranded</td>
<td></td>
</tr>
<tr>
<td>Helio Medical Supplies, Inc.</td>
<td>11/25/2002</td>
<td>Medical Device/Misleading Statements/Misbranded</td>
<td></td>
</tr>
<tr>
<td>OMRIX biopharmaceuticals, Ltd.</td>
<td>05/27/2004</td>
<td>Promotional Claims/Misbranded</td>
<td></td>
</tr>
<tr>
<td>TherMatrix, Inc.</td>
<td>06/29/2004</td>
<td>Promotional Claims/False &amp; Misleading</td>
<td></td>
</tr>
<tr>
<td>St. Jude Medical Atrial Fibrillation Division Inc.</td>
<td>04/23/2010</td>
<td>Investigational Device Exemptions (Sponsor)/Promoting Unapproved Use/Misbranded/Adulterated</td>
<td></td>
</tr>
<tr>
<td>Solar Wide Industrial Ltd</td>
<td>04/22/2011</td>
<td>CGMP/Quality System, Promotion and Advertising, and Device Registration</td>
<td></td>
</tr>
<tr>
<td>DePuy Orthopaedics, Inc.</td>
<td>12/08/2011</td>
<td>Premarket Approval/Misbranded/Adulterated</td>
<td>09/27/2012</td>
</tr>
<tr>
<td>Beverly Hills Surgery Center, LLC</td>
<td>12/09/2011</td>
<td>Promotion and Advertising/Misleading/Misbranded</td>
<td></td>
</tr>
<tr>
<td>Palmdale Ambulatory Surgery Center</td>
<td>12/09/2011</td>
<td>Promotion and Advertising/Misleading/Misbranded</td>
<td></td>
</tr>
<tr>
<td>San Diego Ambulatory Surgery Center, LLC</td>
<td>12/09/2011</td>
<td>Promotion and Advertising/Misleading/Misbranded</td>
<td></td>
</tr>
<tr>
<td>Valencia Ambulatory Surgery Center, LLC</td>
<td>12/09/2011</td>
<td>Promotion and Advertising/Misleading/Misbranded</td>
<td></td>
</tr>
<tr>
<td>1 800 Get Thin LLC</td>
<td>12/12/2011</td>
<td>Promotion and Advertising/Misleading/Misbranded</td>
<td></td>
</tr>
<tr>
<td>LAPBANDVIP.com</td>
<td>06/25/2012</td>
<td>Medical Device/Misbranded</td>
<td></td>
</tr>
<tr>
<td>oBand Centers Westwood, CA</td>
<td>11/02/2012</td>
<td>Promotion and Advertising/Misleading/Misbranded</td>
<td></td>
</tr>
<tr>
<td>20/20 Institute, Indianapolis Lasik</td>
<td>12/18/2012</td>
<td>Promotion and Advertising/Misleading/Misbranded</td>
<td></td>
</tr>
<tr>
<td>Rand Eye Institute</td>
<td>12/18/2012</td>
<td>Promotion and Advertising/Misleading/Misbranded</td>
<td></td>
</tr>
<tr>
<td>ScottHyver Visioncare, Inc</td>
<td>12/18/2012</td>
<td>Promotion and Advertising/Misleading/Misbranded</td>
<td></td>
</tr>
<tr>
<td>Eye Center of Texas</td>
<td>12/18/2012</td>
<td>Center for Devices and Radiological Health</td>
<td></td>
</tr>
<tr>
<td>Woolfson Eye Institute</td>
<td>12/18/2012</td>
<td>Promotion and Advertising/Misleading/Misbranded</td>
<td></td>
</tr>
</tbody>
</table>
Oratec Interventions WL – Aug. 2001

• Actually 2\textsuperscript{nd} warning letter (prior in 1999) to Oratec on same product – SpineCath Intradiscal Catheter and an Electrothermal Arthroscopy System

• Allegations – unapproved/uncleared uses
  – SpineCath – cleared to be intended for the “coagulation and decompression of disc material to treat symptomatic patients with annular disruption of contained herniated discs.”
    ➢ Website – promoting for degenerative disk disease
    ➢ FDA – not same as herniated disk

» … continued …
• FDA:
  – In Oratec’s May 7, 1999 response to our previous Warning Letter, you indicated that some of the terms used by medical professionals to describe the presence of contained herniations and annular disruptions include phrases such as degenerative disc disease, chronic discogenic syndrome, internal disc disruption, cliscogenic pain, and discopathic syndrome. \textit{We disagree with that assessment.}
  – In addition to annular disruption of contained herniated discs (the cleared intended use), the Office of Device Evaluation has concluded that the claim of degenerative disc disease may also encompass: degenerative arthritis of the facet joints, instability of the motion segment, pain syndromes, and spinal stenosis. \textit{The agency considers the claim of degenerative disc disease to be an expansion and broadening of the intended use requiring the submission of a new 510(k).}
  – Additionally, in our follow up letter to Oratec dated October 4, 1999, we advised that whenever Oratec uses the term "lower back pain" it should be qualified with the modifier "lower back pain associated with herniated discs."
FDA – Intended use regulation:

- **21 CFR 801.4** — The intended use is the objective intent of the persons responsible for the labeling of the device. Such objective intent may be shown by the circumstances surrounding the distribution of the product and maybe shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. *It may be shown by labeling claims that the article is, with the knowledge of such persons or their representatives, offered and used for purposes for which it is neither labeled nor advertised.*
Thermatix WL – Jun. 2004

• Off-label promotion
  – TMx-2000 BPH Thermotherapy System (TMx-2000) – approved under a PMA in 2001 – a “non-surgical device for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men who have a minimum prostatic urethra length of 30 mm and a total prostate volume between 30 and 100 cc
  – Challenged claims
    ➢ Treat median lobe enlargement of the prostate
      ▪ FDA – no clinical data in your PMA to support
    ➢ You can treat other patients during the procedure
      ▪ FDA – precautions in PMA labeling say that attention required by a physician during treatment -- to, among other things, make sure rectal temperatures remain correct
Thermatix WL – Jun. 2004

• Unsubstantiated Efficacy Claims
  – Claim – durable for 4+ years
    ➢ FDA – data in PMA only covers 1 year
  – Claim – “permanent tissue necrosis”
    ➢ FDA – BPH can come back, so this is misleading because it implies a permanent cure for BPH
  – Claim – “superior peak flow rate improvement”
    ➢ FDA – we are not aware of data showing a statistically significant improvement over other therapies
St. Jude Medical WL -- 2010

- **Epicor™ LP Cardiac Ablation System** – cleared for ablation of cardiac tissue (generally)

- **Claims:**
  - "The Epicor LP system is designed specifically to create the critical *Cox Maze III lesions* entirely epicardially, which helps mitigate risks associated with other cardiac ablation technologies."
  - "The Epicor UltraCinch LP Ablation Device ... is designed to safely, effectively and reproducibly create a *classic box lesion* in a single step."
St. Jude Medical WL – 2010 …

• FDA:
  – claims [on your website] to be promotion of these devices for the treatment of *atrial fibrillation*.
  – Although the box lesion and Maze lesions are ablation lesions performed on cardiac tissue during cardiac surgery, they are specifically intended to disrupt abnormal electrical conduction to isolate the pulmonary veins in an attempt to terminate a patient's atrial fibrillation. Therefore, FDA considers references to the classic box or Maze cardiac lesions to be synonymous with the treatment of atrial fibrillation.
Solar Wide WL – 2011

• **GMP problems, plus:**
  – Your TENS device, the Stimplus Pro, cleared under K913522 was cleared for the following uses: symptomatic relief of chronic, intractable pain and from acute post-surgical and acute post-traumatic pain. However, our inspection revealed that the TENS devices were also labeled for the following uncleared uses: (1) smoking severance, (2) eating disorders, (3) stress and insomnia, and (4) “clinically tested as biologically active.”

• Interestingly, company got two WL’s on same day covering (1) same TENS device, but (2) QSR issues at two different plants – Shenzen and Hong Kong
• Impella Recover LP 2.5 Percutaneous Cardiac Support System
  – Clearance:
    ➢ “partial circulatory support using an extracorporeal bypass control unit, for periods up to 6 hours. It is also intended to be used to provide partial circulatory support (for periods up to 6 hours) during procedures not requiring cardiopulmonary bypass. The IMPELLA RECOVER LP 2.5 also provides pressure measurements which are useful in determining intravascular pressure.”
  – FDA – you’re making claims we said were inappropriate in a Jan. 2010 letter

… continued …
Abiomed WL – June 2011 …

• **Claim:**
  – An advertisement placed in the September, 2010, Cath Lab Digest (vol. 18, no.9). The advertisement shows a hand puncturing a red balloon with a pin. Printed on the balloon is text that reads, “Old ideas about heart recovery.” The caption below the balloon reads in part, “After 40 years, there is something other than the intra-aortic balloon [pump] (IABP) for circulatory support in the Cath lab . . . Cardiac Power Output (CPO) is the #1 correlate to mortality for [acute myocardial infarctions] (AMI) in cardiogenic shock patients . . . In the latest USPELLA registry, the CPO of shock patients was observed to increase 120% from 0.5±0.2 prior to IMPELLA to 1.1±0.2 on IMPELLA (p=0.02).”

• **FDA:**
  – As we stated in our January 28, 2010, letter, “comparative statements can be interpreted as efficacy statements regarding the superiority of the IMPELLA RECOVER LP 2.5 to IABP.” When we sent you the January, 2010, letter, ABIOMED had an ongoing investigational device study, G050017, and we advised your firm that the claims violated the regulations at 21 CFR 812.7(d), which prohibit the representation that a device is safe and effective for the purposes being studied. Although the study has since been terminated, the unsupported comparative claims violate 21 CFR 801.6.
Abiomed WL – June 2011 …

• On page 9 of your firm’s presentation to the 2010 Transcatheter Cardiovascular Therapeutics meeting, your firm claimed that use of the IMPELLA RECOVER LP 2.5 in AMI Shock patients improves hemodynamics, and on page 10 your firm states that the use of the IMPELLA RECOVER LP 2.5 improves cardiac output, which is then linked to lower mortality rates.
  – FDA: Both of these indications would need to be supported with an appropriately designed clinical study performed under an Investigational Device Exemption (IDE).

• On the ABIOMED website, your logo includes the tag line, “Recovering Hearts, Saving Lives.”
  – FDA: This is another claim that would require a randomized clinical study performed under an IDE specifically to evaluate whether the device could salvage heart tissue and muscle.

• FDA: Statements such as the ones cited above represent a major change or modification in the intended use of your firm’s device that requires a new premarket notification. 21 CFR 807.81(a)(3)(ii).
Understanding FDA’s Enforcement Power
How to “Avoid” Enforcement?

• The answer is simple – Comply!

• **But, how?** -- **Please Teach Vigorous Risk Avoidance Comprehensively & Corporately**
  – Thus, to ensure you comply, you must have:
    - P = Procedures
    - T = Training
    - V = Validation
    - R = Records
    - A = Audits
    - C = Communications – open channels
    - C = Compliance Culture from the Top
Commissioner Hamburg Revives FDA’s Compliance Culture –

The August 6, 2009 Speech and its Impact
Hamburg: Why We Need Effective FDA Enforcement

- Conceded FDA enforcement efforts have been deficient

- Five key benefits of effective enforcement:
  - Protect public health by promptly intercepting unsafe or fraudulent products – prevents additional harm
  - Deter others who might violate law
  - Informs public of potential harm
  - Creates level playing field for industry
  - Instill public confidence in FDA
Hamburg: Four Essential Elements for Effective FDA Enforcement

• **Vigilance – both FDA and Industry**
  – FDA – Regular inspections and follow-ups
  – Companies
    ➢ Must work quickly and thoroughly to correct problems
    ➢ Must understand
      ▪ if you cross the line, “you will be caught”
      ▪ If you fail to act, FDA will

• **Strategic enforcement –**
  – Greater focus on significant risks and violations
  – More meaningful penalties to “send a strong message to discourage future offenses”
Four Essential Elements for Effective Enforcement …

• **Quick action – FDA must respond rapidly,** especially to:
  – Egregious violations
  – Violations that threaten the public health

• **Visible efforts – FDA must show all stakeholders it is on the job**
  – Will publicize enforcement actions widely – including rationales for action
  – Goal:
    ➢ Increase confidence in FDA
    ➢ Deter non-compliance
Hamburg: Six New FDA Enforcement Mandates

• **Impose clear post-inspection deadlines**
  - Generally –15 business days to respond to 483
  - After that, agency can issue warning letter or take other enforcement action

• **Speed the warning letter process** – by limiting review by FDA Office of Chief Counsel to warning letters that present significant legal issues
Hamburg: Six New FDA Enforcement Mandates …

• **Work more closely with FDA’s regulatory partners**
  
  – Example: in some cases, such as food safety, state, local, and international officials can act more quickly than FDA
  
  – When public health is at risk, the agency will coordinate with its regulatory partners to take rapid action

• **Prioritize follow-up on all warning letters and other enforcement actions**
  
  – FDA will work quickly to assess the corrective action taken by industry after a warning letter, a major product recall, or other enforcement action
  
  – Via new inspection or other form of investigation
Six New Enforcement Mandates …

• **FDA will be prepared to take immediate action to respond to public health risks**
  – Actions may occur before a formal warning letter is issued – at any time
  – Days of multiple responses to inspections – over

• **Develop and implement a formal warning letter “close-out” process**
  – If FDA determines a firm fully corrected violations in a warning letter, agency will issue an official “close-out” notice and post on FDA Web site
  – Seen as an “important motivator” for corrective action
Enhanced Enforcement In Action – Timely 483 Responses Policy

• Aug. 11 Federal Register notice – Post-inspection 483 responses timing policy published – 15 business days

• Timely Responses
  – FDA will conduct “detailed review” in deciding any enforcement action
  – If FDA issues a warning letter, letter will address sufficiency of response
Enhanced Enforcement In Action – Timely 483 Responses Policy …

• **Late responses**
  – Response will not be considered by FDA in deciding to take enforcement action such as a warning letter
  – If warning letter issues after a late 483 response, FDA will consider the 483 response in assessing firm’s later reply to warning letter

• **Purpose of Warning Letter:**
  – “ensure … seriousness and scope of the violations are understood by top management … and that the appropriate resources are allocated to fully correct the violations and prevent their recurrence”
FDA Administrative Enforcement Powers
Administrative Enforcement Tools

• **Inspections**
  – **Planned** and conducted pursuant to FDA annual plan or center compliance program
  – **Pre-approval**
  – **“For cause”** (e.g., public health crisis due to defective or contaminated FDA-regulated product; follow up to 483 response)
  – **Government-wide Quality Assurance Program**
    ➢ FDA may inspect at the request of the DoD or VA to determine, for example, whether a company bidding on a government contract is in compliance with GMPs and otherwise in compliance with the FDCA
Administrative Enforcement Tools …

• **Inspections (continued)**
  – Combination or joint inspections (EPA, OSHA, or a state food and drug regulatory body)
  – Consumer, trade, and other complaints
  – Adverse product effect reports
  – Congressionally inspired

• **Clinical hold**

• **Withdrawal or suspension of marketing permit**

• **Recall (FDA-requested or “voluntary”)**
FDA Administrative Enforcement Tools …

- **Import detention or refusal**
- **Civil money penalties**
- **Warning Letters**
  - addressed to CEOs/other executives; FDA’s effort to get executive buy-in on necessary fixes is often sabotaged by corporate bureaucracy, which sends the letter back down to the person with knowledge of the specifics — **but** — *see* prior Slide 51 on purpose of WL
- **Application Integrity Program (AIP)** — discussed in more detail later
The Pen Is Mightier Than The Sword: Adverse Publicity

- FDA Website
- Press release
- Talk paper
- Press conference/television and radio interview
- Speeches
- Congressional and other testimony
- Articles in scientific, professional and lay publications
Publicity as an Enforcement Tool?

**ORA FOIA Electronic Reading Room**

The ORA Electronic Reading Room displays copies of ORA records. We are making these records publicly available either (1) proactively at our discretion or (2) because they are "frequently requested" per the Electronic Freedom of Information Act Amendments of 1996. Some records may be redacted to remove non-public information (see 21 CFR Part 20). For other ORA documents, please visit the ORA home page and the FDA Warning Letter page; for other FDA documents, please visit the FDA Freedom of Information (FOI) page.

**ORA Postings**

<table>
<thead>
<tr>
<th>Title</th>
<th>Posted Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Red Cross 2009 Adverse Determination Letters</td>
<td>11/12/09</td>
</tr>
<tr>
<td>Halfa Smoked Fish, Inc.</td>
<td>11/10/09</td>
</tr>
<tr>
<td>Aunt Mid's Produce Company</td>
<td>10/15/09</td>
</tr>
<tr>
<td>Care-Tech Labs Inc., Lenexa, KS 483 issued 5/22/2008</td>
<td>09/23/09</td>
</tr>
<tr>
<td>Care-Tech Labs Inc., Signed Consent Decree issued 9/8/2009</td>
<td>10/15/09</td>
</tr>
<tr>
<td>American National Red Cross / Biomedical Services</td>
<td>09/23/09</td>
</tr>
<tr>
<td>ORA Workplans</td>
<td>09/04/09</td>
</tr>
</tbody>
</table>
Pre-Dissemination Review of TV ads …

• Disseminating an ad in violation of 503B – is a “prohibited act” under § 301(kk) of the Act
  – failure to submit at all
  – disseminate before end of 45-day period
  – failure to incorporate required additions to ad as per Section 503B(e) – such as serious risks in labeling or approval dates

• Civil monetary penalties –
  – FDAAA revised § 303 so that any person who disseminates or causes another party to disseminate a false or misleading DTC ad shall be liable for a civil penalty of up to $250,000 for the first violation, and up to $500,000 for subsequent violations in a 3 year period.
DTC Ads – Civil Monetary Penalties

• CMP law does not distinguish between TV and print/radio ads

• Factors
  – whether submitted under §503B or §736A (advisory review)
  – whether disseminated before end of 45-day period
  – whether they incorporated any comments
  – whether they stopped disseminating after getting CMP notice
  – whether they had it reviewed by qualified regulatory, medical and legal reviewers before dissemination
  – any prior CMPs in last year
  – scope and extent of remedial action(s)
Strict Liability and the “Park Doctrine” – Criminal Liability for Responsible Corporate Officials
U.S. v. Park – Strict Criminal Liability in the FDA World

• 1975 – 421 U.S. 658


• Facts:
  – Warehouse – in Baltimore – multiple FDA inspections found rodent and insect infestation
    ➢ 1970 – letter to Park re Baltimore warehouse
    ➢ 1971 – FDA inspection in October and November
    ➢ 1972 – January letter from FDA
    ➢ March 1972 – FDA inspection – still found rodent inspection
U.S. v. Park – Strict Liability …

• Supreme Court, quoting Dotterweich (1943):
  – observed that the Act is of "a now familiar type" which "dispenses with the conventional requirement for criminal conduct - awareness of some wrongdoing. In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."

• “Moreover, the principle had been recognized that a corporate agent, through whose act, default, or omission the corporation committed a crime, was himself guilty individually of that crime. “
U.S v. Park …

• The principle had been applied *whether or not the crime required "consciousness of wrongdoing,"* and it had been applied not only to those corporate agents who themselves committed the criminal act, *but also to those who by virtue of their managerial positions or other similar relation to the actor could be deemed responsible for its commission.*

• *The liability of managerial officers did not depend on their knowledge of, or personal participation in, the act made criminal by the statute.* Rather, where the statute under which they were prosecuted dispensed with "consciousness of wrongdoing," an omission or failure to act was deemed a sufficient basis for a responsible corporate agent's liability. *It was enough in such cases that, by virtue of the relationship he bore to the corporation, the agent had the power to prevent the act complained of.*
U.S. v Park …

• **Duty to seek out and fix violations** -- the Act imposes not only a positive duty to seek out and remedy violations when they occur but also, and primarily, a duty to implement measures that will insure that violations will not occur.
  
  – The requirements of foresight and vigilance imposed on responsible corporate agents are beyond question demanding, and perhaps onerous, but they are no more stringent than the public has a right to expect of those who voluntarily assume positions of authority in business enterprises whose services and products affect the health and well-being of the public

• But the Act, in its criminal aspect, does not require that which is *objectively impossible* -- the Act permits a claim that a defendant was "powerless" to prevent or correct the violation to "be raised defensively at a trial on the merits."
U.S. v. Park …

• **Objective impossibility** – not construed by Supreme Court since Park.
  – One federal court of appeals – would have to show that you took extraordinary measures, but still the violation occurred
  – Delegation is not a defense

• **March 2010** – Commissioner Hamburg writes Congress -- renewed commitment to use Park
  – issued a revision to its Regulatory Procedures Manual (RPM) on factors FDA will use in invoking Park
FDA -- Factors for Park Prosecutions

*(FDA RPM § 6-5-3)*

- Individual’s position in the company and relationship to the violation
- Does the violation involve actual or potential harm to public?
- Is the violation obvious?
- Does the violation reflect a pattern of illegal acts or a failure to heed prior warnings?
- Is the violation widespread?
- Is the violation serious?
- The quality of the legal and factual support for proposed prosecution
- Is the proposed prosecution a prudent use of agency resources?
The Park Doctrine – A Recent Example – OxyContin

- **May 10, 2007** -- Purdue Frederick Company, Inc. – as a company -- agreed to pay more than $600 million to resolve felony criminal charges and civil liabilities in connection with a long-term illegal scheme to promote, market and sell OxyContin

- Purdue trained its sales representatives to falsely represent:
  - to health care providers about the difficulty of extracting oxycodone, the active ingredient, from OxyContin
  - to health care providers that OxyContin did **not** cause euphoria and was less addictive than IR opiates;
  - to health care providers the erroneous belief that OxyContin was less addictive than morphine.
The Park Doctrine – A Recent Example – Oxycontin …

• As part of the plea, Purdue paid a $600 million settlement, which included:
  – a criminal fine
  – restitution to government agencies
  – over $276 million in forfeiture,
  – civil settlement of $100.6 million to the United States.

• Purdue's then current and former executive employees, Michael Friedman, Howard Udell and Dr. Paul Goldenheim, pled guilty to a misdemeanor violation of misbranding OxyContin as being the responsible corporate officers during the long-term illegal promotion of the drug.
Why is Park Being Resurrected?

• Congress and Executive Branch – concerned that even huge fines and Corporate Integrity Agreements are “cost of business”

• Corporate Executives – being targeted under premise that:
  – Organizational misconduct cannot occur without individuals
  – What officials could prevent a violation if they tried?
  – Answer: the “Responsible Corporate Official” (RCO)
Criminal Prosecution: Misdemeanors

• **Misdemeanor -- under Park Doctrine**
  – Fines up to $100,000 and $200,000 per misdemeanor offense for an individual and a corporation respectively ($250,000 and $500,000 if the misdemeanor offense resulted in death)
  – Imprisonment – up to a year in jail per violation
Criminal Prosecution -- Felony

- Must prove intent
- Fines are greater
- More common than misdemeanor prosecutions
- Often will combine FDA violations with other federal crimes (e.g., conspiracy, false statements)
Seizure

- **Civil action**
  - Technically, is against the goods themselves
  - Owner or others with interest must intervene to defend the goods
    - If do, then trial on merits of alleged violations
  - Lose – goods usually destroyed, but may be reconditioned if possible
  - Win – goods go free
Injunction

• **Action to either:**
  – Compel compliance
  – Prevent future violations

• **Personal against individuals or corporations**

• **Can result in an order that will involve tremendous allocation of resources over a long period of time to address**
Consent Decree

- Order of a court
- Entered by consent of the parties
- Not technically a judicial verdict, but a negotiated contract between the parties under the sanction of the court
- Parties represent that it is a just determination of their rights as if the alleged facts of the case had been proven
Consent Decrees …

• How do they come about??
• Settlement of a court case after FDA has filed for an injunction
  – “Voluntary” negotiations with FDA after an adverse inspection
  – Most terms/conditions negotiable -- but depends on your leverage point
  – companies more often concerned about naming executives as individually responsible: FDA finds this point important as a deterrent and necessary to pursue contempt charges if decree becomes ineffective
Disgorgement

- Government (FDA doesn’t get) recovery of company profits
- Can’t profit from sales of an illegal product that is nonetheless medically necessary
- FDA refrains from enjoining production of non-compliant products because it would compromise patient care by causing significant shortages of medically necessary products
- In return, firms will pay a fixed % of future sales to ensure that they did not profit from the violative products
Collateral Consequences of Serious Enforcement Actions
Collateral Damage – Worst Case Scenario from FDA Enforcement

• *This is a picture you do not want to see ….*
  – *in your newspaper ….*
  – *on your local news ….*
  – *on the Internet ….*
  or
  – *in an FDA lawyer’s presentation for years to come* ….
Purdue Pharma Executives Outside Court in Virginia

Udell  Friedman  Goldenheim
HHS Disqualification – The “Death” Sentence

• 2008 – HHS Office of Inspector General – proposed to disqualify all three from participating in federal health care programs (e.g., Medicare, Medicaid)
  – Did not allege direct involvement, but based on RCO theory

• 2010 – Twelve year exclusion upheld by federal district court – Friedman v. Sebelius (on appeal to D.C. Court of Appeals)

• July 2012 – Federal Court Appeals – agreed, although remanded to see if length of exclusion was consistent with prior exclusions
HHS Disqualification …

• Guidance for Implementing Permissive Exclusion Authority under Section 1128(b)(15) of Social Security Act – [http://oig.hhs.gov/fraud/exclusions/asp](http://oig.hhs.gov/fraud/exclusions/asp)

• Distinguishes between different types of corporate officials as to the “scienter” needed for disqualification
  – Owners or control interest – knew or should have known of violation to be disqualified
  – Officers/officials – can be strictly liable – “managing employee” – an individual (including a general manager, a business manager, an administrator, or a director) who exercises operational or managerial control or who directly or indirectly conducts the day-to-day operations of the entity.
OIG Disqualification – Factors

• Circumstances of the misconduct and the seriousness of the offense
• Individual’s role in sanctioned entity
• Individual’s actions in response to the misconduct
• Information about the entity
• Forest/Solomon – OIG threatened to disqualify him even though he had not been convicted; later backed off
Problems For Individuals If Convicted

• Lose right to vote
• Lose right to run for public office
• Damage to reputation
Problems For Individuals If Convicted …

- Can be deported if not a U.S. citizen
- Financial ruin -- lose your job
- May not be able to ever work in industry again:
  - Debarment (FDA)
  - Disqualification (HHS, Clinical Investigator)
Problems For Companies Caused By Criminal Convictions …

- Shareholders sue the company, its officers and directors
- Other companies may sue the company (e.g., Mylan Labs sued Par and others)
- Federal government may suspend or “debar” company from selling to government
- “Qui Tam” actions under the False Claims Act -- e.g., GSK (GMP) & Pfizer cases -- “whistle blower” cases - - leading to civil damages and may also spawn a criminal prosecution
Problems For Companies Caused By Criminal Convictions …

- FDA may refuse to approve applications – the AIP Program
- May lose state licenses
- Customers abandon you
- Decreased sales may force lay-offs of employees
Problems For Companies Caused By Criminal Convictions …

• Financing disappears -- banks may refuse to lend money
• May violate lending agreements, real estate mortgages or leases
• A criminal investigation can cause great disruption to normal business activities
Problems For Companies Caused By Criminal Convictions …

- **High financial cost of an investigation:**
  - lost sales
  - stock price falls
  - attorney’s fees and costs
  - costs of complying with requests by government for documents
Another Picture that You Don’t Want to Star in …
Ex-Imclone CEO exits federal court after entering guilty plea …
Final Sermon:

Please Teach Vigorous Risk Avoidance Comprehensively and Corporately

- P = Procedures
- T = Training
- V = Validation
- R = Records
- A = Audit
- C = Communications – Open Channels
- C = Compliance Culture from the Top
End of Part 4 – FDA Enforcement