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FDA Regulation of Promotion & Advertising

Part 6: First Amendment, Off-Label and False Claims

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First Amendment

- **Adopted December 15, 1791**
  - Congress shall make no law respecting an establishment of religion, or prohibiting the free exercise thereof; or abridging the freedom of speech, or of the press; or the right of the people peaceably to assemble, and to petition the Government for a redress of grievances.
- **"Commercial Speech" – does not get "full" 1st Am. protection**
  - Advertising – clearly is commercial speech

Caronia and Off-Label Promotion

- **Alfred Caronia –**
  - Sales rep for Orphan Medical (now Jazz Pharm.)
  - convicted of conspiracy to introduce a misbranded drug into commerce – for an unapproved use (off-label)
  - Appealed
    - Caronia -- contended that he was prosecuted for his speech
    - FDA – his speech was not the issue, it was just used as evidence of his intent … to misbrand the drug

Caronia and Off-Label Promotion …

- **The Facts**
  - ***Xyrem*** – powerful central nervous system depressant; approved (GHB – "date rape" drug) – approved (1) to treat narcolepsy patients who experience cataplexy and (2) to treat narcolepsy patients with excessive daytime sleepiness (EDS); severe side effects
    - Black box warning – elderly and pediatric patients under 16
    - Limited distribution – single pharmacy in Missouri
  - Caronia – started a speaker program for Xyrem
    - Caronia – not allowed to answer questions on off-label use; had to send info into company
    - Physician Speakers – could answer off-label questions

Caronia and Off-Label Promotion …

- **The Facts …**
  - "The Conspiracy"
    - Caronia taped
      - 10/26 – Dr. Charno – promoted Xyrem for uses such as fibromyalgia, insomnia, "muscle disorders and chronic pain"
      - 11/2/05 – Dr. Charno and Gleason
    - Caronia and Peter Gleason – pushed Xyrem for children under 16
  - Pled guilty originally; moved to have plea dismissed, claiming that the application of the misbranding theory essentially violated his 1st Am rights to speech

Caronia and Off-Label Promotion …

- **The "Misbranding Theory"**
  - Misbranding theory of off-label promotion – that there are not adequate directions for use for the off-label use, **but** that the off-label use has become an "intended use" as defined in FDA regulations **and** directions for use, under 21 CFR 201.5, must cover all "intended uses" (even off-label)
    - **21 CFR 201.128 –** objective intent of person -- allows "intended use" to be shown by oral or written statement and … "the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised."
    - Government – not possible to write adequate directions for use for an off-label use

Caronia and Off-Label Promotion …

- **Decision …**
  - First, 2nd Circuit concluded that the trial record made clear that the govt prosecuted Caronia for the speech – the off-label promotion
  - On appeal, Caronia argued that the misbranding provisions, by prohibiting off-label promotion, impinge the 1st Am.
  - Court – took a slightly narrower approach –
    - concluded that he was prosecuted for "mere off-label promotion" (speech) and that was improper
      - no proof offered at trial of deficient labeling, for example
    - also concluded that the misbranding provisions don't criminalize speech per se

Caronia and Off-Label Promotion …

- **Court – 1st Am. violated in several ways**
  - ***Sorrell*** case – Heightened scrutiny
    - **Content based** –distinguishes between "favored" and "unfavored" speech based on the ideas expressed
      - favored = approved use
      - unfavored = unapproved use
    - **Speaker based** – distinguished between types of speakers
      - docs – could talk about off-label use
      - drug companies – could NOT
  - ***Central Hudson*** – Intermediate Scrutiny

» ….continued …

"Central Hudson" 4-Prong Test

- **1 -- Is the expression protected by the First Amendment and not misleading and related to lawful activity?**
  - **Yes,** speech; related to lawful activity (off-label use) and not misleading (if true)
- **2 -- Is the asserted government interest substantial?**
  - **Yes,** drug safety and public health
- **3 -- Does the regulation directly advance the governmental interest asserted?**
  - **No,** because off-label use is acceptable and this ban on promotion actually inhibits that ***use*** by docs

"Central Hudson" 4-Prong Test

- **3 -- Does the regulation directly advance the governmental interest asserted? …**
  - ➢ besides, FDA actually allows distribution of off-label info under draft Good Reprint Guidance
- **4 – Is the restriction narrowly drawn to further gov't interest**
  - **No,** there are other ways to address that FDA and government are not pursuing. For example, the law actually bars off-label use of HGH – Section 303(f) of Act
  - **Regulating speech should be last resort**

Future after Caronia?

- **Wild West? Snake Oil?**
  - 2nd Circuit -- is just NY, VT, & CT
  - Government – will probably focus on:
    - failure to provide adequate directions for use, because the product is being promoted for an off-label use, in future actions
    - unapproved drug actions
  - Off-label promotion – must essentially be in writing
  - **21 CFR 801.4** – device maker required to provide info on labeling if it learns that its product is being used off-label
    - See **Dexcom Warning Letter**; May 2010, where FDA asked for labeling changes on off-label uses (pediatrics; incision location)

False Claims Act and Off-Label Promotion

False Claims Act

- **Enacted during Civil War; creates a bounty for anyone who blows whistle on unscrupulous government contractors**
  - Qui Tam – actions filed under seal; government can later join
  - Recovery – percentage (varies) – can go to the "relator" (the whistleblower)
- **Late 1990's – began to emerge in FDA-regulated violations**
  - Neurontin – one of the first big ones -- $430,000,000
    - (whistleblower got about $25 mil.)

False Claims Act Settlements

- **Orphan Medical – Xyrem -- $20 million**
- **BMS/Otsuka – Abilify – $50 million**
  - Pediatric and to treat dementia (approved for MDD, PD, etc.)
- **Cephalon -- $375 million for three drugs**
  - Actiq – pain in non-cancer patients (approved in cancer)
  - Gabitril – anxiety, insomnia, pain (approved for partial seizures)
  - Provigil – fatique and other "stimulant" uses(approved for narcolepsy)
- **Lilly – Zyprexa -- $1.4 Billion –** anti-psychotic marketed for numerous off-label uses

False Claims Act Settlements

- **Pfizer I – Bextra, Geodon, Lyrica -- $2.3 billion**
  - six whistleblowers shared $102 million
- **Allergan – Botox -- $600 million – chronic migraines** (later approved for use)
- **Abbott – Depakote -- $1.6 billion**
- **GSK – Paxil, etc. -- $3 billion**

FCA – What's' Involved

- **Civil monetary penalties – range from $5,500 to $11G per violation; up to 3 times amount of damage sustained by government**
- **Focus of off-label liability – Federal healthcare programs --** not responsible for paying for unapproved uses
- **Filed under seal** – although you likely know if you're under investigation
- **Whistleblower** – protected from retaliation

End of Part 6 –

First Amendment, Off-Label and False Claims