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Quantifying Off-Label Prescriptions and Isolating Those Caused by Off-Label Promotion:

Addressing These Measurement Challenges Using Health Economics Tools

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There are many types of off-label promotion

Type	Examples	
	Approved for …	… but promoted for
Disease treatment	Breast cancer	Colon cancer
Disease prevention	-	Heart attacks
Dose	Doses up to 50mg	Doses >50mg
Line of therapy	Second line of therapy	Treatment naïve patients
Patient population	Adults	Adolescents
Course of therapy	Acute episodes	Maintenance therapy
Pattern of administration	Monotherapy	Combination with other drugs
Comparative claims	-	Compares to drug X

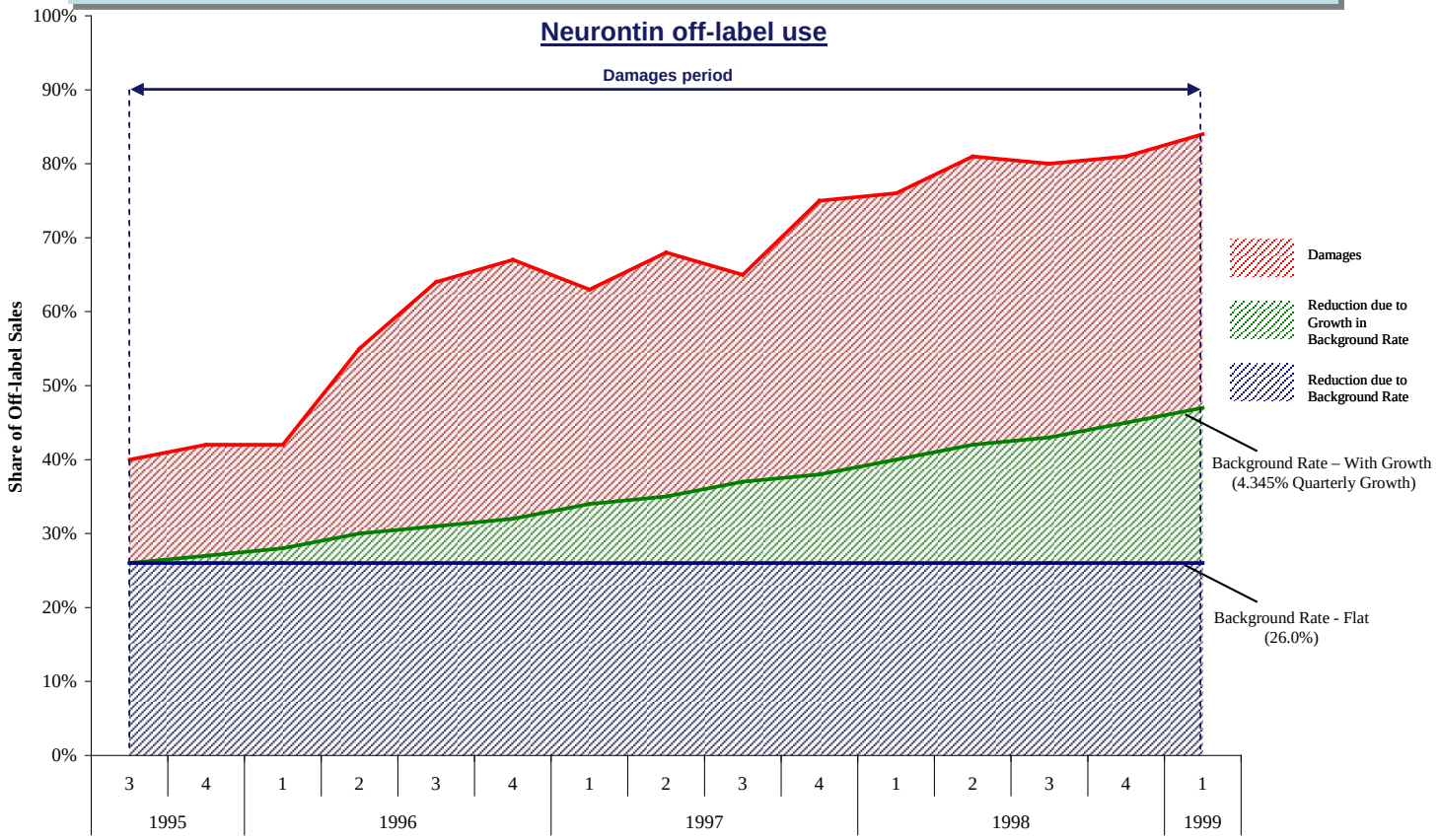
Measurement issues in assessing extent of off-label use: Disease treatment example

- Determining which data sources are likely to have detailed information on uses at issue (e.g., medical claims data, hospital electronic records, patient/physician survey data)
- Translating the language of the label into specific ICD-9 diagnosis codes used to capture diseases in the data
- Establish the disease giving rise to the prescription by investigating the relative timing of diagnoses and prescriptions
- Isolating off-label conditions at issue from other off-label conditions

Causation analyses – yardstick approach

Examples of yardsticks:

- Off-label use of the drug before the conduct at issue ("before and after")
- Off-label use of similar drugs
- Off-label use of the drug in another geographic region without conduct at issue



Source: Neurontin Sentencing Memorandum, Exhibit A, 6/2/04.

Causation analyses – carve-out approach

In some cases, it may be more practical to isolate specific categories of prescriptions not caused by the conduct at issue.
These uses would be excluded from the damages assessment.

- Examples of potential carve-out analyses:
  - Off-label uses pre-dating the initiation and following the termination of the conduct at issue (i.e., in the aggregate or at the physician-specific level)
  - Off-label uses in geographic regions without conduct at issue (e.g., sales territories without off-label promotion, other countries with different labels)
  - Off-label uses in patients with unmet need (e.g., after failure of on-label treatments)

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Off-Label Promotion:
The FDCA and FDA Regulations

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FDA Oversight

- The FDA has broad authority to protect public health.
  - Food, Drug and Cosmetics Act (FDCA)
    - Grants authority to the FDA to regulate labeling and advertising of pharmaceutical products.
  - Food and Drug Administration Modernization Act (FDAMA)
  - The FDA promulgates regulations in accord with these two acts (See 21 CFR §99 and 21 CFR §202).

FDA Drug Approval Process

- New Drug Application (NDA)
  - Drug tested for specific indication(s).
  - Resulting label includes usages, appropriate patient populations, warnings, dosages.
  - The FDA approves drugs with proof that, when used in accord with proposed label (which is included with the NDA), the drug is both safe and effective.

Food, Drug and Cosmetics Act

- -Imposes liability for off-label promotion of drugs. 21 U.S.C. §331.
- -“labeling”: all labels and other written, printed, or graphic matters upon any of a product’s containers or wrappers or accompanying a product. 21 U.S.C. §321(m)
- -To be considered “labeling,” material need not physically accompany a product. Kordel v. U.S., 335 U.S. 345, 346-348, 350 (1948).
- -Brochures, file cards, movies, booklets may all be “labeling” under some circumstances. 21 C.F.R. §202.1(l)(2). Advertisements are also within the scope of “labeling.” 21 C.F.R. §202.1(l)(1).

Misbranding

- -Under the FDCA, a drug or device is “misbranded” if “its labeling is false or misleading in any particular.” 21 U.S.C. §352.
- -Manufacturers are prohibited from distributing “misbranded” products. 21 U.S.C. §331.

- In effect, manufacturers are prohibited from selling drugs or devices for which they have falsely advertised.

Food and Drug Administration Modernization Act

- -Created exception to prohibition on off-label marketing.
- -Manufacturers may provide doctors with publications on off-label uses of a drug, in response to an unsolicited request.

Dissemination of Off-Label Publications

- 21 C.F.R. §99.101 details the types of information that may be disseminated
- Unabridged reprints of peer-reviewed articles (but not letters to the editor, abstracts, Phase 1 trials for healthy people, or observations of four or fewer people)
- Unabridged sections of reference publications

- "Unabridged" means a reprint or copy that "retains the same appearance, form, format, content, or configuration as the original article or publication."

Dissemination of Off-Label Publications

Even dissemination of unabridged reprints is not an unfettered right of manufacturers.
Dissemination of off-label reprints:

- Must not pose a significant risk to public health
- Must not be false or misleading
- Cannot be derived from research of another manufacturer, without that manufacturer's permission
- Cannot be disseminated with information that is promotional in nature

False or Misleading

Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (http://www.fda.gov/oc/op/goodreprint.html)

False or Misleading: “For example, a distributed journal article or reference text should not be characterized as definitive or representative of the weight of credible evidence derived from adequate and well-controlled clinical investigations if it is inconsistent with that weight of credible evidence or a significant number of other studies contradict the article or reference text’s conclusions;” and “should not discuss a clinical investigation where FDA has previously informed the company that the clinical investigation is not adequate and well-controlled...”

Curbs on Off-Label Promotion through Litigation

Federal Government:

-FDA warning letters

-Administrative remedies (suspension/debarment)

-Corporate criminal fines

-Park Doctrine criminal fines for individuals (FDCA)

-Gov't-instituted False Claims Act cases

Individuals:

-*Qui tam* False Claims Act cases

-Class actions (consumer protection or fraud acts, RICO)

-Personal injury

Physician's Role

- FDCA governs drug and device manufacturers; not doctors.
- Doctors are free to prescribe FDA-approved drugs off label, whenever they deem it appropriate.

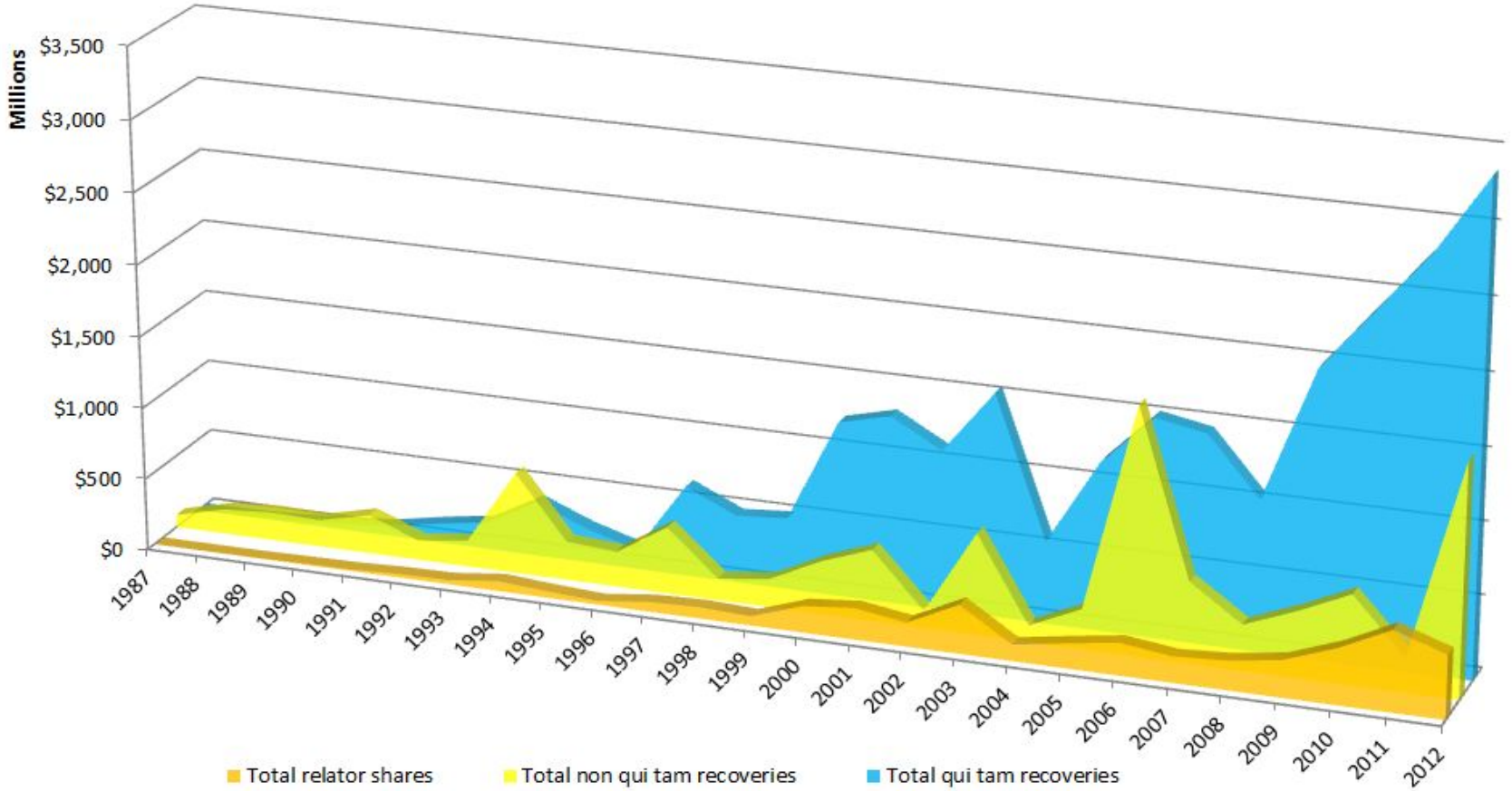
That does not mean, however, that the government will actually pay for it.

The False Claims Act

- Companies or individuals may be liable to the gov't for treble damages if they submit or cause to be submitted false claims to the gov't – or if they make false statements material to the submission of false claims. 31 U.S.C. §3729.
- Private citizens may initiate cases under the *qui tam* provision of the statute. 31 U.S.C. §3730(b).
- Most states have False Claims Acts at least as robust as the federal version.
- $35.19 billion recovered since 1986; $24.07 billion of that amount in health care

The False Claims Act

Most FCA recoveries come from *qui tam*, whistleblower-initiated cases.



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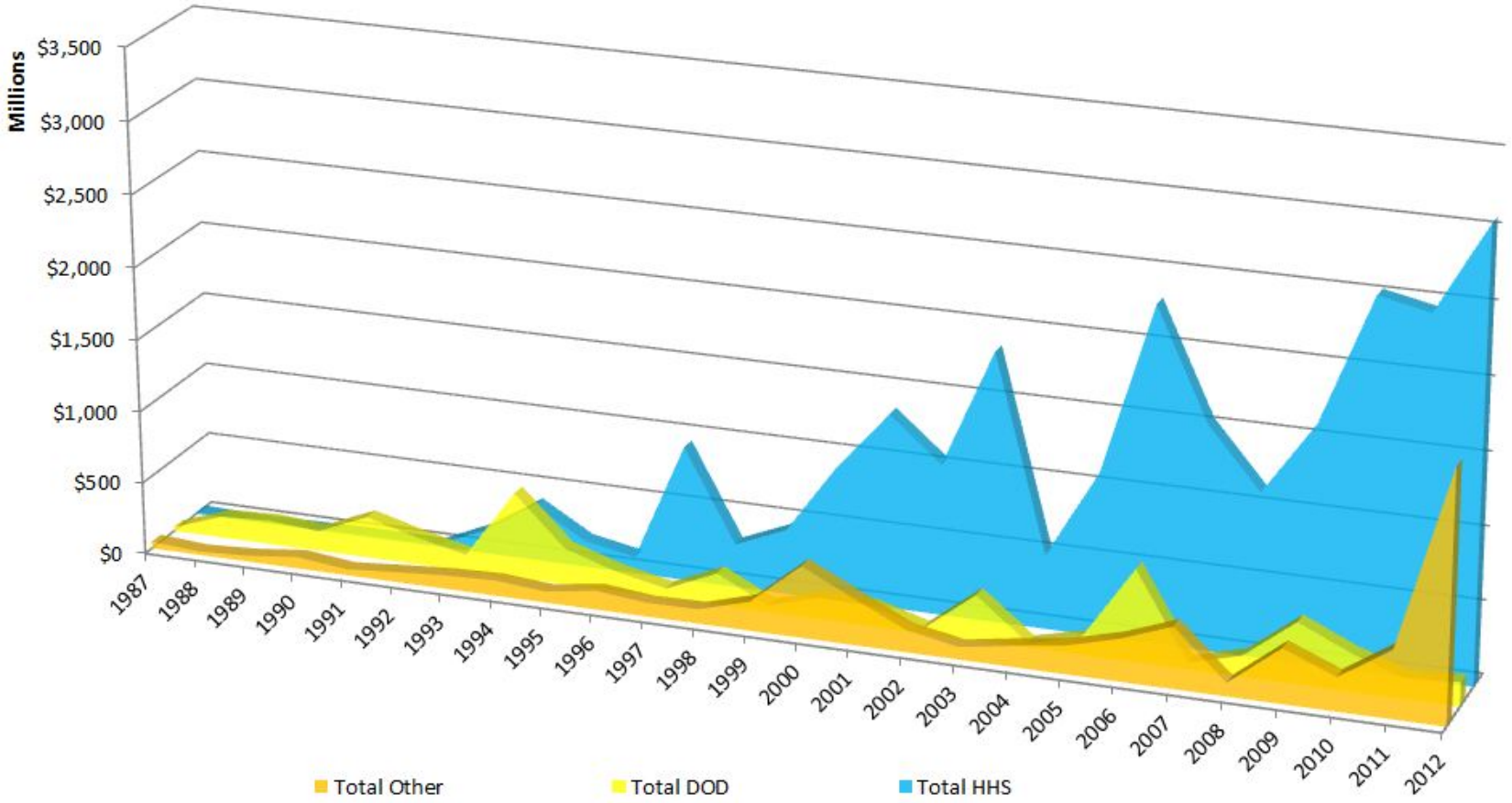
The False Claims Act

Most recoveries under the FCA come in the health care and pharmaceutical industries.



Off-Label Promotion & the False Claims Act

With few exceptions, Medicare and Medicaid are not authorized to purchase off-label drugs.

- Can only pay for "covered outpatient drugs." 42 U.S.C. § 1396r-8(k)(2).
- For "medically accepted indications."
  - 42 U.S.C. § 1396r-8(k)(6) [Medicaid]
  - 42 U.S.C. § 1395w-102(e)(4) [Medicare]
- The use must be (1) approved by the FDA, OR (2) used as supported by reference in a specified medical compendium

Hence, if a manufacturer promotes off label illegally, causing pharmacists to submit claims to the government for payment when the drugs are not actually eligible for reimbursement, FCA liability may be triggered.

Consumer Protection Acts and RICO

While manufacturers may be liable under the FCA for causing claims for payment that may be "false," something more is required under state statutes and RICO – fraud.

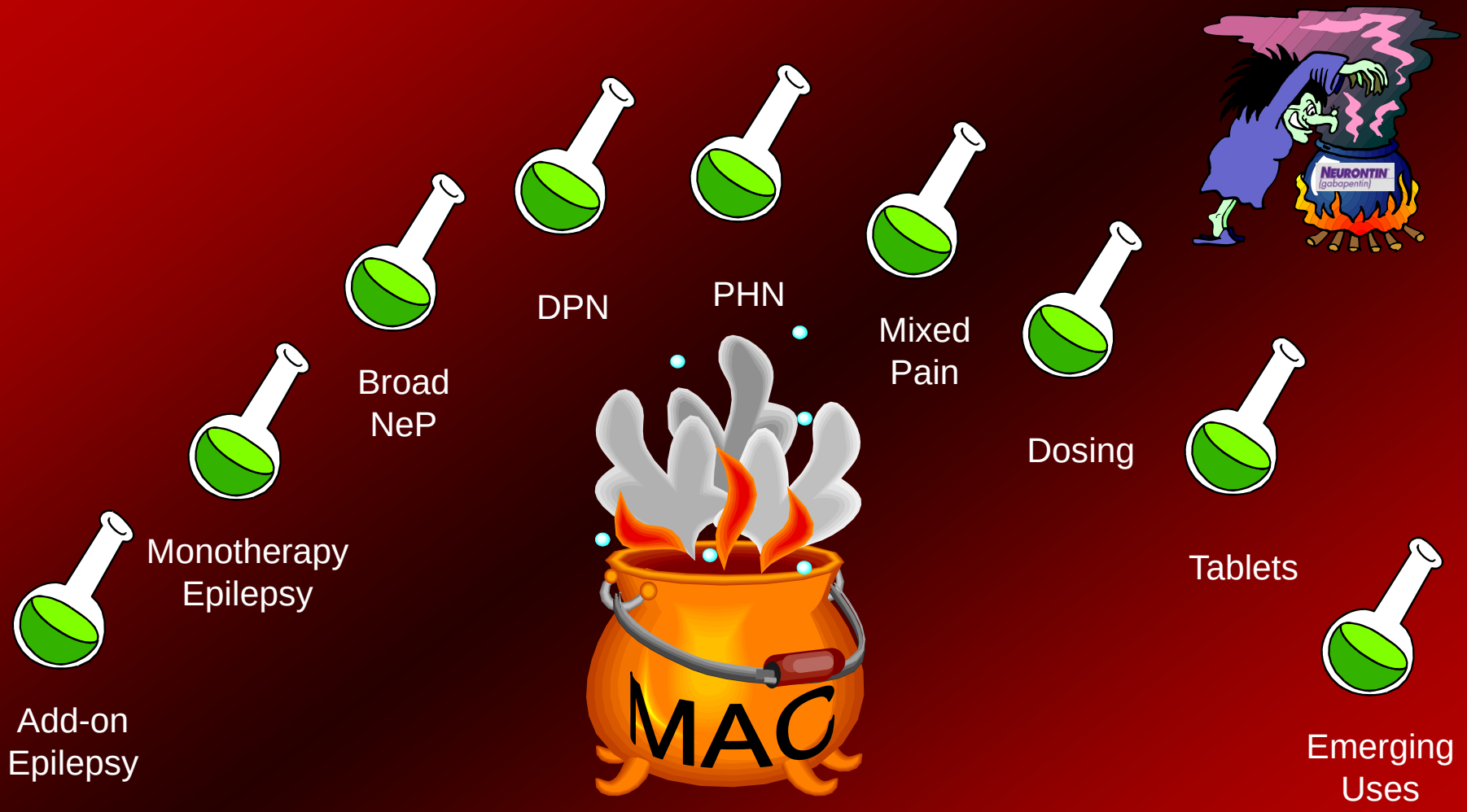
Truthful off-label promotion that is not misleading is unlikely to lead to a viable state claim or RICO case against a manufacturer.

Case Study: Neurontin

- Approved by the FDA in 1994 as an adjunctive (secondary) therapy for treating epilepsy.
- Promoted first by Parke-Davis and then Pfizer for a variety of off-label indications.
- First FCA settlement under an off-label promotion theory of recovery, in 2004.

U.S. ex rel. Franklin v. Parke-Davis

Expanding the resources to address priorities

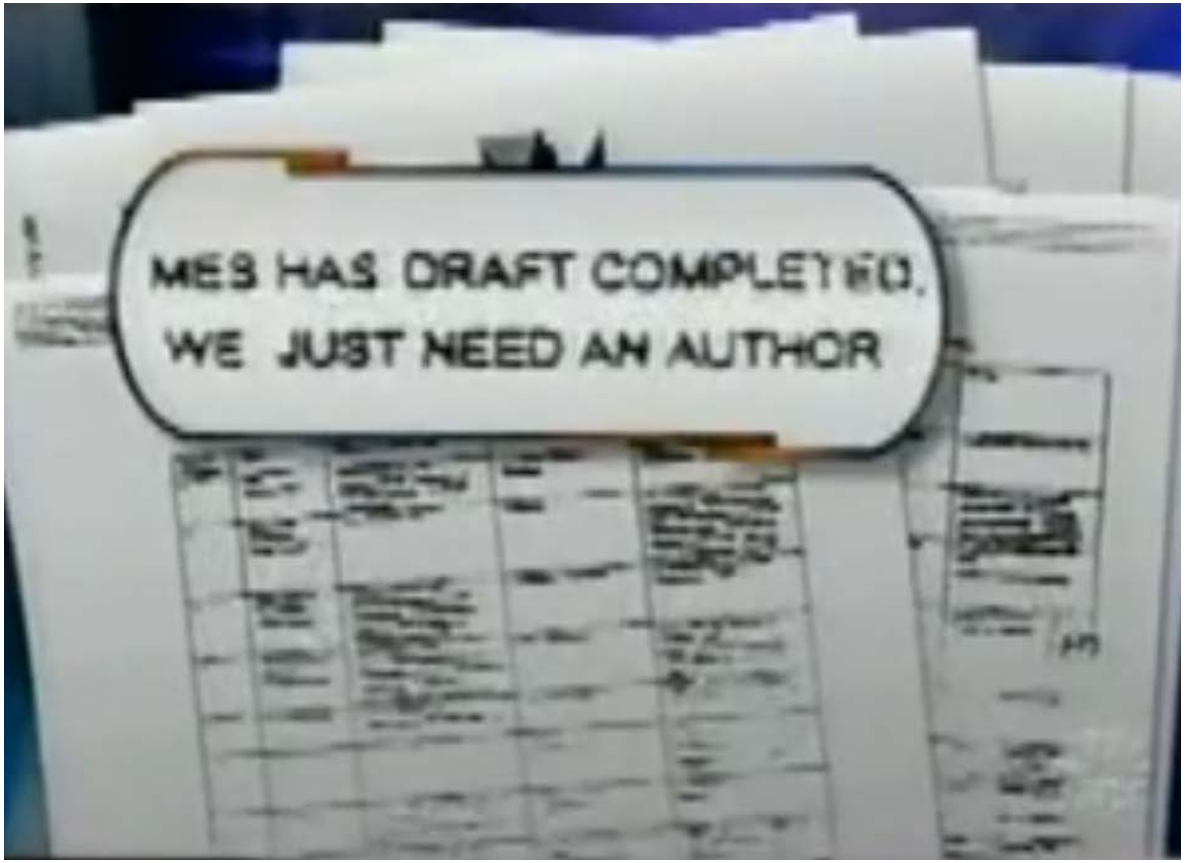


Through case studies and case reports, MAC can recruit KOLs to address multiple priorities simultaneously

MEDICAL ACTION COMMUNICATIONS

Using the FDAMA Reprint Loophole

Reprints allowed; but manufacturers can and do surreptitiously author documents and submit them to journals under cooperating doctors' names.



Neurontin: Fraudulent Promotion

- After *Franklin*, third-party payors sued Pfizer for off-label prescriptions they paid for only because of Pfizer's misstatements.
- Cases were consolidated into an MDL.
  - Class certification of RICO and New Jersey Consumer Fraud Act claims is the subject of a pending First Circuit appeal
  - One TPP's case was selected for a bellwether trial: Kaiser Foundation Health Plan

Kaiser v. Pfizer

- Kaiser pursued two claims: California Unfair Competition Law and RICO.
  - UCL bench claim successful
  - RICO claim also successful, and jury verdict trebled under the statute; Kaiser successfully argued that Pfizer had associated with medical marketing firms to form RICO enterprises, and that the enterprises had engaged in a pattern of racketeering activity (mail and wire fraud).

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Update On Off Label Issues

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FDCA

- Statute does not expressly prohibit off-label promotion
- But a crime to misbrand a drug 21 USC 331
- Misbranding: if drug does not have adequate directions for use 21 USC 352(f)
- Evidence of intent to distribute for unapproved use might be shown by promotional statements

U.S. v. Caronia

- Specialty sales rep, a physician speaker and company prosecuted for misbranding
- Company and doctor pleaded guilty
- Rep convicted at trial, but asserted First Amendment defense
- Prosecuted solely on basis of truthful promotional speech
- Second Circuit (2-1) reversed conviction

U.S. v. Caronia

- Off-label use legal
- Non-distributor can speak about off-label use
- FDA targets one type of speaker: company and its reps
- Heightened scrutiny required under *Sorrell*
  - regulation did not advance govt interest
  - not narrowly drawn
- FDCA allows truthful off-label speech

Open Question

- Could promotional speech ever serve as basis as evidence of intent to distribute for unapproved use, *i.e.* misbranding?
  - doubtful under Majority reasoning
  - speech is protected because truthful and restriction is content- and speaker-based
  - govt has less restrictive alternatives, such as regulating off-label uses

False Claims Basics

- Concept for liability is that govt paid for goods/services that would not have paid for
- Pharma a major target
- Lawsuits often based on alleged promotion for off-label use:
  - but Medicaid has to pay for all on-compendia prescriptions even if off-label
  - Medicaid prior authorization cannot be used to refuse payment for off-label

FCA Liability

- Liability requires that plaintiff show misrepresentation of compliance with precondition of payment. *New York v. Amgen, Inc*., 652 F.3d 103, 110 (1st Cir. 2011)
- Liability also requires defendant caused submission or claim or false record

Who Brings Claims?

- Relators bring many lawsuits
  - PPACA weakened the public disclosure bar for qui tam claims.
  - Bar now applies only to actions based on disclosures from federal sources or the news media
  - Allows relator to maintain a claim based on public information if relator has “independent knowledge that materially adds to the publicly disclosed allegations.”

Violation Of FDA Regs Not Enough

- "mere fact" of "violating FDA regulations does not translate into liability for causing a false claim to be filed." *United States ex rel. Polansky v. Pfizer*, 2009 U.S. Dist. LEXIS 43438, at *17 (E.D.N.Y. May 22, 2009)
- Alleged promotion of Lipitor for off-label uses finally dismissed in 2012 after court found no adequate allegations of off-label marketing

Withholding Safety Information Not Enough

- "assuming that a patient was prescribed Baycol to reduce his/her cholesterol levels, and assuming Baycol successfully lowered the patient's cholesterol, there would be nothing false or fraudulent about the claim for payment for that patient. A claim under the FCA focuses on the claims, not the underlying fraudulent activity."

  In re Baycol Prods. Litig., 2012 U.S. Dist. LEXIS 171964 (D. Minn. July 18, 2012)

Failure to Report AEs Not Enough

- Court dismissed claims where the plaintiff relied on aggregate expenditure data, and failed to establish that compliance with the FDA's adverse-event reporting requirements was a material precondition to payment of the claims at issue. *United States v. Takeda Pharm. Co*., 2012 U.S. Dist. LEXIS 156752 (D. Mass. Nov. 1, 2012).

Causation Requirement

- Because the FCA does not contain its own definition of causation, courts look to common-law tort concepts – the separate "substantial factor" and "foreseeability" tests. *United States ex rel. Carpenter v. Abbott Labs., Inc.*, 723 F. Supp. 2d 395, 407 (D. Mass. 2010).

Aggregate Proof Not Accepted

- Plaintiffs often seek to use general/aggregate proof
- Most courts reject this:
  - *UFCW Local 1776 v. Eli Lilly* (2d Cir. 2010)
  - *In re Actimmune Mktg Litig* (N.D. Cal. 2009)
  - *In re Neurontin* (D. Mass 2010)
  - *In re Bextra & Celebrex Mktg Litig*. (N.D. Cal 2012)