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Constitutional, Policy, and Statutory Problems with the Off-Label Enforcement Environment

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Summary

- Off-label use is legal, vital, and often the standard of care
- In other contexts, the USG recognizes both the value of off-label prescribing and of information about off-label use
- Nonetheless, the USG is prosecuting companies for disseminating even truthful, not misleading scientific communications that advance the public health
- The USG's interpretation, based on a novel interpretation adopted in the mid-1990s, raises severe constitutional questions
- These questions can be avoided by hewing to the traditional view of intended use and a narrower conception of what constitutes "labeling"

Disconnect Between FDA-Approved Labeling and State of the Art Medical Practice

- Many of the most beneficial uses for approved drugs are discovered in the post-FDA approval stage.
- There is often a substantial time lag between scientific discoveries and FDA approval:
 - FDA approval of supplemental drug applications takes an average of more than two years
 - By the time of approval for a new use of a drug, two-thirds of medical journal articles regarding that use have already been published
 - New uses are recognized in U.S. Pharmacopoeia – Drug Information an average of 2½ years before FDA approval

Disconnect Between FDA-Approved Labeling and State of the Art Medical Practice

- Many medically accepted off-label uses never become FDA-approved uses
 - There is frequently no rational economic incentive to seek supplemental approval for new uses late in a drug's patent life
 - For certain diseases, it may be difficult, if not impossible, to find patients willing to participate in the large, randomized clinical trials required to obtain FDA approval for a new use

Off-Label Prescribing is **Lawful**, Common and Vitally Important to the Practice of Medicine

- Physicians may lawfully prescribe FDA-approved drugs for any use consistent with available scientific data and appropriate medical practice

"[A] physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert."

37 Fed. Reg. 16503 Aug. 15, 1972

Off-Label Prescribing is **Lawful**, Common and Vitally Important to the Practice of Medicine

- The FDA has no jurisdiction over the practice of medicine:

“FDA does not have the authority [under the FDCA provisions] to control decisions made by qualified healthcare practitioners to prescribe products for conditions other than those described in FDA-approved professional labeling, or to otherwise regulate medical or surgical practice.”

FDA Guidance for Industry on Development of Risk
Minimization Action Plans, March 2005

“The physician is responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him.”

37 Fed. Reg. 16504 Aug. 15, 1972

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Off-Label Prescribing is Lawful, **Common** and Vitally Important to the Practice of Medicine

- Off-label prescribing is pervasive in the practice of oncology:
 - 60% of oncologists report that they frequently prescribe medications off-label
 - More than half of all cancer patients have received an anti-cancer drug for an off-label use
 - Nearly every type of cancer is treated with off-label regimens
 - Roughly 95% of all oncology drugs are used off-label

The Rationale for Off-Label Prescriptions, 12(3) Johns Hopkins Medical Letter: Health After 50 (May 2000); General Accounting Office, Report to the Chairman, Comm. On Labor and Human Resources, U.S. Senate, Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies 20, 27 (1991); American Society of Clinical Oncology Daily News (May 2001).

Off-Label Prescribing is Lawful, **Common** and Vitrally Important to the Practice of Medicine

- Extensive clinical experimentation in oncology leads to off-label prescribing:

“The labeling of anticancer products frequently presents an incomplete or even inaccurate picture of the current state of medical knowledge. For virtually every cancer drug, appropriate medical dosage differs from the terms on the product labeling.”

John R. Durant, M.D., Executive Vice President, American Society of Clinical Oncology, 1998

“The off-label uses of approved drugs have been an important tool for advancing the treatment of cancer.”

American Society of Clinical Oncology, 2003

“[I]n some cases, if you didn’t use the drug in the off-label way, you’d be guilty of malpractice.”

M. Roy Schwarz, Vice President for Science and Education, American Medical Association

Off-Label Prescribing is Lawful, Common and Vitally Important to the Practice of Medicine

- FDA recognizes off-label usage may be the standard of care:
 - FDA's Oncologic Drugs Advisory Committee (ODAC) rejected accelerated approval of Marqibo in December 2004
 - Cited Rituxan as an available therapy, recognizing the widespread off-label use of Rituxan in the treatment of both front-line and refractory aggressive Non-Hodgkin's Lymphoma

Off-Label Prescribing is Lawful, Common and **Vitally Important to the Practice of Medicine**

- The AMA has also affirmed the importance of off-label prescribing:

“The prevalence and clinical importance of prescribing drugs for unlabeled uses are substantial.... Thus, the prescribing of drugs for unlabeled uses is often necessary for optimal patient care.”

1997 AMA Annual Meeting

“The AMA affirms that a physician may lawfully use an FDA-approved drug for an unlabeled indication when such use is based upon sound scientific evidence and sound medical opinion.”

AMA Policy 120.988

“Up-to-date, clinically appropriate medical practice at times requires the use of pharmaceuticals for ‘off-label’ indications as distinct from the specific approved indication(s) from the US Food and Drug Administration. . . .”

AMA House of Delegates, Resolution 820, “Off-Label Use of Pharmaceuticals,” September 24, 2005

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Many Government Policies and **Practices** Encourage Off-Label Prescribing

- The Government supports the off-label usage of oncology drugs:

“Off-label use of drugs is widespread in cancer treatment for several reasons. ... Some cancer drugs are found to be effective against a variety of tumor types. ... Cancer chemotherapy often involves the use of multiple drugs. ... Cancer treatment is always evolving.”

National Cancer Institute, Q&A Off-Label Drugs, posted December 31, 1999

Many Government **Policies** and Practices Encourage Off-Label Prescribing

- Medicare Federal Coverage Policy:
 - Medicare policy guidance specifically includes, as eligible for coverage, off-label uses supported by recognized compendia or peer-reviewed medical journals

The Social Security Act defines a “medically accepted indication” for use of a drug to be any FDA-approved use, as well as other uses if- the drug has been approved by the FDA, and

(i) the use is supported by certain compendia; or

(ii) the use is medically accepted based on supportive clinical evidence in certain peer-reviewed medical literature.

Social Security Act § 1861(t)(1)

“FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if the carrier determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice.”

Medicare Benefit Policy Manual (CMS Pub. 100-2) Chapter 15 §50.4.2

Open Communication of Clinical Trial Data is Essential to Public Health

- Access to scientific information regarding off-label uses is of particular importance outside of urban areas of academic medical excellence:

Physicians outside of major urban areas "have very little time to pursue information; therefore, information must be immediately accessible, concise, high quality, presynthesized, and up-to-date."

Dee and Blazek, *Information Needs of the Rural Physician: A Descriptive Study*,
Bull Med Libr. Assoc 81(3), July 1993, at 263.

Failure to Communicate Clinical Trial Data is a Major Public Health Problem

- President's Cancer Panel affirms that the sharing of clinical information is important:

"Disseminating prompt, accurate information in usable formats to community health care providers and the public about cancer prevention and treatment advances is a critical step in the translation - the link between an intervention's development and its adoption in clinical practice."

President's Cancer Panel, 2004-2005 Annual Report, at 65.

"Simply put, we are not applying what we know – interventions demonstrated to be efficacious and validated through the clinical trials process – nearly well enough, quickly enough, or widely enough."

The National Cancer Program: Assessing Past,
Charting the Future, 1999 Annual Report

"To achieve the ultimate goal of dissemination - enabling individuals and organizations to adopt evidence-based approaches that will help reduce the risk and burden of cancer - specific education and communication needs of the public, health care professionals, and research community must be met."

President's Cancer Panel, 2004-2005 Annual Report, at ix.

Open Communication of Clinical Trial Data is Essential to Public Health

"[I]t is well-documented that physicians rely upon the [pharmaceutical] industry for much of their drug information."

Spiller and Wymer, *Physicians' Perceptions and Uses of Commercial Drug Information Sources: An Examination of Pharmaceutical Marketing to Physicians*, *Health Marketing Quarterly* Vol. 19(1) (2001), 94

Federal Prosecutors are Pursuing the Dissemination of Off-Label Information as **Criminal** and Civil Misconduct

- It is estimated that there are roughly 500 other drugs under investigation.

Assistant U.S. Attorney General Peter Keisler

"Cases, Fines Soar in Fraud Probes" *Wall Street Journal*, June 7, 2005

- The following major pharmaceutical manufacturers have disclosed that they are currently being investigated for off-label promotion of their drugs:

Abbott Labs

AstraZeneca

Forest

Genentech

GlaxoSmithKline

Johnson & Johnson

Eli Lilly

Novartis


Pfizer

sanofi-aventis

Schering

Wyeth

Many Government Policies and Practices Encourage Off-Label Prescribing

 **NIH NEWS RELEASE**

NATIONAL INSTITUTES OF HEALTH National Cancer Institute

EMBARGOED FOR RELEASE Contact: NCI Press Office
Tuesday, June 15, 1999 (301) 496-6641
4:00 p.m. EST NSABP Operations Center
(412) 330-4657

**Publication of the MORE Trial Results
Supports Study of Tamoxifen and Raloxifene (STAR)**

The publication of results from the Multiple Outcomes of Raloxifene Evaluation, or MORE trial, which show that the osteoporosis prevention drug raloxifene (Evista®) reduced the incidence of breast cancer in postmenopausal women with osteoporosis, brings additional peer-reviewed data to the body of evidence that supports the rationale for the Study of Tamoxifen and Raloxifene (STAR).

STAR is a study of 22,000 postmenopausal women at increased risk of breast cancer to determine whether raloxifene is as effective in reducing the chance of developing breast cancer as tamoxifen (Nolvadex®) has proven to be. STAR is being conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), a network of researchers, and is supported by the National Cancer Institute (NCI). Recruitment to the study began May 25 at more than 400 centers across the United States, Puerto Rico, and Canada, and the first participants will be randomized by June to receive either tamoxifen or raloxifene. STAR is limited to postmenopausal women because raloxifene has not been adequately safety tested in premenopausal women, although such a study is under way.

The MORE data clearly show the potential of raloxifene for decreasing women's chances of getting breast cancer. As is standard in cancer research, promising preventive or treatment agents are compared to the standard of care, which in this case is tamoxifen. At the American Society of Clinical Oncology's (ASCO) May 1999 annual meeting, the society stated that it is premature to recommend the use of raloxifene to lower the risk of developing breast cancer outside a clinical trial. NCI and NSABP agree with ASCO in this regard.

Preliminary data from the MORE trial were presented at three scientific meetings previously, in May 1998 and May 1999 at the ASCO annual meetings and at the December 1998 San Antonio Breast Cancer Conference. STAR researchers were aware of these preliminary data during the design of the STAR protocol. Therefore, publication of MORE data in the June 16, 1999, *Journal of the American Medical Association* finalizes its peer review, but does not provide any additional data that would affect the design of STAR.

Tamoxifen was shown to reduce the chance of developing breast cancer by about half in the Breast Cancer Prevention Trial, a study of over 13,000 premenopausal and postmenopausal women at high risk of breast cancer. Tamoxifen has been in clinical trials for about 30 years. It has been approved for use to treat women with breast cancer for more than 20 years. Last October, the U.S. Food and Drug Administration (FDA) approved it for use to reduce the incidence of

"The publication of results from the Multiple Outcomes of Raloxifene Evaluation, or MORE trial, which show that the osteoporosis prevention drug raloxifene (Evista®) reduced the incidence of breast cancer in postmenopausal women with osteoporosis, brings additional peer-reviewed data to the body of evidence that supports the rationale for the Study of Tamoxifen and Raloxifene (STAR)."

Many Government Policies and Practices Encourage Off-Label Prescribing

- The National Cancer Institute Recognized Off-Label Indications of Rituxan as Standard of Care
 - Front Line Aggressive Adult Non-Hodgkin's Lymphoma
 - "Standard treatment options: ... 1. CHOP plus rituximab"
 - Indolent, Noncontiguous Stage II/III/IV Adult Non-Hodgkin's Lymphoma:
 - "Standard treatment Options: ... Ribuximab may be considered a first line therapy."
 - Stage I, II, III, and IV Chronic Lymphocytic Leukemia:
 - "Treatment options: ... 2. Rituximab,, and anti-CD20 monoclonal antibody."

Federal Prosecutors are Pursuing the Dissemination of Off-Label Information as **Criminal** and Civil Misconduct

- In these cases and investigations, the government has pursued criminal off-label charges that do not require a showing of false or misleading representations or other inherently wrongful conduct
- The government is targeting practices that FDA generally permits
 - scientific exchange
 - responses to unsolicited requests
 - dissemination of enduring materials
 - continuing medical information
 - The damages the government seeks are based on ALL off-label prescriptions
- Government asks only if there was an intended commercial benefit from the conduct

Federal Prosecutors are Pursuing the Dissemination
of Off-Label Information as **Criminal** and Civil Misconduct

- The cases against pharmaceutical companies to date have all settled without legal challenge, notwithstanding substantial legal infirmities with the government's prosecution theory, due to:
 - Risk of exclusion that may be realized upon the return of a criminal charge under permissive exclusion and debarment provisions
 - Rational corporations conclude, as a business matter, that the risks associated with incurring an indictment and going to trial are prohibitively high

Federal Prosecutors are Pursuing the Dissemination
of Off-Label Information as **Criminal** and Civil Misconduct

- Policy concerns
 - The government’s campaign to criminalize the dissemination of truthful, non-misleading off-label information has already resulted in a substantial reduction in funding by pharmaceutical companies for clinical research and educational programs in the off-label arena.
 - As a result, the government’s prosecution effort may have an adverse impact on scientific development and the acknowledged beneficial role of off-label uses in the treatment of many diseases, to the direct detriment of patients and their families.

Statutory Theories

- Unapproved new drug
- Misbranding
 - false or misleading
 - lack of adequate directions for use

USG Basis for Expanding FDA Authority

- Historically, FDA pursued false and misleading cases
- Changed in the mid-1990s
- Expanded interpretation of intended Use – cigarette cases
- Expanded definition of labeling – “accompany the drug”

Constitutional Issues

- These prosecutions raise profound First Amendment problems
- They often concern speech that is truthful, not misleading about a lawful use (Caputo)
- As a result they cannot be sustained under the Central Hudson test
 - substantial government interest
 - but there are other government interests
 - do not directly advance the government's interest
 - swiss cheese\inconsistency problem
 - lack of a reasonable fit
 - other means to communicate

How to Harmonize FDCA and the 1st Amendment?

- Avoidance canon
- Traditional view of intended use
- Narrower view of “labeling”
- Allows “space” for truthful, not misleading communications
 - e.g., reprints or CME
 - also allows FDA to pursue true cases of off-label promotion

Conclusion

Thank You!

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