All the Ways You Can Be Tagged for Off-Label Promotion of Medical Products

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Today's Presenters

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Today's Agenda

I. What is "off-label promotion" in the first place and why do we need to avoid it?

II. How do government agencies become aware of off-label promotional activity?

III. What are the short-term and long-term risks of such promotional activity?

IV. How do companies manage those issues and create systems to mitigate the risk of off-label promotion by their employees or agents?

"The FDA-required labeling is the primary tool that communicates the essential information needed for the safe and effective use of the product, and firms have an obligation to update their FDA-required labeling as needed to ensure it is not false or misleading."

- FDA CFL Guidance, 2018

What Does “Off Label” Mean?

- ✓ **Prescription drugs and biologics**
  = inconsistent with the FDA-approved labeling for the product
- ✓ **Class 2 and 3 medical devices**
  = inconsistent with the FDA-cleared or approved labeling
- ✓ **Class 1 and 510(k)-exempt devices**
  = inconsistent with the intended use or device description set forth in the relevant classification regulation

Off-label promotion is when manufacturers **promote** uses for their products outside of the relevant prescribing information, instructions for use (IFU), or otherwise agency-sanctioned intended uses.

“Intended Use” – Defining Regulation

Drugs (21 C.F.R. § 201.128) & Devices (21 C.F.R. § 801.4)

“The words *intended uses*…refer to the objective intent of the persons legally responsible for the labeling of an article (or their representatives). ***The intent may be shown by such persons' expressions, the design or composition of the article, or by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. Objective intent may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered or used for a purpose for which it is neither labeled nor advertised***; provided, however, that a firm would not be regarded as intending an unapproved new use for an [approved drug/approved or cleared device] based solely on that firm's knowledge that such [drug/device] was being prescribed or used by health care providers for such use. …”

Marketing activities and communications regarding the safety and effectiveness of a medical product for a particular use that are not properly supported by scientific evidence may…create a false or misleading impression about the safety and efficacy of the medical product for that use, which can lead to prescribing or use decisions that harm patients.

– FDA's Jan. 2017 "First Amendment Considerations" Memo

“Off-Label Claims” Can Come in Various Flavors

Unapproved/Uncleared Uses

“[Y]our device was cleared under K163512 for long-term monitoring of arrhythmia events for non-critical care patients where real-time monitoring is not needed as reporting timeliness is not consistent with life-threatening arrhythmias. **However, your marketing materials and other documentation, such as the document titled “Zio AT Notification Criteria,” and your website**…state that the Zio AT Patch System is intended for “near real-time monitoring” as a “mobile cardiac telemetry monitor,” can provide notifications “immediately,” and that it is intended for “high-risk patients.” The claim that the device is intended as a mobile cardiac telemetry monitor implies this device is intended for high-risk patients and near real-time monitoring. … This change could significantly affect the safety or effectiveness of the device because it **suggests that the device is intended for a new patient population – high-risk patients**. High risk patients need near real-time monitoring because they are more likely to have a life-threatening arrhythmia, which requires timely treatment to prevent serious injury or death. Accordingly, these changes required the submission of a new 510(k).”

- May 25, 2023 Warning Letter to iRhythm Technologies, Inc.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/irhythm-technologies-inc-643474-05252023

Product Features/Clinical Claims

Certain “sales representatives marketed Opana ER to prescribers by touting Opana ER’s purported abuse deterrence, tamper resistance, and/or crush resistance, despite a lack of clinical data supporting those claims. According to the plea agreement, … sales managers were aware that the **sales representatives were making claims of purported abuse deterrence, tamper resistance, and/or crush resistance during sales calls, including hitting demonstration ‘blister packs’ of non-medicated sample pills with hammers and conducting other demonstrations to convey the message that Opana ER was, in fact, crush proof and tamper resistant.** The approved labeling for Opana ER did not provide adequate information for healthcare providers to safely prescribe Opana ER for use as an opioid that is abuse deterrent.”

- February 29, 2024 DOJ Press Release announcing a global resolution of criminal and civil investigations into sales and marketing of branded opioid drug

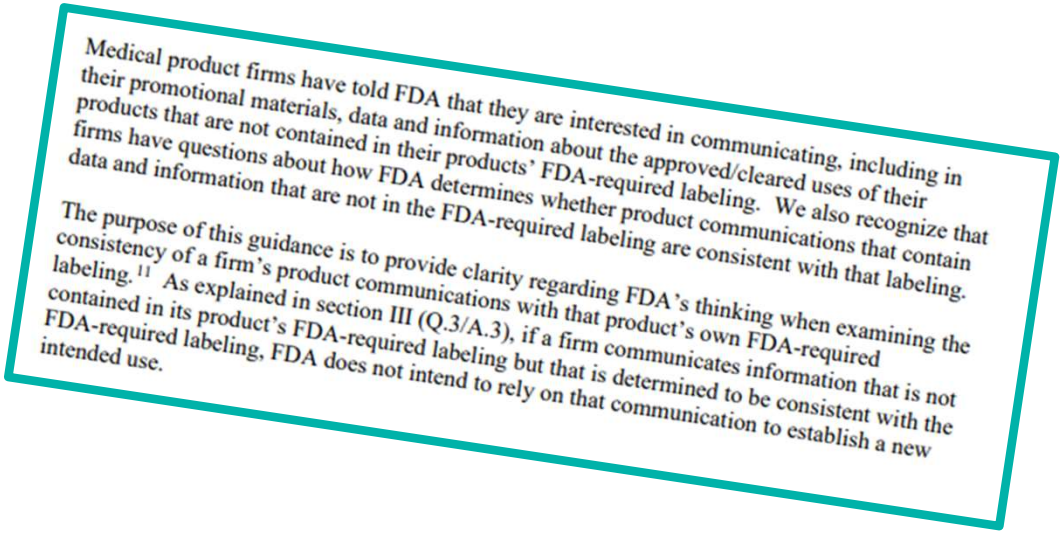
https://www.justice.gov/opa/pr/opioid-manufacturer-endo-health-solutions-inc-agrees-global-resolution-criminal-and-civil

Medical Product Communications That Are Consistent With the FDA-Required Labeling Questions and Answers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)
Office of the Commissioner (OC)

June 2018
Procedural



Medical product firms have told FDA that they are interested in communicating, including in their promotional materials, data and information about the approved/cleared uses of their products that are not contained in their products' FDA-required labeling. We also recognize that firms have questions about how FDA determines whether product communications that contain data and information that are not in the FDA-required labeling are consistent with that labeling.

The purpose of this guidance is to provide clarity regarding FDA's thinking when examining the consistency of a firm's product communications with that product's own FDA-required labeling.[11] As explained in section III (Q.3/A.3), if a firm communicates information that is not contained in its product's FDA-required labeling but that is determined to be consistent with the FDA-required labeling, FDA does not intend to rely on that communication to establish a new intended use.

“Promotion” = Distinct from Scientific Exchange

- Promoting or advertising a medical product is characterized by seeking to induce sales or purchases of the product in question.
  - Can be printed, graphic, or spoken communications
  - The medium itself does not matter
  - Substantive content or tone of the claims is what will determine whether the labeling is objectively promotional. Always consider the “net impression” as well as individual representations.
- In contrast, companies may distribute published articles from scientific journals that discuss experimental, off-label uses of FDA-approved drugs and devices (through Medical Affairs function; non-promotionally) and may otherwise engage in *bona fide* scientific exchange activities for both approved and investigational products.
- Today’s presentation will not delve into the complex issues of scientific exchange or FDA’s evolving enforcement policies in that area (*e.g.*, the recently revised guidance on “scientific information on unapproved uses” or SIUU).

“Off-Label” vs. Pre-Approval Promotion

In contrast to FDA-approved or cleared products that cannot be marketed by their owners outside of their labeled intended uses or instructions for use, investigational products that are not authorized in any way **should not be promoted** at all.

Investigational products should only be the subject of scientific exchange or non-promotional factual information disseminated by the company (*e.g.*, “JSH-02 is currently being tested in a Phase 1 clinical trial…).

> **21 C.F.R. § 312.7(a):** “*Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, ***shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation*** or otherwise promote the drug. This provision is not intended to restrict the full ***exchange of scientific information*** concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.”

How Does the FG Learn About Off-Label Claims or Pre-Approval Promotion?

FG = federal government

1

Surveillance Monitoring of Regulated Products

- FDA reviewers and compliance officers are consumers too; they may run across noncompliant claims in their day-to-day lives and also when attending medical/scientific conferences.
- Assessments of company or product websites can be done either in response to a complaint/ as part of a broader investigation or more generally as part of FDA's compliance function.

2

3rd Party Complaints (HCPs, Competitors, Consumers)

- "Bad Ad" Program for drugs launched in 2010 and has led to >2,400 reports of potentially false or misleading promotion and at least FDA 22 compliance actions (WLs or untitled letters).
- CDRH "Allegations of Regulatory Misconduct" online form makes it easy for complainants to submit their concerns to the agency.

3

Facility Inspections & Mandatory Submissions

- Routine facility inspections for GMP/QSR compliance can uncover marketing violations.
- Form 2253 promotional labeling submissions by drug/biologic sponsors may trigger concerns about particular claims or the net impression that go beyond the FDA-approved prescribing information.

4

Internal Whistleblowers

- Employees, consultants, or vendors may become whistleblowers and either submit their own complaint to the FG for further investigation or, in certain situations, initiate a *qui tam* False Claims Act case against the company.

Examples of FDA Letters Resulting from "Bad Ad" Complaints

Nephron SC Inc. – Budesonide Inhalation Suspension Warning Letter dated 9/22/2020

Lack of Adequate Directions for Use

7/14/2020 email

- **"BUDESONIDE** RELIEVES RESPIRATORY SYMPTOMS ASSOCIATED WITH COVID-19" (emphasis in original)
- **"**Over the last few weeks, doctors and researchers have touted the benefits of using Budesonide as a treatment for symptoms associated with COVID-19. One physician, who went viral this month, called Budesonide a 'silver bullet.'"

7/07/2020 email

- Subject line, "COVID-19-Budesonide-Video"
- Links to YouTube video of a physician discussing "treating COVID patients successfully with Budesonide and an antibiotic…You may want to share this with your respiratory team and pulmonary docs. Cost effective way to treat Coronavirus!"

"These claims and representations [in its marketing emails to HCPs] provide evidence that Nephron is **promoting Budesonide with a new use** for which it lacks approval and for which its labeling does not provide adequate directions for use."

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/nephron-sc-inc-610867-09222020

Eisai Inc. – Fycompa (perampanel) Untitled Letter dated 10/11/2018

- Schedule 3 drug with a Boxed Warning
- According to the report submitted to the Bad Ad Program:
  - a sales representative made **oral statements** during a lunch presentation to HCPs and "in his capacity as an employee of Eisai"
  - that the product is "intended for new uses for which it lacks approval, and for which its labeling does not provide adequate directions for use."
- As a separate issue, the sales rep also apparently downplayed the serious, life-threatening risks of homicidal ideation and aggressive behavior described in the product's Boxed Warning by suggesting the HCPs "not worry about it" and by providing anecdotal information about other facilities that had procured the drug and "were not concerned" about the BW.

https://www.fda.gov/media/117097/download?attachment

Examples of FDA Letters Resulting from Routine Surveillance/Inspections

ZYTO Technologies Warning Letter dated 6/21/23

- Issues were identified during FDA inspection of the firm's facility for post-marketing compliance.
- Company had received 510(k) clearance for a device only to "measure Galvanic Skin Response." It was being marketed as a scan to identify "stressors" and "balancers" as part of a "journey to wellness."
  - However, according to the Warning Letter, some of the "stressors" identified or diagnosed by the device + its associated proprietary software "include diseases and conditions such as **Alzheimer's disease, human immunodeficiency virus (HIV), Parkinson's disease and melanoma**, and some of the 'balancers' recommended by the software represent specific treatments or mitigations for a given 'stressor.'"
  - Therefore, although the company had a premarket clearance for the hardware, the "firm's promotion of the device represents a **major change or modification to its intended use**, for which your firm lacks clearance or approval. Thus, although originally classified as Class II under 21 CFR 882.1540, the device does not qualify for the exemption from 510(k) granted in 2019 for that generic type of device… because, among other things, the device "is intended for a use different from the intended use of a legally marketed device in that generic type of device."

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/zyto-technologies-inc-652316-06212023

ZYTO Technologies Warning Letter dated 6/21/23

- Issues were identified during FDA inspection of the firm's facility for post-marketing compliance.
- Company had received 510(k) clearance for a device only to "measure Galvanic Skin Response." It was being marketed as a scan to identify "stressors" and "balancers" as part of a "journey to well
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    or approval. Thus, although originally classified as Class II under 21 CFR 882.1540, the device does not qualify for the exemption from 510(k) granted in 2019 for that generic type of device… because, among other things, the device "is intended for a use different from the intended use of a legally marketed device in that generic type of device."

NCI Dictionary of Cancer Terms

galvanic skin response

(gal-VA-nik ... reh-SPONTS)

A change in the heat and electricity passed through the skin by nerves and sweat. Galvanic skin response increases in certain emotional states and during hot flashes that happen with menopause. Also called electrodermal response and skin conduction.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/zyto-technologies-inc-652316-06212023

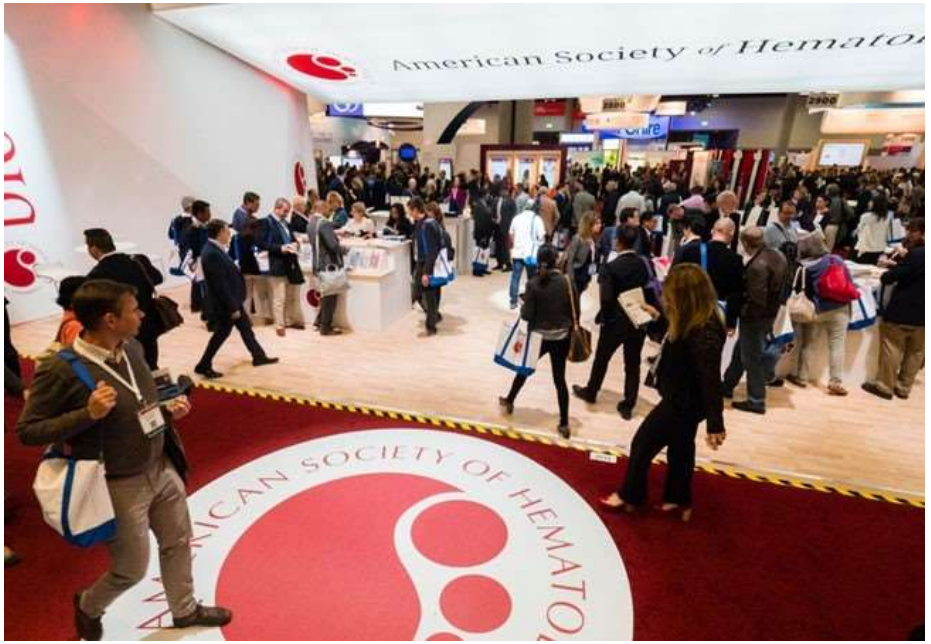
RightEye, LLC Warning Letter dated 12/20/2022

- FDA investigators became aware of issues during facility inspection
- RightEye Vision System was 510(k)-cleared with the following indications: “recording, viewing, and analyzing eye movements in support of identifying visual tracking impairment in human subjects”
- “However, your firm’s promotion of the device provides evidence that the device is **intended to improve vision problems** and measure and analyze eye movements for **the broader genre of ‘neurological disorders,’ including Parkinson’s disease**, which would constitute a major change or modification to its intended use for which your firm lacks clearance or approval.”
  - “Uncover & Improve Vision Problems That Interfere With Reading and Learning”
  - “RightEye EyeQ tests help health care providers assess patients’ brain health, visual dysfunction, concussions, reading disorders, and athletic performance issues by following an evidence-based, metrics-driven methodology.”

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/righteye-llc-643192-12202022

Pre-Approval Promotion – Untitled Letter dated 6/28/2018

- FDA reviewed the Arog Pharmaceuticals, Inc.'s booth display at the American Society of Hematology's 59th Annual Meeting and the Company's corporate webpage, both of which were highlighting the company's investigational product Crenolanib.
- Both the booth display and the webpage suggested, "in a promotional context," that the drug was safe and effective for the purposes for which it was being investigated.
- **Conclusory statements** included but were not limited to: "*Combinable with* Chemotherapy at full doses"; "*potent inhibitor* of FLT3…"; "*for use* in FLT3-mutated AML"; "*set apart from other therapeutic options.*"
- Booth display contained **no information about the drug's investigational status** and appeared in main hall alongside approved products.
- Website had no investigational drug disclosures but did have comparisons to approved products and efficacy claims.



https://www.fda.gov/media/114446/download

Potential Consequences of Off-Label Promotion

FDA's Enduring Enforcement Priorities

Prescription Drug/Biologic

- Promotional materials for high-risk drugs, such as opioids; drugs approved with a Risk Evaluation and Mitigation Strategy (REMS); and drugs labeled with Boxed Warnings regarding potentially serious side effects
- First impression launch materials for newly approved drugs, as well as new uses for approved therapies
- Products that have been the subject of previous compliance letters from FDA
- Drugs cited in complaints to the agency or promoted in far-reaching campaigns

Medical Device

- Unapproved devices and unapproved/ uncleared indications or intended uses
- Specific claims for devices cleared for general intended use (often "tool" uses)
- Comparative claims
- Imbalance of benefit/risk information
- Combination products
- Practitioner promotion (see 21 U.S.C.§ 396)

Enforcement Options

- When FDA determines that a product is misbranded or adulterated, it can take the following actions (some of which require the support of DOJ):
  - Issue Warning Letters or Untitled Letters;
  - Request (drugs) or require (device) the product to be recalled;
  - Impose civil money penalties;
  - Seize the violative product;
  - Seek an injunction to prevent the company from operating;
  - Require companies to enter into consent decrees regarding future behavior; and
  - Criminally prosecute offenders.

Other Implications

- Bad publicity
- Whistleblower complaints (inc. *qui tams*)
- Product liability
- State prosecution
- Fraud and abuse prosecution
  - Including False Claims Act, Anti-Kickback, etc.
- Loss of good reputation in the medical and patient communities
- Other regulatory agencies (*e.g.*, SEC, State AGs)
- Competitor challenges (*e.g.*, Lanham Act, NAD)
- Individual liability

DOJ Health Care Fraud and Abuse Enforcement

- In FY2023, DOJ recovered more than **$2.68 billion** in civil settlements and judgments in **False Claims Act** cases.
  - **$2.3 billion** arose from lawsuits filed under the *qui tam* provisions of the FCA
  - 543 settlements and judgements in FY2023 (highest-ever in a single year)
  - **712 *qui tam*** suits were filed in FY2023 alone (3rd highest number on record)

- **$1.8 billion** of the over $2.68 billion recovered stemmed from **Health Care Matters**

See Feb. 22, 2024 release, "False Claims Act Settlements and Judgments Exceed $2.68 Billion in Fiscal Year 2023" – available at:

https://www.justice.gov/opa/pr/false-claims-act-settlements-and-judgments-exceed-268-billion-fiscal-year-2023#:~:text=Of%20the%20more%20than%20%242.68,long%2Dterm%20acute%20care%20facilities%2C

Off-Label Schemes Can Lead to Serious Liability

- **May 2004** – Warner-Lambert agreed to pay **$430 million** to resolve all civil and criminal liability stemming from its alleged off-label marketing of epilepsy drug Neurontin (first litigated off-label case under the FCA); *note that the qui tam relator here received $24.64 million for his trouble*
- **Sept. 2010** – Allergan agreed to a **$600 million** settlement to resolve all civil and criminal liability surrounding the promotion of Botox for treatment of chronic migraines (FDA had not yet approved the drug for such use)
- **May 2012** – Abbott Labs pleaded guilty and agreed to pay **$1.5 billion** to resolve its criminal and civil liability arising from promotion of the prescription drug Depakote for unapproved uses
- **Nov. 2016** – Biocompatibles Inc. agreed to pay **$25 million** to resolve FCA allegations stemming from its alleged promotion of an embolization device (designed to be inserted into blood vessels to block bloodflow to tumors) for unapproved use as a "drug-delivery" device
- **July 2017** – Celgene agreed to pay **$280 million** to settle allegations that it caused the submission of false claims or fraudulent claims for non-reimbursable uses of two drugs to Medicare and state Medicaid programs; off-label promotion as well as "false and misleading" statements to conceal or minimize adverse events were cited under the covered conduct

Best Practices to Mitigate Off-Label Risks Within Your Organization

Critical Practices for Compliance

Ensuring regulatory compliance of product promotional labeling is a critical part of every manufacturer's quality and regulatory system for commercial products, as is ensuring investigational products are not "promoted" or advertised in any way.

Critical Practices for Compliance

- Manufacturers should take steps to help ensure all promotional materials comply with applicable regulations:
  - ✓ Establish a formal review process for all labeling, press releases, investor presentations, and any other public statements.
  - ✓ Train all relevant employees on the policies and procedures, and refresh training periodically.
  - ✓ Make sure the Regulatory and Legal Departments are included in every substantive review.
  - ✓ Implement effective document and change control procedures for all labeling (packaging + promotional labeling).
  - ✓ Conduct periodic reviews of all product labeling to make sure that the content still complies with recently issued FDA rules or guidances, especially all online promotional materials.
  - ✓ If the manufacturer has an online blog or social media accounts to promote products, establish a social media and online communication policy, which should include endorser/influencer policies.

Red Flags During Promotional Content Review

- × Express or implied claims (e.g., imagery) or other representations that expand the FDA-authorized patient population
- × Express or implied claims or other representations that suggest a different intended use for the medical product that what it has been approved/cleared for
  - *For example,* information re. a different stage, severity, or manifestation of a disease than what the product is approved to treat or diagnose; information re. use as a monotherapy when it's only approved for use as an adjunct to something else
- × Representations that conflict with the limitations of use and/or directions for handling, preparing, or using the medical product (as set forth in the product's FDA-required labeling)
- × Representations that conflict with the recommended dosage or use regimen or route of administration set forth in the product's FDA-required labeling
  - *For example,* information re. IV injection of the product even though it's approved only for IM; information re. once-a-day dosing even though it's approved for 2x/day dosing

Helpful Resources for In-House Counsel

- FDA Warning Letter database: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters
- CDER Office of Prescription Drug Promotion (OPDP) Regulatory Information page, including link to database of OPDP-issued Untitled Letters: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-regulatory-information
- CBER Advertising and Promotional Labeling Branch (APLB) main page: https://www.fda.gov/vaccines-blood-biologics/labeling-cber-regulated-products/about-advertising-and-promotional-labeling-branch-aplb
- Centers for Medicare & Medicaid Services (CMS) 10/2015 Fact Sheet for HCPs on "Off-Label Pharmaceutical Marketing: How to Recognize and Report It": https://www.cms.gov/medicare-medicaid-coordination/fraud-prevention/medicaid-integrity-education/downloads/off-label-marketing-factsheet.pdf
- James Beck, *Off-Label Use in the Twenty-First Century: Most Myths and Misconceptions Mitigated, 54* UIC J. Marshall Law Review 1 (2021): https://repository.law.uic.edu/cgi/viewcontent.cgi?article=2839&context=lawreview

Questions?

Thank you for your attention!