

DuaneMorris

Labeling/Advertising and Promotion Import/Export, Enforcement Actions

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Part I:

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Labeling/ Advertising and Promotion

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Basic Concepts for Labeling, Advertising, and Promotion

- **“Label” vs. “Labeling”**
 - **“Label”** means written, printed, or graphic matter upon the immediate container. (FDCA § 201(k)).
 - Information Required to be on the “label” must also be on (or legible through) the outside container.
 - **“Labeling”** means all labels and other written, printed, or graphic matter:
 - Upon any Article or Any of its Containers or Wrappers, or
 - Accompanying such Article. FDCA § 201(m).

Labeling

- **FDA Interpretation of “Labeling”:**
 - Printed, Audio, or Visual Matter
 - For Use by Medical Community or Users
 - Containing Information Supplied by Manufacturer, and
 - Disseminated on Behalf of Manufacturer or Distributor
 - “Accompanies” – in very broad sense
- **Includes:** Physicians Desk Reference (PDR), Detailing Pieces, Calendars, Price Lists, Company Publications, Letters, Exhibits, Sound and Video Recordings (See 21 C.F.R. § 202.1(1)(2))

Misbranding

- **False or Misleading in Any Particular:**
 - Labeling (FDCA § 502(a))
 - Restricted Device Advertising (502(q))
- **Fails to Meet Rx Drug Advertising Requirements in FDCA § 502(n):**
 - Established Name
 - Quantitative Formula
 - “Brief Summary” of Side Effects, Contraindications, and Effectiveness

Misbranding

- **Fails to Meet Restricted Device Advertising Requirements in FDCA § 502(r):**
 - Established Name
 - Brief Statement of Intended Uses, Warnings, Precautions, Side Effects, Contraindications

Misbranding

- **Includes Failure to Reveal Material Facts (FDCA § 201(n))**
 - Material in Light of Representations Made
 - Material with Respect to Consequences that May Result from Use of the Article
- **Labeling must bear:**
 - Adequate Directions for Use (FDCA § 502(f)(1))
 - Adequate Warnings (FDCA § 502(f)(2))
 - Exceptions: Directions for Common Uses known to the Ordinary Individual (21 C.F.R. §§ 201.116; 801.116)

Fair Packaging and Labeling Act (FPLA)

- Incorporated into 21 C.F.R. Part 201, Subpart C: OTC Drugs and 21 C.F.R. Part 801, Subpart C: OTC Devices
 - Principal Display Panel
 - Statement of Identity
 - Net Quantity of Contents

Advertising and Promotion

- **Advertising and Promotion not defined in FD&C Act**
- **Dictionary Definitions (American College Dictionary):**
 - “Advertising”: “The act or practice of bringing anything . . . into public notice.”
 - “Promotion”: Furthering the “growth, development, progress, etc.”
- **Unofficial (FDA): Any Activity Used by the Sponsor to Create an Interest in the Company’s Products.**
- **Advertising includes advertisements in journals and broadcast through media (21 C.F.R. 202.1(l)(1))**
 - This includes the Internet

Drug Advertising

- **FDA Regulates Advertising of Prescription Drugs (FDCA § 502(n))**
 - Brief Summary (including side effects, contraindications, and effectiveness)
 - 21 C.F.R. Part 202 – Prescription Drug Advertising Regulations
 - NDA Requirements for Advertising
 - Pervasive, Complicated, and Highly Specific Regulatory Scheme

Device Advertising

- **FDA can Regulate Advertising of Restricted Devices (FDCA §§ 502 (q) and (r))**
 - Restricted by Regulation, PMA Approval Conditions
 - Misbranded if Advertising is False or Misleading in Any Particular (502(q))
 - Section 502(r) requires “Brief Statement” of:
 - Intended Uses
 - Relevant Warnings, Precautions, Side Effects, Contraindications
 - Prior Approval of Content only under “Extraordinary Circumstances” (502(r))

FTC Regulation of Advertising

- **Regulates Advertising where FDA lacks Authority**
- **Looks at Overall Impression Created**
- **More Power to Look at Overall Marketing Scheme**
- **Lanham Act, Unfair Competition**

Fair Balance

- **Advertising and Promotional Material (See 21 C.F.R. 202.1(e)(5)(ii))**
- **“Fair balance” means that Advertisements must Communicate Fairly and in a Balanced Manner Information Relating to Side Effects and Contraindications and Information Relating to Effectiveness of the Product. (See 21 C.F.R. 202.1(e)(5) and (6)).**
 - Information about Side Effects and Contraindications must be Comparable in Depth and Detail with claims for Safety and Effectiveness.

Promotion and Intended Use

- **Products are Cleared or Approved for Certain Intended Uses**
- **Change in Intended Use may Require a New Clearance or Approval**
- **New Intended Use Can be Created by:**
 - Labeling, Advertising, or Promotional Claims
 - Oral Statements
 - Manifestations of Objective Intent (21 C.F.R. §§ 201.128, 801.4)
 - Expressions
 - Circumstances of Distribution
 - Offered with Knowledge of Use

Objective Intent

Section 801.4 Meaning of “intended uses” (for Devices)

The words “intended uses” or words of similar import in §§ 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons’ expressions or may be shown 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. It may be shown by 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. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the devices, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. **But if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put.**

Intended Use in Premarket Approval Conditions of Approval

- **“No Advertisement or Other Descriptive Printed Material ... shall Recommend or Imply that the Device may be Used for any Use that is not Included in the FDA-approved Labeling for the Device.”**
- **Do not Rely on Perceived Tacit Acceptance of Other Data in the PMA.**

New Indications for Use (510(k))

- **New Intended Uses Require new 510(k)s**
- **Specific Indications within a General Cleared Use may Require new 510(k)s:**
 - Example (FDA): “New Indications for Use Require a 510(k) Submission and Must be Based on Valid Scientific Evidence that Provides Reasonable Assurance of Safety and Effectiveness of the Laser for the Proposed Use. The Type of Data that is Acceptable will Vary Depending on the Indication.”
 - *E.g.*, Laser cleared for General Surgery but promoted for removal of Liver Cancer

Comparative Claims

- **In general, Comparative Claims are Discouraged**
- **Drug – general guidelines**
 - Claims of Comparability (Safety or Effectiveness):
 - At least Two Adequate and Well-controlled Clinical Studies
 - Superiority Claims
 - Provide Data related to the Specific Claims of Superiority
 - Partial Comparisons:
 - Adequate and Well-controlled Studies or Substantial Clinical Experience
 - Fair Balance

Comparative Claims – Other Considerations

- **FTC -- generally silent in law; but by case, has gone as far as 2 - RWCCT**
 - For Drugs, Many covered by FDA Regs at 21 C.F.R. Part 202
 - For Devices, FTC is Preempted Only for Restricted Devices
 - Nevertheless, FTC may Regulate some Comparative Claims
- **Lanham Act — Private Right of Action** (FDCA does not have a private right of action)

Overview -- Off-Label Issues

- **Tension – FDA, approved labeling and the First Amendment**
- **Manifestations**
 - Scientific information exchange – concern – improper influence by company on content of educational activity
 - Off-Label promotion (to be discussed in Part 6)
 - Our approach – *disregard “Caronia” for now*
- **Guidance -- Industry-Supported Scientific and Educational Activities [*Hot link*] -- 1997**

1997 Scientific Exchange Guidance

- **To be “safe,” must be both independent and non-promotional**
 - if so, not subject to FDA jurisdiction
- **Unapproved uses** – not permissible if program is subject to “substantive influence” by regulated industry
- **Factors influencing “independence” determination**
 - Content influence -- whether and to what extent company can
 - speaker or moderator selection or recommendation, especially if speaker has promoted company’s products or were subject of complaints as to past presentations that were biased or misleading in favor of company

1997 Scientific Exchange Guidance ...

- Factors influencing “independence” determination

... continued ...

- topic selection, e.g., via targeting points for emphasis
- scripting done

- Disclosures to audience –

- company funding of project
- relationships between company and speakers (e.g., financial, employee)
- whether any unapproved uses would be disclosed

- Program Focus

- intent to be free of commercial bias (not clear how proved)
- Title and content really match

1997 Scientific Exchange Guidance ...

- Factors influencing “independence” determination
 - ... continued ...*
 - Program Focus ... *continued*
 - Balanced discussion of all treatment modalities
 - Relationship with provider –
 - e.g., if provider believes continued financial support is dependent on having programs about company products
 - intertwining ownership or control of provider with company
 - Provider involved in sales & marketing – including provider employees
 - Provider’s Demonstrated Failure to Meet Standards – of independence, balance, objectivity, or scientific rigor

1997 Scientific Exchange Guidance ...

- Factors influencing “independence” determination
 - ... continued ...*
 - Multiple presentations – of same material – could be factor; FDA recognizes there are benefits to repeated info
 - Audience selection – how done can influence
 - generated by company Sales & Marketing – e.g., to reward big “rx writers” or Key Opinion Leaders (KOLs)
 - Opportunities for discussion – if not present, not good
 - Post-event dissemination of information – except if done via unsolicited request or thru independent provider
 - Ancillary promotional actions –
 - exhibit materials
 - Sales & marketing presentations

1997 Scientific Exchange Guidance ...

- **Factors influencing “independence” determination**
... continued ...
 - Complaints – any raised that company tried to influence content
- **Document independence**
 - Contract between company and provider that provides for independence and that provider will be solely responsible for managing program
- **Promotional vs. non-promotional**
 - If supported activity is not about the company’s products OR competitive products, is not promotional

Good Reprint Practices

January 2009 – Guidance

- [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](#) *[Hot Link]*
- **Genesis of guidance**
 - **FDAMA § 401** – had added § 551 of Act (sunsetting in late 2006) – on off-label use dissemination; led to promulgation of 21 CFR Part 99 (also now void) – if complied, would not be used as evidence of intent of off-label use – “safe harbor”
 - limited to HCPs and certain healthcare entities (e.g., PBMs)
 - sunsetting – led to guidance in 2009

Feb. 2014 – New Draft Guidance

- [Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices](#)
[Hot Link]
 - will replace 2009 guidance – still applies only to 3rd party pubs.
 - Key differences:
 - Adds “clinical practice guidelines” (CPGs) to items covered by guidance
 - Clarifies that it also applies to “off-label” promotion of exempt medical devices for uses outside those covered by classification regulation
 - Discusses the different types of documents separately: (1) scientific journal articles; (2) scientific or medical reference texts; and (3) clinical practice guidelines (CPGs)

FDA -- Legal Analysis of Unapproved Use

- **Drug**
 - approved drug marketed for an unapproved use is an unapproved drug for that use – violation of § 505(a) – is a “prohibited act” under § 301(d) of Act
 - unapproved drug that is marketed lacks adequate directions for use in violation of § 502(f) of Act – in turn, it is a prohibited act under § 301 of Act to market a misbranded drug
- **Medical Device** – if promoted for unapproved or uncleared use is also misbranded and adulterated
 - Marketing an adulterated or misbranded device = prohibited act under § 301 of the Act.

The 2014 Draft Guidance

Scientific or Medical Journal Articles

- **Requirements for Publishing Entity**
 - Must have editorial board of experts ('09)
 - independent of the organization that publishes the article
 - Public policy of full disclosure of conflicts of interest for authors, editors, and contributors
- **Article – must:**
 - Be peer reviewed and published per peer review procedure
 - Be an unabridged reprint or copy of article
 - Contain information that:
 - Describes adequate and well-controlled clinical investigations that are considered scientifically sound by experts qualified to evaluate safety or effectiveness of product

Scientific or Medical Journal Articles ...

- **Article – must ...:**
 - Contain information that is such that ... :
 - Devices – articles on following, “also may be consistent with this guidance:”
 - “significant investigations other than adequate and well-controlled studies, such as meta-analyses, if they are testing a specific clinical hypothesis
 - “significant non-clinical research” – such as well-designed bench or animal studies
 - Send with approved labeling for each product discussed in article
 - Send with a “comprehensive bibliography” of other articles about the off-label use (pro or con) – unless the bibliography is in article

Scientific or Medical Journal Articles ...

- **Article – must ...:**
 - Send with a “representative publication” (if existing) that reaches contrary or different conclusions on unapproved use, especially those calling into question the article you are sending
 - Send separately from any promotional material
 - If a sales rep get a question on the article, rep must direct questioner to a medical/scientific department that is independent of sales/marketing
 - Can’t disseminate in the exhibit hall of a conference or during promotion speakers’ programs
- **Article – must not:**
 - Be false or misleading
 - Suggest a use that is dangerous to health

Scientific or Medical Journal Articles ...

- **Article – must not:**
 - Be funded, wholly or partially, be the maker of the product
 - Be “marked, highlighted, summarized, or characterized” by product maker to “emphasize or promote” the off-label use
 - Be primarily distributed by product maker; *rather*, must be generally available publicly where periodicals are sold
 - Be written, edited, excerpted or published at request of product maker
 - Be edited or “significantly influenced”** by product maker or any individual having a “financial relationship” to product maker
 - ** see discussion on influence on ISSEA (slides 3 to 7, *infra*)

Scientific or Medical Journal Articles ...

- **Article – must not:**
 - Be attached to any product info other than approved labeling or cleared indications for use statement
- **Reprint should be accompanied by a “prominently displayed and permanently affix statement” that:**
 1. Lists the drugs or devices in the reprint in which product maker has an interest
 2. That some (or all) of the uses in the article have not been blessed by FDA “as applicable to the described drug(s) or device(s)”
 - I interpret that you have to say which uses are not blessed

Scientific or Medical Journal Articles ...

- Reprint should be accompanied by a “prominently displayed and permanently affix statement” that ... :
 3. Lists any author “known to the manufacturer” as having a financial interest in the mfr. or the product of the mfr. or receiving compensation from the mfr.; must state:
 - Nature and amount of financial interest
 - Affiliation of author
 4. States any person known to the mfr. to have funded the study
 5. All significant risks or safety concerns associated with the unapproved use that are known to mfr., but not discussed in article
 - **Note:** no direct mandate to do a literature search; however, one should be done for liability reasons

Scientific or Medical Journal Articles ...

- **Unacceptable Reprints**
 - Letters to the editor
 - Abstracts of a publication
 - Reports of healthy volunteer studies
 - Publications consisting of statements or conclusions but which contain little or no substantive discussion of the relevant investigation or data on which they are based

Scientific or Medical Reference Texts

- **Handled separately under guidance because texts are much longer than articles, but still may discuss off-label uses**
- **If disseminated in its entirety, must:**
 1. Be based on a systematic review of the existing evidence
 2. Be published by an independent publisher that is:
 - not “substantially dependent on financial support” from drug or device mfrs.; and
 - Who publishes scientific or medical educational content for health care professional and students
 3. Be the most current version

Scientific or Medical Reference Texts ...

- **If disseminated in its entirety, must ...:**
 4. Be authored, edited or contributed by experts with “demonstrated expertise” on subject
 5. Be peer-reviewed per published peer-review procedures of the publisher
 6. Sold through “usual and customary” independent channels directed at HCP’s and students
 7. Be distributed separately from promotional materials
 - If a sales rep get a question on the article, rep must direct questioner to a medical/scientific department that is independent of sales/marketing
 - Can’t disseminate in the exhibit hall of a conference or during promotion speakers’ programs

Scientific or Medical Reference Texts ...

- **If disseminated in its entirety, must ...:**
 8. Contain prominently displayed and permanently affixed statement that:
 - Some of the uses may be off-label
 - Some of the authors might have a financial interest in the mfr. or product being written about, unless mfr. verifies that none of the authors has such a financial interest
 9. If a text contains a chapter with a “primary substantive discussion” to mfr.’s product, have to send with the product labeling for each discussed product.

Scientific or Medical Reference Texts ...

- **If disseminate a single chapter, must:**
 1. Meet above criteria for entire text, subject to modifications
 2. Be unaltered/unabridged and directly extracted from the text in which chapter appears
 3. If “necessary to provide context,” must disseminate with other chapters from the same text
 4. Contain prominent and permanently affixed statement identifying the mfr. and disclosing:
 - Drug or device in which mfr. has an interest
 - That some or all of the uses are off-label
 - Disclosure of financial interests in the mfr. or product of any author, including author’s affiliation and nature of fin. interest

Scientific or Medical Reference Texts ...

- **If disseminate a single chapter, must ...:**
 - Disclose “all significant risks or safety concerns” associated with the unapproved uses that are known to mfr. but not discussed in the chapter
 - Disseminate with the approved labeling for each product in the chapter
- **Can't be:**
 1. False or misleading
 2. Suggest a use that makes product dangerous to health

Scientific or Medical Reference Texts ...

- **Other restrictions:**
 - Must be generally available in publishing channels; can't be primarily distributed by the mfr.
 - Can't be edited or significantly influenced by mfr. or by individuals have a financial relationship with the mfr.
 - Can't be marked, highlighted, summarized, etc. as to the unapproved use, verbally (e.g., by sales rep) or in writing
 - Can't be written or published specifically at the request of the mfr.
 - Can't be abridged or excerpted (except for sending a single chapter consistent with the guidance)
 - Can't be attached to product information, except for approved labeling

Promotion on the Internet

- **Subject to the Same Regulatory and Statutory Requirements as Materials Distributed by Other Means.**
- **Issues:**
 - Is it Labeling, Advertising, or Promotional Material?
 - Company Control or Sponsorship of Information on a Site
 - Links to Sites with Unapproved Uses

Promotion on the Internet (cont.)

- **Products Sold in Foreign Countries**
 - Disclosure of Unapproved Status in U.S. Required on U.S.–accessible site
 - Warning Letter: A Use with only a Foreign Approval was on Internet
 - Use of Country Flags has been Allowed

Promotion on the Internet (cont.)

- **Promotion with Disclaimers has Resulted in Warning Letters**
- **Links to Independent Internet sites Sponsored by Peer-Reviewed Journals Permitted, as Long as they do Not Violate Fair Balance**
- **Links to Sites Describing Off-Label Uses have Drawn Warning Letters**
 - “Significant Focus” Standard
- **E-commerce Internet sites must Prevent Purchase of Prescription Products without Physician Approval**

Do's and Don'ts

- **Do Treat Internet Like Other Media (to the Extent Possible)**
- **Do Not Promote Off-label Uses**
- **Do Use Links to Full Labeling of Product**
- **Avoid Sponsoring or Linking to Internet sites Promoting Off-Label Use**
- **“Fire Walls” can be Useful, if Practicable**

In Vitro Diagnostic Labeling

- **21 C.F.R. § 809.10 Contains Specific Requirements**
- **Labeling Requirements for:**
 - Immediate and Outer Containers
 - Package Insert

IUO and RUO Exemptions — 21 C.F.R. § 812.2(c)(3)

- **Exemptions from Investigational Use Regulations for IVDs if:**
 - Noninvasive
 - No Invasive Sampling Procedure that Presents Significant Risk
 - Does Not Introduce Energy into Subject
 - Not to be Used as the Diagnostic Procedure

RUO Exemption — 21 C.F.R. § 809.10(c)(2)(i)

- **Research Use Only (RUO)**
 - Laboratory Research Phase of Development or Not Represented as an Effective IVD (*i.e.*, “Looking for a Use”)
 - Labeled: “For Research Use Only. Not for Use in Diagnostic Procedures.”

IUO Exemption — 21 C.F.R. § 809.10(c)(2)(ii)

- **Investigational Use Only (IUO)**
 - Testing Prior to Full Commercial Marketing
 - Labeled: “For Investigational Use Only. The Performance Characteristics of this Product have Not been Established.”

FDA Failure to Control IUO and RUO Use

- *E.g., Warning Letter* —
 - Western Blot Kits Shipped for Commercial Use Without an Approved Market Clearance or Investigational Approval
- **Draft Policy (January 5, 1998)**
 - 510(k)s, PMAs for IVDs
 - Attempts to Prioritize, Triage
 - Enforcement Categories
 - New IVD's need 510(k) or PMA before Marketing

Prescription Drugs and Devices

- **Not Safe to Use Except Under Supervision of Licensed Practitioner (FDCA §§ 503(b)(1); 21 C.F.R. §§ 201.100, 801.109)**
- **Exemption from Adequate Directions for Use**
- **Rx Legend:**
 - “Caution, Federal Law Restricts this Device to Sale by or on the Order of a _____.”
 - “Rx only” allowed for drugs.

Prescription Drugs and Devices

- **Labeling must be Adequate for a Licensed Practitioner**
- **Follow FDA Regulations, Product Approvals and Clearances, and Guidances for Specific Products**

Other Exemptions from Adequate Directions for Use

(See Applicable Regulations for Specifics)

- **Retail Exemption for Rx Devices (21 C.F.R. § 801.110)**
- **Medical Devices having Commonly Known Directions (Ordinary Individual) (21 C.F.R. § 801.116)**
- **General Purpose Laboratory Reagents (21 C.F.R. § 809.10(d)) – Uses generally known by persons trained in their use**

Other Exemptions from Adequate Directions for Use (cont.)

(See Applicable Regulations for Specifics)

- **Intended for Processing, Repacking, or Manufacturing Use – (21 C.F.R. § 801.122)**
 - “Caution: For Manufacturing, Processing, or Repacking.”
- **For Use in Teaching, Law Enforcement, Research, or Analysis – (21 C.F.R. § 801.125)**
 - “Research” is nonclinical Research

Part II:

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Imports and Exports

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Import Detention

- **FDA has Power to Detain on Appearance of Violation**
- **Destruction, Re-exportation, Reconditioning**
 - Reconditioning Bond – typically three times Value of Shipment
- **Import Alerts**

U.S. Agent

- **Foreign Device Manufacturers Exporting into U.S. Must Designate a U.S. Agent**
- **U.S. Agent Duties**
 - Submit MDR Reports
 - Submit Annual Certifications
 - Act as Official Correspondent
 - Must Submit Registration, Listing, 510(k)s

Exports

- **If a Device can be Legally Marketed in the U.S., it can be Exported freely**
- **If not Legally Marketed in the U.S., must meet the Requirements of one of the following Sections of the FDCA:**
 - Section 801(e)(1)
 - Section 801(e)(2)
 - Section 802

Section 801(e)(1)

- **Product for Export not Adulterated or Misbranded if:**
 - Accords to the Specifications of Foreign Purchaser
 - Not in Conflict with Laws of Importing Country
 - Shipping Container Labeled for Export
 - Not Sold in Domestic Commerce
- **Does not Apply to Devices that do not Comply with §§ 514 or 515 (Performance Standard or PMA)**
 - “510(k)-able” Devices Generally are Allowed to be Exported under 801(e)(1)

Section 801(e)(2)

- **FDA Export Approval**
 - For Devices Not Eligible for § 801(e)(1)
 - *E.g.*, Investigational Devices requiring PMAs
 - FDA Can Provide an Export Approval Letter (Export Permit)
- **Standard:**
 - Export Not Contrary to Public Health and Safety
 - In practice, Standard is Similar to that for approval of IDE
 - Must have Approval of Importing Country

Section 802

- **Alternative to Section 801(e)(2)**
- **Applies to Drugs and Devices that would Otherwise Need FDA Market Approval for Export**
 - *E.g.*, Unapproved Class III Devices
 - Devices Not Meeting a Performance Standard
 - Banned Devices
 - Synthetic Hair Fibers for Implant
- **May be Exported to Any Country in the World if:**
 - The Drug or Device Complies with the Laws of the Receiving Country, and

Section 802 (cont.)

- **May be Exported to Any Country in the World if:**
 - The Drug or Device has Valid Marketing Authorization by the Appropriate authority in One of the Following Listed Countries:
 - Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or
 - A Country in the European Economic Area (*i.e.*, Countries in the European Union or the European Free Trade Association)
 - Labeled in Accordance with Marketing Authorization
 - Substantially Meets QSR
 - Not Adulterated (other than by lack of Marketing Approval)
 - Not Subject to Notice of Imminent Hazard

Section 802 (cont.)

- **If not Exported to a Listed Country, FDA expects Receiving Country to have Recognized the Listed Country Marketing Authorization**
- **Any Exporter of a Drug or Device Shall Maintain records of All Drugs or Devices Exported and the Countries to which they were Exported**
- **FDA must Notify Country to which Drug or Device will be Exported if FDA has Disapproved an NDA, Biological License, or PMA**

Section 802 --Exports for Investigational Use

- **For Listed Countries, Compliance with Laws for Investigational Use in the Listed Country Sufficient for FDA**
 - No FDA Notification Required
- **For Unlisted Countries, Need to Export under Section 801(e)(2)**
 - Even if Product is Authorized for Investigational Use in a Listed Country
 - Requires FDA Permission

Export Certificates

- **Upon Request by Company**
- **Types of Certificates:**
 - Certificate to Foreign Governments (CFG) provides written Assurance that Product can be Sold Legally in the U.S.
 - Drugs, Biologics, Animal Drugs, Medical Devices
 - Certificate of Quality for a Pharmaceutical Product (CQPP) provides assurance that a Human Drug Product conforms with WHO Certification Requirements
 - Certificate of Free Sale (CFS) for Food and Cosmetic products
 - Certificate of Exportability (CEX) Provides Assurance that a product that may Not be Sold in the U.S. may be Exported under 801(e) or 802

Simple Notice Requirement

- **“Simple Notice” to FDA at Time of Export**
 - Only One Notice for all Listed Countries
 - Separate Notice for Each Unlisted Country

Export Certificates (cont.)

- **Certificates are Issued by FDA, Based on Certification by the Exporter**
 - CFG, CQPP, CEx Not issued if Product's Manufacture does Not conform with GMPs
 - Various compliance issues can affect various certificates
 - See CPG 110.100
- **Fraud relating to Certificates can result in Criminal Action**
 - *E.g.*, False Information, Substitution of Product, Counterfeiting a Certificate

Other regulations to be aware of

- **Animal Health**
- **CITES – Convention in Trade of Endangered Species**
- **Radioactive materials**
- **Chemical Hazards**

Part III:

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Enforcement Actions

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FDA's Mission

- **To Protect the Public Health**
 - Included in FDAMA Mission Statement
- **Inspections and Enforcement Necessary to Meet the Mission**
- **Public Cannot Perform own Inspections**
 - *E.g., Upton Sinclair, The Jungle*

Why Does FDA Use Enforcement?

- **To Warn Companies**
- **To Stop Continuing Bad Behavior**
- **To Put Entire Industry on Notice**
- **To Control Dangerous Products**
- **To Establish Legal Precedent**
- **To Punish Wrongdoers**

Federal Food, Drug, and Cosmetic Act

- **Police Act**
- **Coverage:**
 - Definitions
 - Prohibited Acts
 - Penalties
 - Specific Provisions Regulating Foods, Drugs and Devices, Cosmetics
 - Imports and Exports
 - General Authority

Examples of Prohibited Acts

- **Involving Adulteration or Misbranding:**
 - Introduction into Interstate Commerce
 - Adulterating or Misbranding in or after I/S
- **Shipment without necessary Market Clearance or Investigational Exemption**
- **Refusal to Permit Access to or Copying of Certain Records**
- **Refusal to Permit Inspection**
- **Counterfeiting Drugs**
- **Revealing of Trade Secret Information (by FDA Employees)**

Examples of Adulteration

- **Adulteration, *e.g.*,**
 - Filthy, Putrid, or Decomposed
 - Not Made in Conformance with Current Good Manufacturing Practice
 - Prepared, Packed, or Held under Unsanitary conditions whereby it May have been Rendered Injurious to Health
 - Section 519 Violations (MDRs, Correction and Removal Reports)

Examples of Misbranding

- **Misbranding, *e.g.*,**
 - Labeling False or Misleading in Any Particular
 - Failure to have Adequate Directions for Use
 - Failure to have appropriate Warnings on Labeling
 - Failure to have a necessary 510(k)

Instructions to Field Force

- **Compliance Programs**
 - What to Inspect
 - How to Make Compliance Decisions
- **Investigator Operation Manual**
 - Tactics
 - How to Behave
- **Guide to Inspections of Quality Systems: Quality System Inspection Technique (QSIT)**
- **Etc.**

Inspectional Authority – FDCA § 704

- **Duly Designated Officers or Employees May:**
 - Upon Presenting to Owner, Operator, or Agent in Charge:
 - Credentials
 - Notice of Inspection

Inspectional Authority – FDCA § 704 (cont.)

– Enter:

- Factory, Warehouse, Establishment, Vehicle
- In which Food, Drugs, Devices, or Cosmetics:
 - are Manufactured, Processed, Packed, or Held
 - for introduction into Interstate Commerce or after such introduction

Inspectional Authority – FDCA § 704 (cont.)

- Inspect:
 - Factory, Warehouse, Establishment, Vehicle
 - All Pertinent Equipment, Finished and Unfinished Materials, Containers, and Labeling

Inspectional Authority – FDCA § 704 (cont.)

- Inspect (cont.):
 - For Drugs and Restricted Devices:
 - All Things therein bearing on whether articles are Adulterated or Misbranded or otherwise in Violation
 - Includes Records, Files, Papers, Processes, Controls, Facilities
 - Exemptions: Pharmacies, Licensed Practitioners, Research Use.

Inspectional Authority – FDCA § 704 (cont.)

- Reasonable Times, Limits, Manner
- Commenced and Completed with Reasonable Promptness

Inspection Does Not Extend To:

- **Financial Data**
- **Sales Data (other than Shipment Data)**
- **Pricing Data**
- **Personnel Data (other than Pertinent Qualifications of Technical and Professional personnel)**
- **Research Data (other than Research Data regulated under rules for IND, NDA, ANDA, Antibiotic Certifications, § 519, IDE)**

Upon Leaving:

- **FDA 483 – List of Observations**
 - Statutory Requirement:
 - Report of Conditions or Practices that indicate:
 - Filthy, Putrid, Decomposed
 - Prepared, Packed, or Held under Unsanitary Conditions
 - Covers much more in Practice
 - Some Things will Not be on FDA 483
 - *E.g.*, 510(k), PMA, NDA deficiencies
 - Ask Specifically if there are any such things
- **Receipt for Samples**

Search Warrants

- **Administrative Warrant**
 - To Compel Inspection under § 704
- **Criminal Warrant**
 - Scope Not Limited to § 704

Types of Inspections

- **Routine**
 - District Work Plan
 - Preapproval Inspections
 - Sample Collections
- **Directed**
 - Complaints, MDRs, etc.
 - Ongoing Investigation (of you or someone else)
 - Compliance Inspection
 - Sample Collection

Inspection Techniques

- **Quality System Inspection Technique (QSIT)**
 - QSIT:
 - 7 Subsystems
 - 4 Major Subsystems
 - Focus on Management
- **Traditional**
 - Directed and Compliance Inspections
- **See FDA's QSIT Guide, Investigator Operations Manual, FDA Compliance Programs, and other FDA Guidance Documents**

Find Out:

- Reason for Inspection
- Is it For-Cause?
- What is Inspectional Plan?
- How Long will it Take?
- What can we do to Expedite it?

Companies' Rights

- **No Photographs**
- **No Affidavits, No Signatures**
- **Statute does not provide FDA with Right to Interview Employees – but have to handle delicately**
- **Reasonable Time, Place, Manner**
- **Have Policies in Place to Cover these Areas**

Special Situations

- **Foreign Inspections**
- **Inspections of Contractors and Suppliers**
- **BIMO Inspections: Investigators, CROs, Sponsors, IRBs**
- **Portions of Plant that do Not Involve Regulated Activities**
- **Visits to Employee Homes**

Enforcement Options

- **Warning Letter**
- **Recall, Notification, Refund**
 - Voluntary
 - Mandatory (Section 518)
- **Publicity**
- **Administrative Detention**
- **Seizure**
- **Import Detention**
- **Injunction**

Enforcement Options (cont.)

- **Debarment**
- **Consent Decree**
- **Withdrawal of Market Clearance or Approval**
- **Civil Penalties**
- **Criminal Prosecution**
 - Companies should Institute a Compliance Plan designed to Detect Criminal Violations

Seizure

- **Purpose: To Control Bad Products**
- ***In Rem* Action**
 - Articles are Placed Under Custody of U.S. District Court
 - Violation of 18 USC §§ 2232 - 2233 to Move a Seized Article

Seizure (cont.)

- **Types of Seizure:**
 - Single
 - Multiple
 - Mass
 - Direct Reference

Injunction

- **Purpose: To Stop an Activity**
- **Temporary Restraining Order (TRO)**
 - Risk of Irreparable Harm if Immediate Action is Not Taken
 - Damages are Not a Sufficient Remedy
- **Preliminary Injunction**
 - Sufficient Urgency exists to Enjoin the action until there can be a Trial

Injunction (cont.)

- **Permanent Injunction**
 - (May later Petition Court for Modification)
- **Consent Decree of Injunction**
- **Defense: Changed Circumstances**
- **Violation of Injunction or Consent Decree = Contempt of Court**

Injunction: Typical Requirements

- **Do Not Sell Adulterated/Misbranded Product**
 - Stop Sale until Pass Inspection
- **Submit an Annual Certification of GMP Compliance by an Outside Consultant**
- **Provisions that Cure Specific FDA Observations, *i.e.*:**
 - Do Not Fail to Validate Processes
 - Do Not Fail to Conduct Stability Studies

Injunction: Typical Requirements (cont.)

- **FDA Inspections at Company's Cost**
- **Recalls**
- **Disgorgement**
- **Other Monetary Equitable Relief**

Consent Decree

- **Alternative to Injunction**
- **FDA and Company Negotiate Terms**
- **Entered as a Judicial Order**
 - Becomes supervised by Court

Sample Consent Decree

- **GMP Deviations at Two Plants**
 - Four Inspections over 4½ years
 - Last Inspection lasted 3 months
 - Two Warning Letters
 - Regulatory Meeting with FDA
 - Seizure of Product

Sample Consent Decree (cont.)

- **Company made “Substantial Commitments” to FDA**
 - FDA “Working With Company” for eight months after last inspection
 - Company closed a portion of a plant temporarily
 - Company retained Independent Expert Consultants
- **FDA sought Consent Decree “to ensure the Company keeps its Commitments”**

Terms

- **Consent Decree of Permanent Injunction**
- **Signed by Corporation and Top Executives**
- **Third-party audits**
 - Reports given to FDA
 - FDA to approve Schedule for Correcting Audit Findings
- **Disgorgement and Fines**
 - \$30,000,000 disgorgement
 - \$15,000 per day Fine for Failure to Meet Schedule
 - Disgorgement of Profits for Products Sold after Failure to Meet Schedule

Terms (cont.)

- **Independent Audits Yearly for Four Years**
- **Third-Party Experts to:**
 - Evaluate Quality Assurance at all facilities
 - Review Manufacturing Records for products produced

Public Health Need for Products

- **Company Allowed to Make Certain Products, that were needed to fill Critical Health Needs**
 - Under Third-Party Supervision
 - Company had stopped production previously
- **Other consent decrees have included Special Arrangements for Medically Necessary Products**

Other Typical Terms of Consent Decrees

- **Injunction Prohibiting Manufacturing until Compliant with GMPs**
 - Certification of Compliance by Third Party
 - Ship only after FDA Releases Products
 - Continue shipping at Risk of Contempt Action
- **Remediation or Destruction of Existing Stock**

Other Typical Terms of Consent Decrees (cont.)

- **Recall**
- **Disgorgement Payments for Shipping before Certified in Compliance**
- **Other Monetary Equitable Relief**
- **Individuals may be Barred from working in the Industry**
- **Submission of Master Validation/Compliance Plans**

Other Typical Terms of Consent Decrees

(cont.)

- **Liquidated Damages**
- **Provisions allowing FDA to Order the following in case of Future Noncompliance**
 - Cessation of Manufacturing
 - Recall
 - Notification of Users
 - Additional Reports

Other Typical Terms of Consent Decrees

(cont.)

- **Company to Pay for FDA Inspections**
- **Consent Decree to be Posted and/or Disseminated**
- **FDA Permission Required for Certain Business Changes**
- **Petition to Dissolve Decree after a Certain Time Period**

Civil Money Penalties

- **Safe Medical Device Act of 1990**
 - \$15,000 per Violation
 - \$1,000,000 per Person per Proceeding
 - Factors:
 - Nature of Violations/Degree of Culpability
 - Ability to Pay
 - History of Prior Violations

Civil Penalties (cont.)

- **Exempt from Civil Penalties under SMDA:**
 - Good Manufacturing Practices or Device Reporting (Unless Significant or Knowing Departure, or Risk to Public Health)
 - Device Tracking and Field Correction (Minor Violations Exempt)
 - “May” have been Contaminated or rendered injurious to health charge (501(a)(2)(A))

Civil Penalties Procedure

- **Part 17 Civil Money Penalties Hearing:**
 - Complaint
 - Administrative Law Judge (ALJ) assigned
 - Answer or Default
 - Discovery -- No Interrogatories or Depositions
 - Trial-type Hearing
 - Posthearing Briefs

Civil Penalties Procedure (cont.)

- **Initial Decision — 90 Days**
 - Standard: Preponderance of Evidence
- **Appeal Initial Decision to Department Appeals Board (DAB) of HHS**
- **Judicial Review of Final Decision Available to Respondent (FDA Cannot Appeal an Adverse Decision — DAB Decision Is Decision of the Agency)**
 - U.S. Court of Appeals

Criminal Prosecutions

- **Individual Responsibility**
 - No Criminal Intent Required
 - *Dotterweich and Park*
 - Responsible Position
 - Must stand in “Responsible Relation” to the Criminal Act

Criminal Prosecutions (cont.)

- **Misdemeanor**
 - Up to \$100,000 for Individual
 - Up to \$200,000 for Corporation
 - Up to One Year In Jail
- **Felony**
 - FDCA:
 - Intent to Defraud or Mislead
 - Second Offense
 - Up to \$250,000 for Individual
 - Up to \$500,000 for Corporation
 - Up to Three Years in Jail

Title 18 Crimes

- **Prosecuted under U.S. Criminal Code**
- **False Statements**
 - Knowing and Willful Coverups of Material Facts
 - Materially False Representations
 - False Writings or Documents
 - Beware of Affidavits and Certifications

Title 18 Crimes (cont.)

- **Mail Fraud, Wire Fraud**
 - Mail Fraud: Item Delivered by Post Office or Interstate Carrier
 - Wire Fraud: Wire, Radio, or Telephone Communication
 - Includes Writings, Pictures, Sounds, Signals
- **Conspiracy, Racketeering (RICO)**
- **Obstruction of Justice**

Creative Theories

- **Public at Large as Victim of Fraud**
- **Government as Victim of Fraud**
- **Disgorgement**

Factors that May Influence Sentencing

- **Aggravating: Planning, Corporate Officer, Danger to Health, Abuse of Trust, Obstruction of Justice**
- **Mitigating: Plead Guilty, Cooperate, Compliance Program, Little Fish**
- **Fines Driven by the Loss**
 - *E.g.*, Money Made not Following GMPs
- **A Corporate Compliance Plan Designed to Detect Violations Can Be a Mitigating Factor**
 - See PhRMA or AdvaMed Codes
 - State Corporate Compliance Program Laws

Causes of Criminal Conduct

- **Productivity Incentives, Marketing Deadlines, Funding Triggers**
- **Incompetent or Overbearing Bosses**
- **Compounding of Minor Lapses in Judgment**
- **Fear**
- **Greed**
- **Actual Bad Intent**

Administrative Remedies

- **Warning Letter**
- **Administrative Detention**
- **Voluntary or Mandatory Recall**
- **Banned Devices**
- **Section 518 Notification, Repair, Replacement, or Refund**
 - Devices
 - Reasonable Probability of Serious Adverse Health Consequences or Death

Administrative Remedies (cont.)

- **Publicity**
 - Imminent Danger or Gross Deception -- § 705
 - Or Not:
 - Shall publish “all judgments, decrees, and court orders”
 - May “collect, report, and illustrate” the results of investigations
 - Wide latitude to use other publicity
- **Clinical Investigator/IRB/Animal Laboratory Disqualification**
- **Civil Money Penalties**
- **Fraud Policy for Market Clearance Applications**
 - Application Integrity Policy (AIP)

Administrative Remedies (cont.)

- **Refuse, Suspend, or Withdraw Market or Export Approvals**
- **Jawboning**
- **Voluntary Recall**
- **Refer to State or Local Enforcement**

Increased sharing of information between agencies – Total product lifecycle

State Actions

- **Embargo**
- **Product Removal**
- **Injunction (arguably, even if violations corrected)**
- **Civil Penalties**
- **Direct Referral to District Attorney**
- **California Business & Professions Code**
 - False Advertising and Unfair Business Practices

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Michael A. Swit, Esq., is a Special Counsel in the San Diego office of the international law firm, Duane Morris, LLP, where he focuses his practice on solving FDA legal challenges faced by highly-regulated pharmaceutical and medical device companies. Before joining Duane Morris in March 2012, Swit served for seven years as a vice president at The Weinberg Group Inc., a preeminent scientific and regulatory consulting firm in the Life Sciences. His expertise includes product development, compliance and enforcement, recalls and crisis management, submissions and related traditional FDA regulatory activities, labeling and advertising, and clinical research efforts for all types of life sciences companies, with a particular emphasis on drugs, biologics and therapeutic biotech products. Mr. Swit has been addressing vital FDA legal and regulatory issues since 1984, both in private practice with McKenna & Cuneo and Heller Ehrman, and as vice president, general counsel and secretary of Par Pharmaceutical, a top public generic and specialty drug firm. He also was, from 1994 to 1998, CEO of *FDANews.com*, a premier publisher of regulatory newsletters and other specialty information products for FDA-regulated firms. He has taught and written on many topics relating to FDA regulation and associated commercial activities and is a past member of the *Food & Drug Law Journal* Editorial Board. He earned his A.B., *magna cum laude*, with high honors in history, at Bowdoin College, and his law degree at Emory University.