DuaneMorris

FDA Regulation of Promotion & Advertising

Part 1: The Basics

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- This presentation, and the materials included herewith, are provided for general educational purposes and should not be construed as legal advice.

Statutory Definitions – Federal Food, Drug, and Cosmetic Act ("the Act")

- Section 201(k) -- The term **"label"** means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this chapter that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.
- Section 201(l) -- The term **"immediate container"** does not include package liners.

Definitions under the Act …

- Section 201(m) -- The term "labeling" means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.
- Statute does not define "advertising" specifically

Drug Regulatory Definitions -- Advertising

- **21 CFR 202.1(l):**
  - (1) ***Advertisements*** subject to section 502(n) of the act include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.
  - (2) [***Labeling***] -- Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the "Physicians Desk Reference") for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be ***labeling*** as defined in section 201(m) of the act.

Definitions under the Act …

- Section 201(n) -- If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

Who Has Jurisdiction?

- **Depends on:**
  - Type of product – drug, biologic or device,
  - Nature of how sold
    - ***Prescription*** Drugs/Biologics and ***Restricted*** Devices
    - OTC drugs and "unrestricted" Devices
  - Medium via which the information was disseminated
    - Advertising
    - Labeling

Who Has Jurisdiction …

- **Prescription Drugs and Biologics**
  - Labeling -- FDA
  - Advertising – FDA
- **Restricted Devices**
  - Labeling -- FDA
  - Advertising – FDA
- **OTC Drugs**
  - Labeling -- FDA
  - Advertising – Federal Trade Commission

Who Has Jurisdiction …

- **"Unrestricted Devices"**
  - Labeling -- FDA
  - Advertising – Federal Trade Commission
- **Dietary Supplements**
  - Labeling -- FDA
  - Advertising – Federal Trade Commission
- **Cosmetics**
  - Labeling -- FDA
  - Advertising – Federal Trade Commission

Jurisdiction – Snapshot View

Who Has Jurisdiction				
	Rx Drugs and Biologics	**OTC Drugs**	**Restricted Devices**	**"Unrestricted Devices"**
Labeling	FDA	FDA	FDA	FDA
Advertising	FDA	FTC	FDA	FTC
Internet**	FDA	FDA & FTC	FDA	FDA & FTC

** Internet – see next slide

Who Has Jurisdiction …

- **Internet – is it labeling or advertising?**
  - Eye of beholder?
  - FDA has asserted that it can regard as labeling web sites for products such as OTC drugs and dietary supplements that the agency does NOT have jurisdiction over advertising

Federal Trade Commission

- Unfair or deceptive acts or practices affecting commerce are prohibited.
- *Section 12 of FTCA* – "False advertisements for foods, drugs, devices and services are prohibited."

Basics – Drugs and Biologics

Statutory Duties

- **Section 502 – drug or device shall be deemed to be misbranded if:**
  - 502(a) -- its labeling is false or misleading in any particular.
  - 502(e) – lacks established name (if any) for drug or device, or common or usual name if not established
  - 502(f) – lacks adequate directions for use
  - 502(n) – Drug advertising – ***Next Slide …***

Section 502(n) of Act – Advertisement is Misbranded unless..

- … the manufacturer, packer, or distributor thereof includes in all ***advertisements and other descriptive printed matter*** issued or caused to be issued by the manufacturer, packer, or distributor with respect to that drug a **true statement of**
  - (1) the ***established name*** as defined in paragraph (e) of this section, printed prominently and in type at least half as large as that used for any trade or brand name thereof,
  - (2) the ***formula showing quantitatively each ingredient*** of such drug to the extent required for labels under paragraph (e) of this section, and
  - (3) such ***other information in brief summary*** relating to side effects, contraindications, and effectiveness as shall be required in regulations which shall be issued by the Secretary in accordance with section 371(a) of this title, and …

502(n) – Rx Drugs -- Brief Summary ...

- In the case of published direct-to-consumer advertisements the following statement printed in conspicuous text: "You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1–800-FDA-1088." …
  - (A) except in extraordinary circumstances, no regulation issued under this paragraph ***shall require prior approval*** by the Secretary of the content of any advertisement, and
  - (B) no advertisement of a prescription drug, published after the effective date of regulations issued under this paragraph applicable to advertisements of prescription drugs, shall with respect to the matters specified in this paragraph or covered by such regulations, be subject to the provisions of sections 12 to 17 of the FTC Act.

502(n) – Rx Drugs -- Brief Summary …

- This paragraph (n) shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 321(m) of this title. Nothing in the Convention on Psychotropic Substances, signed at Vienna, Austria, on February 21, 1971, shall be construed to prevent drug price communications to consumers.
- In the case of an advertisement for a drug subject to section 353(b)(1) of this title presented directly to consumers in television or radio format and stating the name of the drug and its conditions of use, the ***major statement*** relating to side effects and contraindications ***shall be presented in a clear, conspicuous, and neutral manner***.
  - Added by 2007 FDAAA – Section 901(d)(3)(A)
  - FDA – directed to publish regulations to implement standards on when a major statement meets this requirement – proposed in March 2010 (still pending)

Basics -- Devices

Restricted Devices -- Misbranding

- **Section 502(q) --** In the case of any restricted device distributed or offered for sale in any State, if :
  - (1) its ***advertising is false or misleading in any particular***, or
  - (2) it is sold, distributed, or used in violation of regulations prescribed under section 520(e) of this title [i.e., a regulation restricting sale of device]

Brief "Statement" for Restricted Devices – Section 502(r) and Advertising

- ***Device is Misbranded …*** unless the manufacturer, packer, or distributor thereof includes in all ***advertisements and other descriptive printed matter*** issued or caused to be issued by the manufacturer, packer, or distributor with respect to that device
  - (1) a true statement of the device's established name as defined in subsection (e) of this section, printed prominently and in type at least half as large as that used for any trade or brand name thereof, and

» *….continued …*

Section 502(r) – Device "Brief Statement" …

- (2) a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications and,
  - in the case of specific devices made subject to a finding by the Secretary after notice and opportunity for comment that such action is necessary to protect the public health, a full description of the components of such device or the formula showing quantitatively each ingredient of such device to the extent required in regulations which shall be issued by the Secretary after an opportunity for a hearing.

» .. *continued …*

502(r) – Devices "Brief Statement"

- Except in extraordinary circumstances, ***no regulation issued under this paragraph shall require prior approval*** by the Secretary of the content of any advertisement and no advertisement of a restricted device, published after the effective date of this paragraph shall, with respect to the matters specified in this paragraph or covered by regulations issued hereunder, be subject to the provisions of sections 12 through 15 of the FTC Act.
- This paragraph shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 321(m) of this title.

The Prescription Drug Regulations – 21 CFR 202.1

202.1(a) – Ingredient listings

- (3) -- fanciful name for a drug or ingredient can't be used if it implies a unique effectiveness or composition when the drug or ingredient is a common substance whose limits are known
- (4) -- can't feature inert/inactive ingredients in an ad in a manner that creates an impression of value greater than their true functional role
- (5) -- can't use a proprietary name for a drug or ingredient that might confuse it for another drug or ingredient's proprietary name.

202.1(b) – Established Name Usage

- **Established name of drug (or ingredient) …**
  - shall accompany such proprietary name or designation each time it is featured in the advertisement for the drug; but, except as provided below in this subparagraph, the established name need not be used with the proprietary name or designation in the ***running text*** of the advertisement.
  - ***Running text requirements:***
    - On any page of an advertisement in which the proprietary name or designation is not featured but is used in the running text, the established name shall be used at least once in the running text in association with such proprietary name or designation and in the same type size used in the running text:
    - *Provided, however,* if the proprietary name or designation is used in the running text in ***larger size type***, the established name shall be used at least once in association with, and in type at least half as large as the type used for, the most prominent presentation of the proprietary name or designation in such running text.

202.1(b) – Established Name Usage …

- ***Running text requirements …***
  - ***Columnar text:***
    - If any advertisement includes a column with running text containing detailed information as to composition, prescribing, side effects, or contraindications and the proprietary name or designation is used in such column but is not featured above or below the column, the established name shall be used at least once in such column of running text in association with such proprietary name or designation and in the same type size used in such column of running text:
    - *Provided, however,* That if the proprietary name or designation is used in such column of running text in larger size type, the established name shall be used at least once in association with, and in type at least half as large as the type used for, the most prominent presentation of the proprietary name or designation in such column of running text.

202.1(b) – Established Name Usage …

- **Other requirements**
  - Where the established name is required to accompany or to be used in association with the proprietary name or designation, the established name shall be placed in direct conjunction with the proprietary name or designation, and the relationship between the proprietary name or designation and the established name shall be made clear by use of a phrase such as "brand of" preceding the established name, by brackets surrounding the established name, or by other suitable means. ***202.1(b)(1)***
  - **Non-running text prominence** -- The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. ***202.1(b)(2)***

202.1(b) – Established Name Usage …

- **Guidance – January 2012 -- Product Name Placement, Size, and Prominence in Advertising and Promotional Labeling (PDF - 86KB)** ***[Hot Link]***
  - Gives examples of how placements should occur both in running text and elsewhere in ads/promotional labeling
  - For example:

PROPRIETARY NAME® (established name)

♠ PROPRIETARY NAME™ (established name)

PROPRIETARY NAME® CII
(established name)

202.1(e) -- Brief Summary

- ***When required* – per 21 CFR 202.1(e)(1), *all* advertisements for any human or veterinary prescription drug shall present:**
  - A true statement of information in ***brief summary*** relating to **side effects, contraindications** (when used in this section "side effects, contraindications" include side effects, warnings, precautions, and contraindications and include any such information under such headings as cautions, special considerations, important notes, etc.) and **effectiveness**.
  - Advertisements broadcast through media such as radio, television, or telephone communications systems shall include information relating to the ***major side effects and contraindications*** of the advertised drugs in the audio or audio and visual parts of the presentation and ***unless adequate provision*** is made for dissemination of the approved or permitted package labeling in connection with the broadcast presentation shall contain a brief summary of all necessary information related to side effects and contraindications.

202.1(e)(2) – Brief Summary – Exempt Ads

- **Reminder Ads –**
  - those that call attention to the drug name, but do not include "indications or dosage recommendations" for the drug
    - ➢ only contain
      - proprietary name/established name; and, optionally:
      - quantitative ingredients statements, dosage form, quantity of contents, price, name & address of mfr., packer or distributor
    - ➢ can't contain: "other written, printed or graphic matter" that makes a "representation or suggestion" about the drug
    - ➢ not available with drugs with boxed warnings on labels or DESI "possibly effective" drugs
    - ➢ Consumer price reminder ads – subject to 21 CFR 200.200 (very similar rules)

202.1(e)(2) – Brief Summary – Exempt Ads …

- **(ii) *Advertisements of bulk-sale drugs*. Advertisements of bulk-sale drugs that promote sale of the drug in bulk packages in accordance with the practice of the trade solely to be processed, manufactured, labeled, or repackaged in substantial quantities and that contain no claims for the therapeutic safety or effectiveness of the drug.**
- **(iii) *Advertisements of prescription-compounding drugs*. Advertisements that promote sale of a drug for use as a prescription chemical or other compound for use by registered pharmacists in compounding prescriptions**
  - if the drug otherwise complies with the conditions for the labeling exemption contained in § 201.120 [relating generally to Rx Compounding drugs] and;
  - the advertisement contains no claims for the therapeutic safety or effectiveness of the drug.

Brief Summary – Satisfying the Rule

- **If drug has more than one "purpose," can limit an ad to a single purpose, which then limits the brief summary requirements to addressing that purpose**
  - The information relating to effectiveness shall include ***specific indications for use*** of the drug ***for purposes claimed in the advertisement***; for example, when an advertisement contains a broad claim that a drug is an antibacterial agent, the advertisement shall name a type or types of infections and microorganisms for which the drug is effective clinically as specifically as required, approved, or permitted in the drug package labeling.

Brief Summary – Satisfying the Rule …

- **Must disclose *<u>each</u>* specific "side effect and contraindication" -- a term of art that includes:**
  - side effects, warnings, precautions, and contraindications and include any such information under such headings as cautions, special considerations, important notes, etc., contained in required, approved, or permitted labeling for the advertised drug dosage form(s): *Provided, however,*
    - if you limit the purpose of the Ad to an indication, the side effects can be limited to those linked to that purpose

» … continued …

Brief Summary – Satisfying the Rule …

- **Must disclose *each* specific "side effect and contraindication" -- a term of art that includes …**
  - The use of a single term for a group of side effects and contraindications (for example, "blood dyscrasias" for disclosure of "leukopenia," "agranulocytosis," and "neutropenia") -- permitted only to the extent that the use of such a single term in place of disclosure of each specific side effect and contraindication has been previously approved or permitted in drug labeling conforming to the provisions of §§ 201.100 or 201.105.

Brief Summary – Satisfying the Rule …

- **Ad for a Rx drug approved under an NDA can not "recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement." 21 CFR 202.1(e)(4)(i)(a)**

Brief Summary – Satisfying the Rule …

- **When a brief summary is not a "true statement":**
  - it is false or misleading as to side effects, contraindications or effectiveness
  - It fails to present a ***fair balance*** between information relating to ***side effects and contraindications*** vs. ***effectiveness***
    - in that the information relating to effectiveness is presented in ***greater scope, depth, or detail*** than is required by section 502(n) of the act and ***this information is not fairly balanced by a presentation of a summary of true information relating to side effects and contraindications*** of the drug;

      Source: 21 CFR 202.1(e)(5)(ii)

» … continued …

Brief Summary – Satisfying the Rule …

- It fails to present a ***fair balance*** …
  - But, no advertisement shall be considered to be in violation of this section if the presentation of true information relating to side effects and contraindications ***is comparable in depth and detail*** with the claims for effectiveness or safety. 21 CFR 202.1(e)(5)(ii)

- **Other brief summaries not involving a true statement**
  - It fails to reveal facts material in the light of its representations or material with respect to consequences that may result from the use of the drug as recommended or suggested in the advertisement. 21 CFR 202.1(e)(5)(iii)

Brief Summary – Violative Ads

- **Brief summary regulation, at 21 CFR 202.1(e)(6), details ads that *are* –** "false, lacking in fair balance, or otherwise misleading. An advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act, among other reasons, if it: …"

  - ***Let's look at the "are" violative ads in detail …***

Brief Summary – Violative Ads – (e)(6) …

- **(i)** Contains a representation or suggestion, ***not approved or permitted for use in the labeling***, that a drug is better, more effective, useful in a broader range of conditions or patients (as used in this section patients means humans and in the case of veterinary drugs, other animals), safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience (as described in paragraphs (e)(4)(ii) (b) and (c) of this section)
  - whether or not such representations are made by comparison with other drugs or treatments, and
  - whether or not such a representation or suggestion is made directly or through use of published or unpublished literature, quotations, or other references.

Brief Summary – Violative Ads – (e)(6) …

- **(ii)** Contains a ***drug comparison*** that represents or suggests that a drug is safer or more effective than another drug in some particular when it has not been demonstrated to be safer or more effective in such particular by substantial evidence or substantial clinical experience.
- **(iii)**
  - Contains ***favorable information or opinions about a drug previously regarded as valid but which have been rendered invalid*** by contrary and more credible recent information, or;
  - Contains ***literature references or quotations that are significantly more favorable to the drug than has been demonstrated by substantial evidence*** or substantial clinical experience.

Brief Summary – Violative Ads – (e)(6) …

- **(iv)** Contains a representation or ***suggestion that a drug is safer than it has been demonstrated to be by substantial evidence or substantial clinical experience,*** by
  - selective presentation of information from published articles or other references that report no side effects or minimal side effects with the drug or
  - otherwise selects information from any source in a way that makes a drug appear to be safer than has been demonstrated.
- **(v)** Presents information from a study in a way that ***implies that the study represents larger or more general experience with the drug than it actually does***.

Brief Summary – Violative Ads – (e)(6) …

- **(vi)** Contains references to literature or studies that misrepresent the effectiveness of a drug by ***failure to disclose that claimed results may be due to concomitant therapy***, or by failure to disclose the credible information available concerning the extent to which claimed results ***may be due to placebo effect*** (information concerning placebo effect is not required unless the advertisement promotes the drug for use by man).
- **(vii)** Contains ***favorable data or conclusions from nonclinical studies*** of a drug, such as in laboratory animals or in vitro, ***in a way that suggests they have clinical significance when in fact no such clinical significance has been demonstrated***.

Brief Summary – Violative Ads – (e)(6) …

- **(viii)** Uses a ***statement by a recognized authority*** that is apparently favorable about a drug but ***fails to refer to*** concurrent or more recent ***unfavorable data or statements from the same authority*** on the same subject or subjects.
- **(ix)** Uses a ***quote or paraphrase out of context*** to convey a false or misleading idea.
- **(x)** Uses literature, quotations, or ***references*** that purport to support an advertising claim but ***in fact do not support the claim or have relevance to the claim***.

Brief Summary – Violative Ads – (e)(6) …

- **(xi)** Uses literature, quotations, or references for the purpose of recommending or ***suggesting conditions of drug use that are not approved or permitted*** in the drug package labeling.
- **(xii)** Offers a combination of drugs for the treatment of patients suffering from a condition amenable to treatment by any of the components rather than limiting the indications for use to patients for whom concomitant therapy as provided by the ***fixed combination drug*** is indicated, unless such condition is included in the uses permitted under paragraph (e)(4) of this section [*i.e., approved under an NDA or demonstrated by substantial effectiveness*].
- **(xiii)** Uses a study on ***normal individuals*** without disclosing that the subjects were normal, unless the drug is intended for use on normal individuals.

Brief Summary – Violative Ads – (e)(6) …

- **(xiv)** ***Uses "statistics"*** on numbers of patients, or counts of favorable results or side effects, derived from pooling data from various insignificant or dissimilar studies in a way that suggests either that such "statistics" are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case.
- **(xv)** ***Uses erroneously a statistical finding of "no significant difference"*** to claim clinical equivalence or to deny or conceal the potential existence of a real clinical difference.

Brief Summary – Violative Ads – (e)(6) …

- **(xvi)** Uses statements or representations that ***a drug differs from or does not contain a named drug or category of drugs***, or that it ***has a greater potency per unit of weight***, in a way that suggests falsely or misleadingly or without substantial evidence or substantial clinical experience that the advertised drug is safer or more effective than such other drug or drugs.
- **(xvii)** Uses ***data favorable to a drug derived from patients treated with dosages different from those recommended in approved or permitted labeling*** if the drug advertised is subject to section 505 of the act, or, in the case of other drugs, if the dosages employed were different from those recommended in the labeling and generally recognized as safe and effective (e.g., OTC drug). This provision is not intended to prevent citation of reports of studies that include some patients treated with dosages different from those authorized, if the results in such patients are not used.

Brief Summary – Violative Ads – (e)(6) …

- **(xviii)** Uses headline, subheadline, or pictorial or other graphic matter in a way that is misleading.
- **(xix)** Represents or suggests that drug dosages properly recommended for use in the treatment of certain classes of patients or disease conditions are safe and effective for the treatment of other classes of patients or disease conditions when such is not the case.

Brief Summary – Violative Ads – (e)(6) …

- **(xx)** Presents required information relating to side effects or contraindications by means of a general term for a group in place of disclosing each specific side effect and contraindication (for example employs the term blood dyscrasias instead of "leukopenia," "agranulocytosis," "neutropenia," etc.) unless the use of such general term conforms to the provisions of paragraph (e)(3)(iii) of this section – i.e., approved in the labeling

Brief Summary – "May be" Violative Ads

- **Brief summary regulation, at 21 CFR 202.1(e)(7), details ads that *may be* –** "Advertisements that may be false, lacking in fair balance, or otherwise misleading. An advertisement may be false, lacking in fair balance, or otherwise misleading or otherwise violative of section 502(n) of the act if it:"

  - ***Let's look at the "may be" violative ads in detail …***

"May be" Violative Ads – (e)(7)

- **(i)** Contains favorable information or conclusions from a ***study that is inadequate in design, scope, or conduct to furnish significant support*** for such information or conclusions.
- **(ii)** Uses the concept of ***"statistical significance"*** to support a ***claim that has not been demonstrated to have clinical significance or validity***, or fails to reveal the range of variations around the quoted average results.

"May be" Violative Ads – (e)(7)

- **(iii)** Uses statistical analyses and techniques on a ***retrospective basis*** to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluations.
- **(iv)** Uses ***tables or graphs to distort or misrepresent*** the relationships, trends, differences, or changes among the variables or products studied; for example, by failing to label abscissa and ordinate so that the graph creates a misleading impression.

"May be" Violative Ads – (e)(7)

- **(v)** Uses reports or statements represented to be statistical analyses, interpretations, or evaluations that are
  - ***inconsistent with or violate the established principles of statistical theory, methodology,*** applied practice, and inference, or
  - that are ***derived from clinical studies the design, data, or conduct of which substantially invalidate the application of statistical analyses,*** interpretations, or evaluations.
- **(vi)** Contains ***claims concerning the mechanism or site of drug action that are not generally regarded as established*** by scientific evidence by experts qualified by scientific training and experience without disclosing that the claims are not established and the limitations of the supporting evidence.

"May be" Violative Ads – (e)(7)

- **(vii)** ***Fails to provide sufficient emphasis for the information relating to side effects and contraindications***, when such information is contained in a distinct part of an advertisement, because of repetition or other emphasis in that part of the advertisement of claims for effectiveness or safety of the drug.
- **(viii)** ***Fails to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug,*** taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis.

"May be" Violative Ads – (e)(7)

- **(ix)** ***Fails to provide adequate emphasis*** (for example, by the use of color scheme, borders, headlines, or copy that extends across the gutter) ***for the fact that two facing pages are part of the same advertisement when one page contains information relating to side effects and contraindications***.
- **(x)** In an advertisement promoting use of the drug in a ***selected class of patients*** (for example, geriatric patients or depressed patients), ***fails to present with adequate emphasis the significant side effects and contraindications or the significant dosage considerations,*** when dosage recommendations are included in an advertisement, ***especially applicable to that selected class of patients.***

"May be" Violative Ads – (e)(7)

- **(xi)** Fails to present on a page facing another page (or on another full page) of an advertisement on more than one page, information relating to side effects and contraindications ***when such information is in a distinct part of the advertisement.***
- **(xii)** Fails to include on each page or spread of an advertisement the information relating to side effects and contraindications or a prominent reference to its presence and location ***when it is presented as a distinct part of an advertisement.***
- **(xiii)** Contains ***information*** from published or unpublished reports or opinions ***falsely or misleadingly represented or suggested to be authentic or authoritative***.

Other Parts of 202.1

- **202.1(k) - *An advertisement*** issued or caused to be issued by the manufacturer, packer, or distributor of the drug promoted by the advertisement and which is ***not in compliance with section 502(n) of the act and the applicable regulations*** thereunder shall ***cause stocks of such drug*** in possession of the person responsible for issuing or causing the issuance of the advertisement, and stocks of the drug distributed by such person and still in the channels of commerce, ***to be misbranded*** under section 502(n) of the act.

Other Parts of 202.1 …

- **Requiring Prior Approval of Ads – 202.1(j) –** rarely used (I have never heard of it being used) –
  - if there's new info about a drug's safety [i.e., use "may cause fatalities or serious damage"] that has not been widely publicized, FDA can require prior approval of ads, after notice to drug maker and the drug maker's failure to implement a program ensuring dissemination of the safety info to the "medical profession" via subsequent advertisements

Other Drug Advertising Regulatory Duties

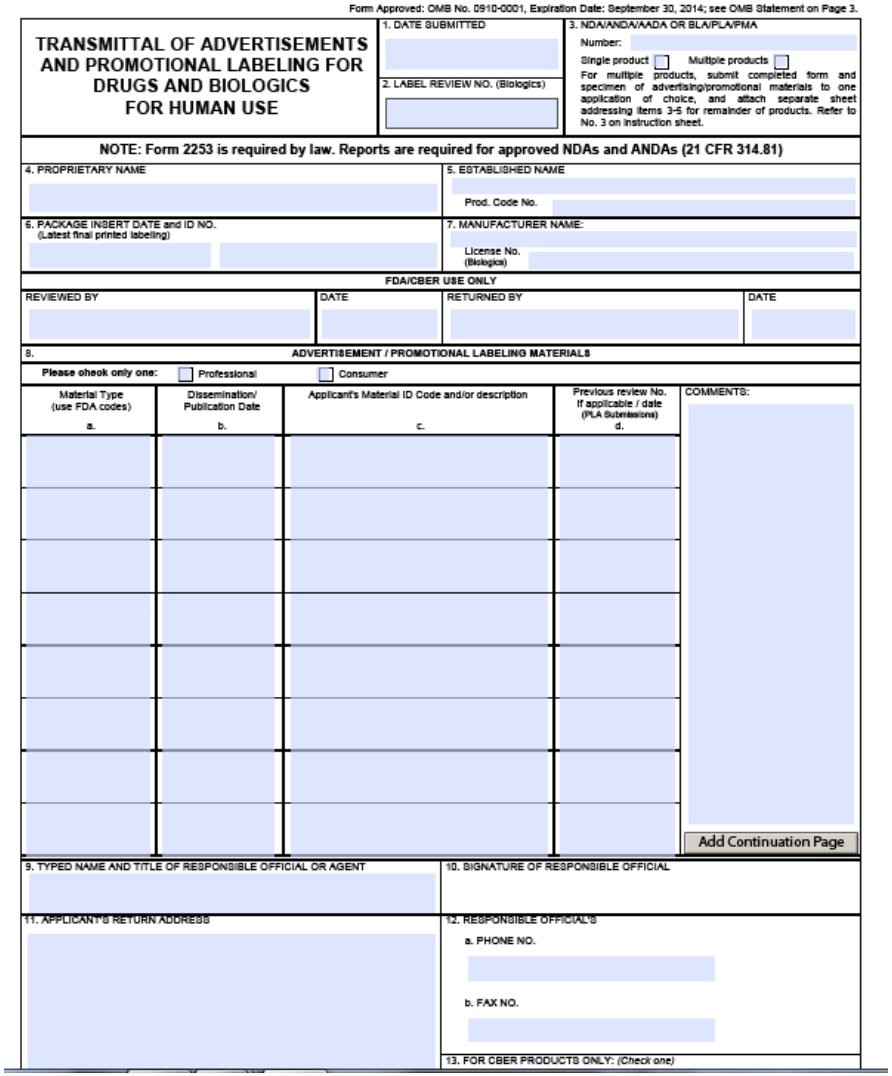
Promotion of an Investigational Drug

- **21 CFR 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.

The 2253 – Reporting NDA Drug Ads to FDA

- **21 CFR 314.81(b)(3) --*Other reporting* --(i) *Advertisements and promotional labeling.*** The [NDA] applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. Form FDA-2253 is available on the Internet at *http://www.fda.gov/opacom/morechoices/fdaforms/cder.html* .

Form 2253 …



Form Approved: OMB No. 0910-0001, Expiration Date: September 30, 2014; see OMB Statement on Page 3.

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. DATE SUBMITTED

2. LABEL REVIEW NO. (Biologics)

3. NDA/ANDA/AADA OR BLA/PLA/PMA
Number:
Single product ☐ Multiple products ☐
For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice, and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.

NOTE: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)

4. PROPRIETARY NAME

5. ESTABLISHED NAME
Prod. Code No.

6. PACKAGE INSERT DATE and ID NO. (Latest final printed labeling)

7. MANUFACTURER NAME:
License No. (Biologics)

FDA/CBER USE ONLY

REVIEWED BY	DATE	RETURNED BY	DATE

8. **ADVERTISEMENT / PROMOTIONAL LABELING MATERIALS**

Please check only one: ☐ Professional ☐ Consumer

Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS:

Add Continuation Page

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT

10. SIGNATURE OF RESPONSIBLE OFFICIAL

11. APPLICANT'S RETURN ADDRESS

12. RESPONSIBLE OFFICIAL'S
a. PHONE NO.
b. FAX NO.

13. FOR CBER PRODUCTS ONLY: *(Check one)*

Biologics Advertising

- **21 CFR 601.12(f)(4):**
  - ***Advertisements and promotional labeling***. Advertisements and promotional labeling shall be submitted to the Center for Biologics Evaluation and Research or Center for Drug Evaluation and Research in accordance with the requirements set forth in 314.81(b)(3)(i)** of this chapter, except that Form FDA-2567 (Transmittal of Labels and Circulars) or an equivalent form shall be used.

    ** **i.e.,** at time of dissemination or publication
  - **Uses 2253 now**; not 2567
  - **E-filing -- Draft Guidance** -- Providing Regulatory Submissions in Electronic Format - Prescription Drug Advertising and Promotional Labeling (PDF - 28KB) ***[hot link]***

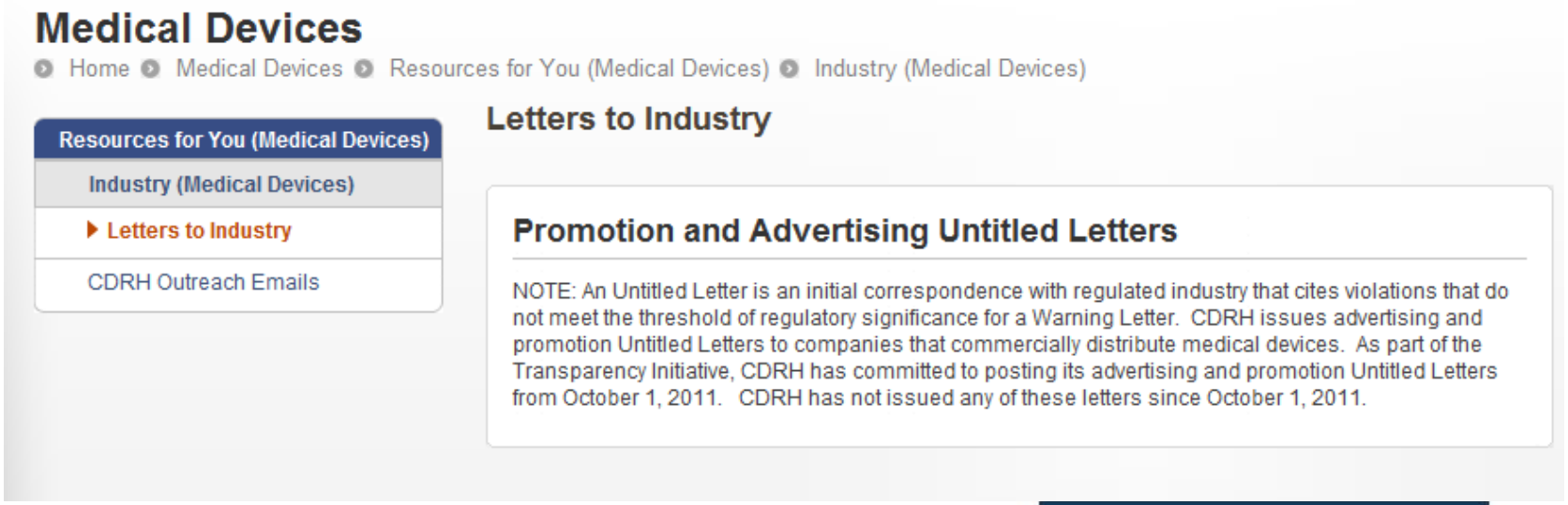
Accelerated Approval and Advertising

- **21 CFR § 314.550 and 21 CFR 601.45 --**
  - ***Submission prior to approval*** -- unless otherwise informed by the agency, [Accelerated NDA or BLA] applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, ***intended for dissemination or publication within 120 days following marketing approval***.
  - ***After 120 days following marketing approval --*** unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.
    - Duty can be removed by FDA later, especially if post-market study requirements lead to "full" approval – 21 CFR 314.560 or 601.46 (biologics)
  - Draft Guidance -- *Accelerated Approval Products: Submission of Promotional Materials (PDF - 17KB)* ***[hot link]***

Device Advertising – General Requirements

Device Advertising Regulations

- Marketed Devices –*no* separate device advertising regulations as in 21 CFR 202.1
- Center for Devices & Radiological Health (CDRH), compared to its drug counterparts -- relatively inactive in ad enforcement – *see:* *FDA website*:



Device Advertising – Warning Letters …

- **Warning Letters – just 19 between 2001 and 2013**
- **Source: Warning Letter search: "device advertising" and "device promotion"**
  - http://www.accessdata.fda.gov/scripts/warningletters/wlSearchResult.cfm?webSearch=true&qryStr=device+advertising

FDA Device Advertising – Warning Letters

Company	Date	Description	Close-out
Oratec Interventions, Incorporated [28]	08/17/2001	Labeling/Premarket Notification Procedure/Adulterated/Misbranded	
Helio Medical Supplies, Inc.[16]	11/25/2002	Medical Device/Misleading Statements/Misbranded	
OMRIX biopharmaceuticals, Ltd. [26]	05/27/2004 CBER	Promotional Claims/Misbranded	
TherMatrx, Inc.[37]	06/29/2004	Promotional Claims/False & Misleading	
St. Jude Medical Atrial Fibrillation Division Inc. [10]	04/23/2010	Investigational Device Exemptions (Sponsor)/Promoting Unapproved Use/Misbranded/Adulterated	
Solar Wide Industrial Ltd8	04/22/2011	CGMP/Quality System, Promotion and Advertsing, and Device Registration	
DePuy Orthopaedics, Inc.[12]	12/08/2011	Premarket Approval/Misbranded/Adulterated	09/27/2012
Beverly Hills Surgery Center, LLC [9]	12/09/2011	Promotion and Advertising/Misleading/Misbranded	
Palmdale Ambulatory Surgery Center [29]	12/09/2011	Promotion and Advertising/Misleading/Misbranded	
San Diego Ambulatory Surgery Center, LLC [32]	12/09/2011	Promotion and Advertising/Misleading/Misbranded	
Valencia Ambulatory Surgery Center, LLC [38]	12/09/2011	Promotion and Advertising/Misleading/Misbranded	
1 800 Get Thin LLC[5]	12/12/2011	Promotion and Advertising/Misleading/Misbranded	
LAPBANDVIP.com[21]	06/25/2012	Medical Device/Misbranded	
oBand Centers Westwood, CA[25]	11/02/2012	Promotion and Advertising/Misleading/Misbranded	
20/20 Institute, Indianapolis Lasik [6]	12/18/2012	Promotion and Advertising/Misleading/Misbranded	
Rand Eye Institute[31]	12/18/2012	Promotion and Advertising/Misleading/Misbranded	
ScottHyver Visioncare, Inc[33]	12/18/2012	Promotion and Advertising/Misleading/Misbranded	
Eye Center of Texas[29]	12/18/2012	Center for Devices and Radiological Health	
Woolfson Eye Institute	12/18/2012	Promotion and Advertising/Misleading/Misbranded	

Pre-Approval Promotion

- **Pending 510(k)**
  - May advertise or exhibit provided the precise regulatory status is stated
  - May not take orders – CPG 300.600
  - May not make safety or effectiveness claims
  - Can describe clinicals so long as no claim for safety or effectiveness

Pre-Approval Promotion – Pending 510(k) for a Restricted Device

- Can not compare to another product
- Descriptions must be "fairly balanced"
- No safety or effectiveness claims
- Can describe clinicals so long as not safety or effectiveness claim made

Pre-Approval – Devices Under IDE

- **21 CFR 812.7 – Prohibition of Promotion – a sponsor, investigator, or person acting on behalf of sponsor, shall not:**
  - **Promote or test market** an IDE device
  - **Commercialize** an IDE device
  - **Represent an IDE device is safe or effective** for purposes for which it is being studied

Pre-Approval – Devices Under IDE …

- **Announce availability of device only:**
  - in medical or scientific publications
  - at medical or scientific conferences
    - Where readership or attendance is comprised primarily of qualified experts
- **State purpose is only to recruit investigators and not to make device generally available**

Pre-Approval – Devices Under IDE …

- **Limit information in notice of availability of device to:**
  - Proposed use of device
  - Name & address of sponsor
  - How to apply to investigator
  - How to obtain device for IDE use
  - Investigator's duties during the study
- **Use direct mail solely to solicit qualified investigators (no mass mailings = promotion)**

Pre-Approval – Devices Under IDE …

- **Need "Caution – Investigational Device" legend on solicitation**
- **No claims – direct or indirect – that device is reliable, safe, or effective**
- **No volume discounts for investigational devices**
- **IRB review needed for recruitment materials**
  - **Source:** *Guidance on Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects*

    [Hot Link]

Devices – Intended Uses

- **"Ordinarily, intended use is determined by reference to 'labeling' or promotional claims; only in rare cases might it be necessary to infer intended use from other types of information."**
  - Source: ODE Blue Book Memorandum #K86-3 entitled *Guidance on the Center for Devices and Radiological Health's Premarket Notification Review Program* ***[Hot Link]***
- **Issue** – relative to off-label promotion issues
- **FDA** – can inhibit off-label use, via statute, in clearing a 510(k) under Section 513(i)(1)(E), which provides …

» ***… continued …***

513(i)(1) (E) – 510(k) Restrictions on Off-Label

- **Sub-sub paragraph (i) -- FDA --** may require a statement in labeling that provides appropriate information regarding a use of the device not identified in the proposed labeling if, after providing an opportunity for consultation with the person who submitted such report, the Director determines and states in writing—
  - (I) that there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device; and
  - (II) that such use could cause harm.

513(i)(1)(E) – 510(k) -- Off-Label Restrictions …

- (ii) Such determination shall—
  - (I) be provided to the person who submitted the report within 10 days from the date of the notification of the Director's concerns regarding the proposed labeling;
  - (II) specify the limitations on the use of the device not included in the proposed labeling; and
  - (III) find the device substantially equivalent if the requirements of subparagraph (A) are met and if the labeling for such device conforms to the limitations specified in subclause (II).
- (iii) The responsibilities of the Director under this subparagraph may not be delegated.

Presenting Risk Information

2009 Draft Guidance

- **May 2009 -- Presenting Risk Information in Prescription Drug and Medical Device Promotion *[Hot Link]***
- ***Purpose –*** factors FDA regards as relevant to adequacy of disclosure of risk information for prescription drugs and restricted devices
  - but also can be used to look at how benefit information is presented
  - "universal concepts" of communicating and understanding risks
  - guidance applies to all types of promotional materials
  - footnote 5 – "over warning" –can detract from the important risk information

Key Factors

- **"Net Impression" – message communicated by all elements of the piece as a whole –**
  - not just individual elements
  - "reasonable consumer" standard – however, if multiple impressions possible, all must be reasonable
  - FTC – uses a similar standard
- **Examples**

Example 1: A broadcast television ad for a cholesterol-lowering drug contains a factually accurate audio risk statement that discloses the drug's major side effects and contraindications. This audio presentation is accompanied by quick scene changes showing comforting visual images of patients benefiting from the drug. It is also accompanied by loud, upbeat music. In this case, the audio disclosure may not adequately communicate risks because of the accompanying discordant visuals and distracting music.

Guidance …

- **Example**

Example 2: A one-page prescription drug ad for an arthritis drug, run in a medical journal, prominently presents the following headline claims in large bolded font and with abundant surrounding white space:

- ***Benefits!*** **DrugX is proven safe and effective for the relief of arthritis pain and stiffness,**
- ***Difference!*** **DrugX's unique gel formulation is convenient and easy to use**, and
- ***Reason to Believe!*** **Drug X is the most frequently prescribed arthritis drug in the United States**

The bottom of the page contains an inconspicuous statement in small, non-bolded font and without surrounding white space: "Like all arthritis medications, Drug X has been associated with a risk of serious infection." The emphasis on benefit information in this piece – in terms of the way the information is formatted and framed – overwhelms the risk information and may cause readers to receive an erroneous impression that the drug is safer than it has proven to be, even though the statements themselves may be factually accurate.

General Considerations in Communicating

- **Consistent Use of Language Appropriate for Target Audience**
  - Example: consumer ad: fainting, not *syncope*
- **Consistent Use of Signaling**
  - Written – relates to formatting (e.g., headlines) –
    - accurate info in text won't offset misleading info in a headline
  - Broadcast – can vary among different audio or visual cues
  - General rule – balance between risk vs. benefit in use of signaling is needed as to frequency and substance
    - e.g., if lots of benefit info in **Bold**, balanced risk info also should be **Bold**

General Considerations in Communicating

- **Consistent Use of Signaling …**
  - text must be balanced as well as to substance – e.g., if risk headline is weak, but benefit headline is strong, the fact that there may be both in headlines, is still not balanced
  - change in voice in video/audio – can be used to help signal switch to risk information
- **Framing Risk Information**
  - how information is slated or conveyed, such as:
    - vague vs. specific
    - positive vs. negative
  - risk and benefit should be balanced as to how they are framed

General Considerations in Communicating

- **Framing Risk Information …**
  - Examples: specificity as to brand name usage – if say **Aleve®** in benefit info, but ***naproxen*** in risk info, not balanced
- **Hierarchy of Risk Information – how ordered**
  - beginning or end – particularly in broadcast ads is vital; stuff in middle is harder to recall
  - print – first is best for most important risk info
    - ➢ end of long paragraph is not ideal

Content Considerations

- **Quantity –** should be balanced in risk vs. benefit info
  - Measuring balance in quantity – main factors:
    - print – space
    - broadcast -- time
    - number of statements
    - completeness and detail of statements
    - use of audio or visual components that enhance or detract from how presented
- **Materiality and Comprehensiveness**
  - "Materiality" – degree to which information is objectively important, relevant, or substantial to the target audience.

Content Considerations …

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Content Considerations …

- **Materiality and Comprehensiveness …**
  - a balanced risk v. benefit presentation can be misleading by omitting material info
  - material facts are ones that influence a person about a product, such as:
    - properties of a product
    - whether product is appropriate for you or your patient
    - whether you are willing to accept the risks of using product
      - most serious risks
      - most frequent risks (even if not serious)
  - ***Target audience consideration*** – is critical to determining what risk info to include

Content Considerations …

- **Materiality and Comprehensiveness …**
  - ***Target audience consideration*** …
    - HCPs – most critical info about product to allow them to decide if product is appropriate for patients and how to safely use
    - Consumers
      - what drug or device is used for
      - who should or should not take product
      - what can be expected of product
      - what they should ask their HCPs about product
      - what they should tell their HCPs (about themselves) before using product

Content Considerations …

- **Materiality and Comprehensiveness …**
  - **Importance of Package Insert**
    - "Highlights" format labeling – includes the most important risks
    - Older labeling (if still out there) – focus on Contraindications, warnings or hazards
    - Boxed warnings – clearly ….
  - **Nature of benefit claims** – if make certain benefit claims, if there is a related risk, must emphasize that risk.
    - Examples: if you stress a benefit of a dosing regimen, you should include any risks related to dosing (e.g., activity restrictions)
    - Example: benefit to postmenopausal women; risks for them as well

Format Considerations

- **Format – relates to noticeability and conspicuousness**
  - **Print:** shape, size, and general layout
  - **Broadcast:** general plan or organization, arrangement and theme (my term: "scripting")
- **General rule – risk and benefit information should be comparably formatted as to noticeability and conspicuousness**
- **Print considerations**
  - **Location** – risk info should be included in main part of piece
    - if not there, can't be cured by putting it in a different part of piece

Format Considerations …

- **Print considerations … key is balance**
  - **Location** –
    - separating risk and benefit can lead to lack of prominence – e.g., two pages of benefit before any risk
    - FDA – essentially suggests that they be intertwined, although guidance does not provide good examples on how to do that …
  - **Font size and style –** should be comparable as well for risk vs. benefit info
  - **Contrast** – in text formatting of **BENEFIT** **vs** **RISK**
  - **White Space** --

Format Considerations …

- **Broadcast Promotion**
  - Qualifiers:
    - vocalized
    - presented through visual images, or
    - in a SUPER that runs concurrently with the claim being qualified
  - "SUPERS" – i.e., super-imposed text – must be handled very carefully especially if used for "qualifying purpose";
    - Factors on their use
      - Don't use if info is complex and requires more than one line of text
      - Visible and on screen long enough and easy to read (e.g., don't use ALL CAPS); good contrast
      - Distinct and not obscured by other graphics or audio

Format Considerations …

- **Broadcast Promotion**
  - "Dual mode" (audio & video) issues – make sure they don't "step" on each other
  - **Audio considerations – balanced risk vs. benefit**
    - pacing
      - Is this OK?
        - benefit – slow, distinct
        - risk – fast, lower volume
    - background music

Evidence Needed to Support Claims

Substantial Evidence

- **Standard – Adequate and Well-Controlled Clinical Trials (A&WCCT)**
  - prospectively defined objectives and methods of analysis
  - design permits a valid comparison to a control
  - adequate measures to minimize bias (e.g., blinded randomization)
  - methods of assessments are well-defined and reliable
- **Comparative claims –** head-to-head to show superiority
- **Not acceptable** -- generally
  - Post-hoc analyses
  - Meta-analyses

Substantial Evidence …

- **Secondary endpoints –** may be used
  - study protocol should:
    - define endpoint measures
    - criteria for statistical analysis and interpretation of results
    - clear specification for what conditions justify a positive study outcome
  - corrections made for multiplicity
- **Composite Endpoints** – only go towards establishing that scale, but not the individual aspects (e.g., depression vs. its symptoms)

End of Part 1 -- Basics