ACI's 3rd FDA & USDA Compliance Boot Camp

September 29-30, 2014

INSIDE THE LATEST FDA INITIATIVES:

WHAT TO EXPECT
AND
HOW TO RE-ADJUST COMPLIANCE PROTOCOLS

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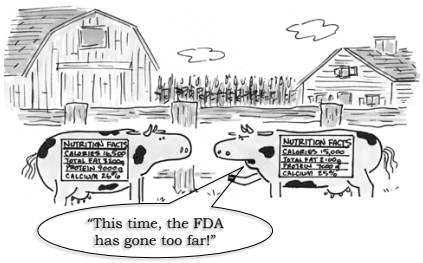
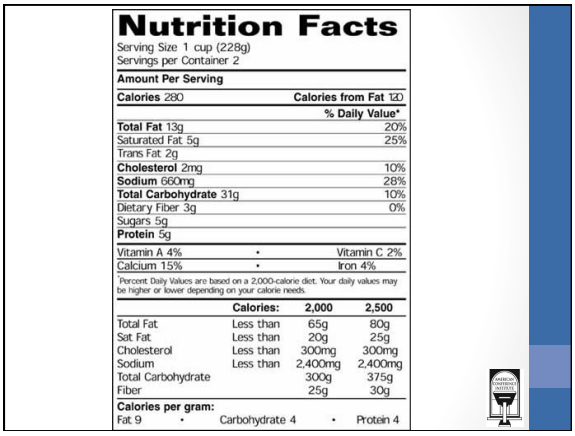
AGENDA

- FDA Labeling Changes
- PHOs ≠ GRAS
- Social Media Guidance Documents
- "Gluten-Free"
- Human Research and IND Applications

FDA LABELING CHANGES





Nutrition Facts

Serving Size 1 cup (228g)
Servings per Container 2

Amount Per Serving

Calories 280	**Calories from Fat** 120
	% Daily Value*
Total Fat 13g	20%
Saturated Fat 5g	25%
Trans Fat 2g	
Cholesterol 2mg	10%
Sodium 660mg	28%
Total Carbohydrate 31g	10%
Dietary Fiber 3g	0%
Sugars 5g	
Protein 5g	

Vitamin A 4% • Vitamin C 2%
Calcium 15% • Iron 4%

*Percent Daily Values are based on a 2,000-calorie diet. Your daily values may be higher or lower depending on your calorie needs.

	Calories:	**2,000**	**2,500**
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Fiber		25g	30g

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

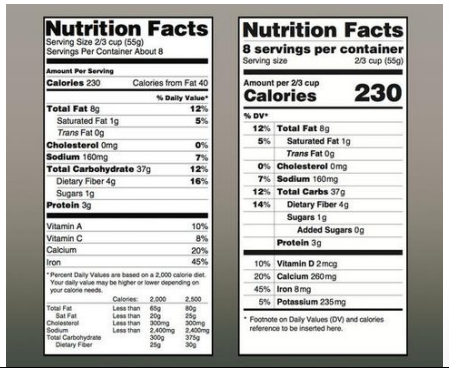
Nutrition Fact Labeling

- "Nutrition Facts" virtually unchanged since their introduction in 1993.
  - In 2006, "Trans Fat" requirement added
- Goal: Give consumers a tool to help make better dietary choices
- The proposed changes are based upon survey data, advances in nutritional science, and new national health priorities (obesity, diabetes, etc.)

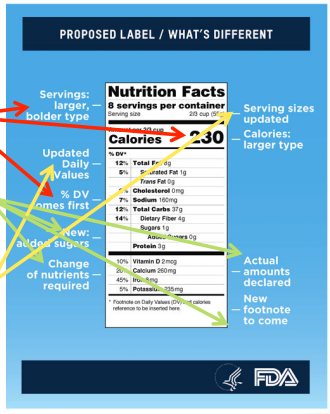
Proposed Labeling Changes

- **Style**
  - Change layout to make label easier to read and understand
  - Emphasize information deemed most important for consumers
- **Contents**
  - Removal of some formerly required nutritional information
  - Addition of formerly unrequired information
- **Serving Size**
  - Update "serving size" information to reflect the actual habits of consumers
  - Prevent "strategic packaging"

Changes in Style:



- Style
- Content
- Serving Size



Changes in Content: Additions

- Added Sugars
  - Increase caloric intake without increasing nutrient intake
  - Empty calories; no %DV, expressed in grams
  - "Not a significant source of added sugars" is required when there is less than 1g per serving, and no additional claims are made about sugars or sweeteners
- Potassium
  - Regarded as a "nutrient of public health significance"
- Vitamin D
  - Regarded as a "nutrient of public health significance"

Changes in Content: Subtractions

- Vitamin C
  - Evidence suggests people get enough
  - Optional labeling permitted; required when added, or claims are made.
- Vitamin A
  - Evidence suggests people get enough
  - Optional labeling permitted; required when added, or claims are made.
- "Calories from Fat"
  - Declaration had "no effect on consumers' judgments of product healthfulness"
    - (79 FR 11950)

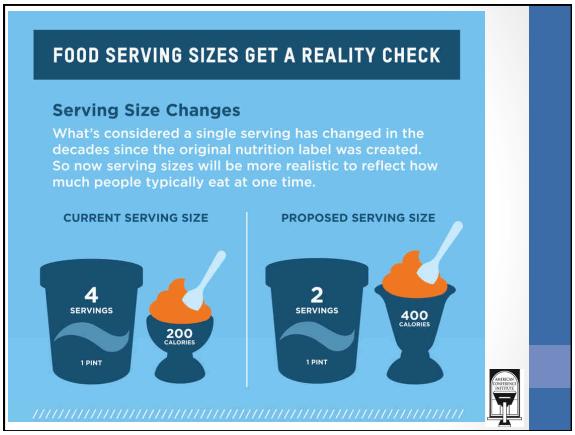
Changes in Content: Updates

- Update Recommended Daily Intake (RDI) for: calcium, copper, folate, iodine, iron, magnesium, molybdenum, niacin, phosphorus, riboflavin, selenium, thiamin, Vitamins A, B_6, B_{12}, C, D, & E, and zinc.
- Update Reference Values for:
  - Sodium: 2300mg/2000cal
  - Dietary Fiber: 28g/2000cal

Changes to "Serving Size"

- Based on research about consumer behavior, the FDA is updating labeling as to what constitutes a single "serving."
  - Now, based upon what and how much people **ACTUALLY** eat.
- Containers typically consumed in a single serving have been labeled as such, while others have been altered to reflect the reality of consumer behavior.

Understanding consumer behavior: *We eat what's in front of us*



Single Servings?

- Packaging affects consumption
  - New proposed rules considered how consumers might consume various products of different size.
- Here, each Coca-Cola® now considered a Single Serving

Compliance

- Amendments will become effective 60 days after the date of publication of Final Rule.
- Compliance will be required 2 years after the effective date.
  - "Intended to provide industry time to revise labeling to come into compliance with new labeling requirements while balancing the need for consumers to have the information in a timely manner." 79 FR 11959.

Compliance cont'd.

- Records: Manufacturers will be required to maintain records of levels of a variety of substances, including sugars, non-digestible carbohydrates (soluble and insoluble), Vitamin E, folic acid, and others.
- Records are required to be retained for 2 years.
- Kept in accordance with § 101.9(g)

PHOs ≠ GRAS

PHOs = Partially Hydrogenated Oils

- PHOs are typically vegetable-based oils that have undergone hydrogenation (saturation of the molecule with hydrogen).
- Results in physical properties favorable to culinary use (e.g. use in baking).
- However, addition of the hydrogen atoms to the oils results in adverse health effects, such as heart disease.

GRAS = Generally Regarded as Safe

- FDA defines safe as "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.
- General recognition, rather than unanimity, is required.
- Substantial disagreement between experts precludes a finding of GRAS.

"Based on new scientific evidence, and the findings of expert scientific panels, **the [FDA] has tentatively determined that partially hydrogenated oils (PHOs…are not generally recognized as safe (GRAS) for any use in food** based on current scientific evidence establishing the health risks associated with the consumption of *trans* fat, and therefore that PHOs are food additives."

Nov. 8, 2013 in 78 FR 67169

"…If finalized, **this would mean that food manufacturers would no longer be permitted to sell PHOs**, either directly or as ingredients in another food product, without prior FDA approval for use as a food additive. ."

Nov. 8, 2013 in 78 FR 67169

Why the change?

- "**Significant recent evidence** demonstrated that the increased risk of coronary heart disease (CHD) from consumption of any amount of trans fat means that **consumption of PHOs, the primary dietary source of trans fat, also leads to an increased risk of Coronary Heart Disease**."

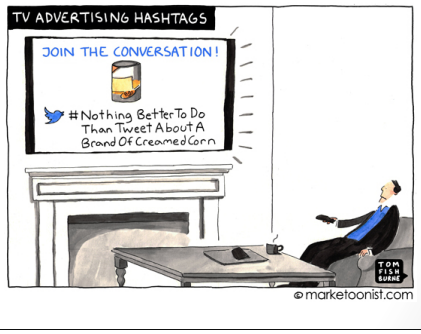
Compliance

- Because this is a tentative determination, the FDA will announce their **final determination in the Federal Register**.
- Compliance **timeline undecided**.
  - 78 FR 67173
- Estimated costs of initial removal: $8b
  - Distribution depends on compliance timeline
- Estimated $12-14b in costs over 20 years compared to $117-$242b estimated savings.

Industry Response

- American Bakers Association (the *other* A.B.A.) opposes the change as "extreme" and "unnecessary."
- Points to W.H.O. Trans Fat policy, which does not include a total ban, but instead only bans some PHOs and types of Trans Fat.
- Urges alternative, nuanced approach.
- Claims withdrawal of GRAS designation is unprecedented and imprudent.

Social Media Guidance



Internet/Social Media Platforms:

Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices

June 2014

Third-Party Misinformation in the Social Media Context

- Present FDA and FTC regulations already govern communications for which the company IS responsible; this guidance document leaves these unchanged.
- Instead, this document applies to those **communications the firm undertakes in response to misinformation by a third party**.
- Such responses are **NOT REQUIRED**.

Applicability

- IF a **THIRD PARTY makes false or otherwise misleading claims** on a firm forum or a forum or other social media platform hosted by a third party,
- and the firm is **not otherwise managing or soliciting the content** of the forum,
- and the firm **decides to correct the misinformation**,
- **THIS GUIDANCE APPLIES**.

Does the guidance apply?

Example 1: As part of a marketing campaign, a member of a firm's marketing department posts incorrect statements about a product's safety or efficacy compared to the efficacy of a competitor's product on a discussion board hosted by an independent third party.

Example 1: As part of a marketing campaign, a member of a firm's marketing department posts incorrect statements about a product's safety or efficacy compared to the efficacy of a competitor's product on a discussion board hosted by an independent third party. **The firm is responsible for the content of the communication because the member of the firm's marketing department is acting on behalf of the firm. Thus, this draft guidance would not apply.**

Example 2: A firm hosts a discussion group on its own website, monitors the discussion for content that does not speak positively about its product, then removes or edits postings that portray its product in a negative light, and adds positive postings about the product.

Example 2: A firm hosts a discussion group on its own website, monitors the discussion for content that does not speak positively about its product, then removes or edits postings that portray its product in a negative light, and adds positive postings about the product. **This firm is exerting control over the user-generated content and is responsible for the resulting content. Thus, the firm's actions would not fall under the scope of this guidance.**

Example 3: A firm becomes aware of a blogger who is posting inaccurate information about the firm's product. The blogger does not have a relationship with the firm and the firm does not compensate the blogger for the blog or for any other activity.

Example 3: A firm becomes aware of a blogger who is posting inaccurate information about the firm's product. The blogger does not have a relationship with the firm and the firm does not compensate the blogger for the blog or for any other activity. **The firm is not responsible for the content of the blog. The firm may decide to attempt to correct the misinformation, but it is not obligated to attempt to correct it.**

Example 4: A firm hosts a discussion forum about its drug's or device's FDA-approved use on its corporate website and does not participate in the discussion, but it does monitor the forum for profanity and obscenity. The forum includes an overarching clear and conspicuous statement that the firm did not create the content of the forum.

Example 4: A firm hosts a discussion forum about its drug's or device's FDA-approved use on its corporate website and does not participate in the discussion, but it does monitor the forum for profanity and obscenity. The forum includes an overarching clear and conspicuous statement that the firm did not create the content of the forum. **The firm is not responsible for the information that is posted by independent third parties and can, if it so chooses, correct misinformation according to this guidance.**

So, if it applies, what does the guidance say?

If correcting misinformation…

- Be relevant and responsive to the misinformation;
- Be limited and tailored to the misinformation;
- Be non-promotional in nature, tone, and presentation;
- Be accurate;
- Be consistent with the FDA-required labeling for the product;

If correcting misinformation…

- Be supported by sufficient evidence;
- Either be posted in conjunction with the misinformation in the same area or forum, or should reference the misinformation and be intended to be posted in conjunction with the misinformation; and
- Disclose that the person providing the corrective information is affiliated with the firm that manufactures, packs, or distributes the product.

"When a firm **voluntarily** undertakes the correction of misinformation **in a truthful and non-misleading manner** pursuant to the recommendations in this draft guidance, **FDA does not intend to object if these voluntary corrections do not satisfy otherwise applicable regulatory requirements**, if any."

"**If** a firm chooses to provide **information outside the scope of this draft guidance**, the firm should ensure the information it provides **complies with any applicable requirements** related to labeling or advertising."

Internet/Social Media Platforms with Character Space Limitations:

Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices

DRAFT GUIDANCE

June 2014

Internet/Social Media Platforms & Character Space Limitations

- Character limitations on social media platforms such as Twitter and internet services such as Google AdWords present challenges in meeting FDA risk disclosure requirements.
- Draft Guidance illustrates FDA's current thinking about how firms should **interact with consumers through such social media platforms** while meeting requirements.
- When in doubt, a firm is urged to **consider whether platforms with character-space limitations are best** suited to communicate the information in question.

Applicability

- A firm should consult this draft guidance when considering interacting with consumers through social media platforms or other internet services with character space limitations.
- Communications through other mediums subject to present regulation.

Guidelines for Character-Limited Communications

1. All information should be **accurate, non-misleading, and reveal material facts.**
2. Communications with include benefit information should include risk information and such information should enjoy similar prominence.
3. **Utilize hyperlinks** to direct consumers to more in-depth information.
4. **Most serious risks should be emphasized**

Example 1

A firm is considering promotion of its prescription drug NoFocus on Twitter, which is limited to 140 character spaces per "Tweet." NoFocus is indicated for mild to moderate memory loss. Any benefit information that the firm communicates about NoFocus should be accurate and non-misleading and include material facts about the use of NoFocus.

The firm considers including the following benefit information within the tweet :

NoFocus for mild to moderate memory loss [40/140 characters]

What should the firm consider in evaluating this communication?

Example 1

NoFocus for mild to moderate memory loss [40/140 characters]

The benefit information for NoFocus that is communicated within the first 40 character spaces of this tweet is accurate and non-misleading and includes material facts about the indication and limitations to the use of NoFocus. **The firm should consider whether the remaining 100 character spaces are enough to include risk information and certain other required information, as applicable, about NoFocus.**

Example 1

NoFocus for mild to moderate memory loss [40/140 characters]

If the firm concludes that adequate benefit and risk information, as well as other required information, cannot all be communicated within the same tweet, then **the firm should reconsider using Twitter for the intended promotional message for NoFocus.**

Example 2

A firm is considering promotion of its prescription drug NoFocus on Twitter, which is limited to 140 character spaces per message or tweet. NoFocusis indicated for mild to moderate memory loss. There are no boxed or other warnings and no known fatal or life-threatening risks included in the PI for NoFocus. The most serious precaution associated with NoFocus is that it may cause seizures in patients with a seizure disorder.

The firm considers including the following benefit information within the tweet :

NoFocus for mild to moderate memory loss; may cause seizures in patients with a seizure disorder www.nofocus.com/risk [117/140]

Example 2

NoFocus for mild to moderate memory loss; may cause seizures in patients with a seizure disorder www.nofocus.com/risk [117/140]

The most serious risks are communicated together with the benefit information within the tweet. The firm includes a direct hyperlink to the "Important Safety Information" webpage that is devoted to providing risk information about NoFocus. Further, the URL www.nofocus.com/risk denotes that the landing page is comprised of risk information. The firm conveys risk information within the tweet in a comparable manner to the benefit information.

"GLUTEN-FREE"

"I've only been gluten-free for a week, but I'm already really annoying."

FDA's Regulation of "Gluten Free" Claims

- The FDA's new regulation of gluten-free food labeling **standardizes what "gluten free" means** on the food label.
- **Gluten free is a voluntary claim** that manufacturers may elect to use in the labeling of their foods.
- However, manufactures that choose to label their foods "gluten free" are **accountable for using the claim in a truthful and non-misleading manner**.

What "Gluten Free" now means

- FDA has set the limit of **less than 20 PPM** for foods that carry the label "gluten free," or an alternative term such as "free of gluten."
- This level is the **lowest that can reliably detected** in foods using scientifically validated methods.
- **Other countries and international bodies use the same threshold**, as moth people with celiac disease can tolerate such low levels.

Can all foods be labeled that way?

- Whether a food is **manufactured to be free of gluten *OR by nature is gluten free*, it may bear a gluten-free labeling claim** if it meets all FDA requirements for a gluten-free food.
- Many foods and beverages like bottled spring water, fruits, vegetables, and eggs are naturally gluten free.
- However, because the **"gluten free" claim isn't required** to be on a food package, it **might not appear even if the food is, in fact, gluten free**.
- The decision to include this label, provided it is accurate, is for private firms to consider.

Final Considerations

- Regulations **went into effect in August 2014**.
- No requirement on formatting of the claim; **firms are free to design their packaging**—and the inclusion of the claim—as they wish.
- The **FDA does not endorse, accredit, or recommend any particular third-party** gluten-free certification program.

IND Applications Involving Human Subjects

September 2013 Guidance

Guidance for Clinical Investigators, Sponsors, and IRBs:

Investigational New Drug Applications (INDs):

Determining Whether Human Research Studies Can Be Conducted Without an IND

Investigational New Drug Apps

- Typically, unless a particular exception applies, an Investigational New Drug Application is required to conduct clinical trials with human subjects.
  - 21 CFR Part 312 (INDs)
- This guidance only applies to whether an IND is required for a drug, not a clinical trial involving a medical device.

Investigational New Drug Apps

- The requirement is driven by two primary goals:
  1. Assure the **safety and rights of subjects** in all phases of the investigation;
  2. To help assure that the **quality of the scientific evaluation of the drug is adequate** to permit an evaluation of the drug's effectiveness and safety.

INDs Are Required When:

1. The **research involves a drug** (as defined in 21 USC 321(g)(1)).
2. Research is a **clinical investigation** as defined under 21 CFR 312.3)
3. The clinical **investigation is not otherwise exempt** from the IND requirements.

What is a drug?

- According to the FD&C Act, drugs are defined as "articles **intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease** . . ." and "articles (other than food) **intended to affect the structure or any function** of the body of man or other animals."
- Biological products may also be considered drugs within the meaning of the Act.

What is a Biological Product?

- ". . . a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. "

What is a Clinical Investigation?

- ". . . [an] experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of [the IND regulations], an experiment is any use of a drug [whether approved or unapproved] except for the use of a marketed drug in the course of medical practice."
  - 21 USC 312.3(b)

Exemptions

- Exemptions from the IND application requirement fall into the following categories:
  1. Certain Research Involving Marketed Drug Products
  2. Bioavailability or Bioequivalence Studies in Humans (e.g. generics)
  3. Studies Involving GRAS Isotopes

Certain Research Involving Marketed Drug Products

- Requirements:
  1. Drug is lawfully marketed in the US;
  2. Research is not intended to be the basis for a new indication or FDA-required labeling changes;
  3. Not intended to support a significant change in advertising;
  4. Nothing about the study would lead to a significantly increased risk associated with the use of the product;
  5. Research conducted in compliance with IRB review requirements; and
  6. The investigation is not intended to promote or commercialize the drug

Bioavailability or Bioequivalence Studies in Humans

Requirements:

1. Drug does not contain a new chemical entity, is not radioactive, and is not cytotoxic;
2. Dose of unapproved drug doesn't exceed the dose specified for the approved version;
3. Investigation is conducted in compliance with IRB review requirements; and
4. The sponsor meets the requirements for retention of test article samples and safety reporting.

Studies Involving GRAS Isotope Labeling

- Research involving **radioactive or cold isotopes** that have been designated as generally recognized as safe (GRAS) for research may not require INDs.
- In research involving radioactive or cold isotopes, respectively, the following requirements apply.

Radioactive Isotope Research Requirements (with no IND)

1. Research must be basic and must not be intended for immediate use;
2. Use in humans is approved by the Radioactive Drug Research Committee (RDRC)
3. At known dosage, radioactive drugs are not known to cause any detectable pharmacological effect in humans; and
4. The total amount of radiation to be administered is the smallest radiation practical to perform the study.

Cold Isotope Research Requirements (with no IND)

1. Research must be basic and must not be intended for immediate use;
2. At known dosage, radioactive drugs are not known to cause any detectable pharmacological effect in humans; and
3. The quality of the cold isotope meets relevant quality standards; and
4. Investigation is conducted in compliance with IRB review requirements.

Questions?

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