

# What You Need to Know About “Labels”

The FDA and Off-Label Use  
Of Medical Devices

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# Goals of Today's Talk

- Understanding the Terminology
- Understanding Who does What?
- Understanding Rules of Labeling
- CYA
  - What you can and cannot market and advertise
  - **Reducing** risk of complaints or litigation
- Reacting Properly
  - What to do, or not do, if something goes badly

# Today's Topics

- Role of the FDA in Medical Device Manufacturing
- Classes of Medical Devices
- The Device Maker's Rule
  - Labels
  - Off-Label Marketing and Promotion
- Why Legal Considerations Matter

# Role of the Food and Drug Administration (FDA)

# The FDA Regulates Medical Devices

- Any medical device manufactured, repackaged, relabeled, and/or imported by any company or firm to sell in the U.S. must meet FDA regulations and have FDA approval.
- To gain FDA approval the medical device manufacturer must present evidence that the device is reasonably **safe** and **effective** for a particular use.
- Once Approved, the FDA regulates the marketing of Medical Devices
- **Medical devices can only be marketed for FDA approved purposes (with exceptions)**

# Role of the FDA

- FDA determines whether a medical product is safe and effective for use under the conditions prescribed, recommended, or suggested in the proposed labeling submitted with the product's marketing application.
- The FDA regulates the marketing approval or clearance, labeling, and promotion of pharmaceutical, medical device, and biologic products in the United States.
  - These products may only be labeled, promoted, and advertised for the uses that the FDA has approved or cleared.
  - This labeling also provides directions on how to use the product safely and effectively.
  - Promotion means all proactive activities (written, oral or otherwise) that directly or indirectly market, sell or support product sales and use, or that contribute to the sales growth of a company's products.
- FDA enforces its rules and regulations

# Limits on FDA Authority

- The FDA does not have the authority to:
  - Regulate a physician's or nurse's practice.
  - FDA does not tell providers what to do when running their business or what they can or cannot tell their patients.
  - Make recommendations for individual doctors, clinics, or home care agencies.
  - Conduct or provide a rating system on any regulated medical devices.

# Medical Device Classes

# Role of the FDA in Contact Lenses

- CL for Daily Wear are Class II Medical Devices
- CL for Overnight are Class III Medical Devices
- <https://www.fda.gov/MedicalDevices/ucm077454.htm>

# Classes of Medical Devices – Class I

- Subject only to “general” regulatory controls that are applicable to all devices.
- Minimal potential for harm to the user and simpler in design than Class II or Class III devices.
- Examples include enema kits and elastic bandages.
  - 47% of medical devices fall under this category
  - Mostly exempt from regulation

# Classes of Medical Devices – Class II

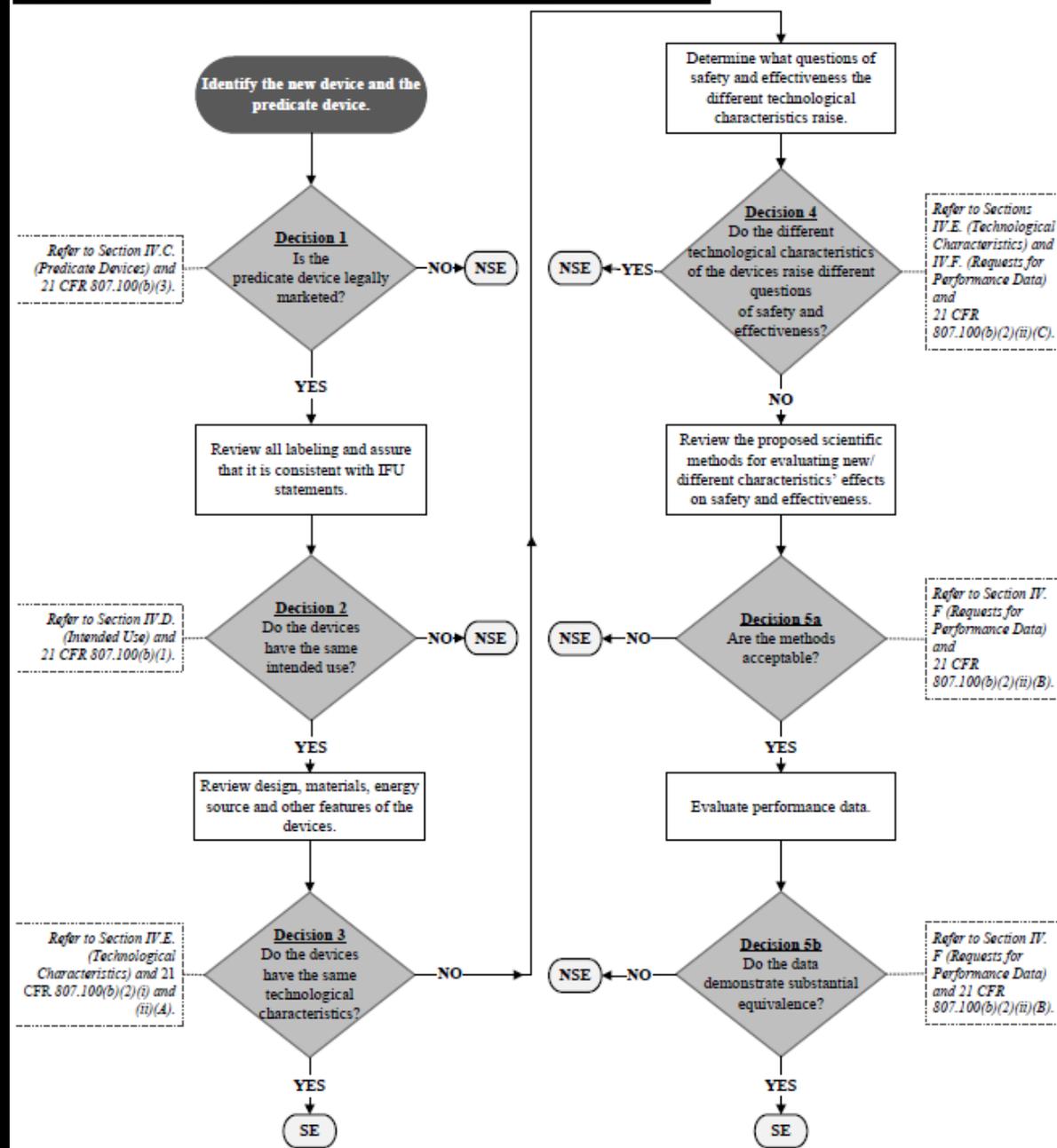
- General regulatory controls are not enough to ensure assurance of safe and effective, but special controls provide that assurance.
- **Most medical devices are Class II devices.** Examples of Class II devices include powered wheelchairs, some pregnancy test kits, and daily use contact lenses.
  - 43% of medical devices fall under this category.
- Requires a 510k (aka pre-market notification) showing “Substantial Equivalence” to a legally marketed device.

# Substantial Equivalence

- SE is shown if the device has the same intended use and
  - (i) same technology, or
  - (ii) different technology but is as safe and effective as a legally marketed device.
- If substantial equivalence is shown the device is given same classification as the equivalent device.
- If substantial equivalence is not shown it is a “new” device and designated as Class III by default.
  - Thus, all new devices “enter the system” through a 501k application.
  - And all new devices start out as Class III

# Substantial Equivalence Flowchart

## Appendix A. 510(k) Decision-Making Flowchart



SE = "Substantially Equivalent"

NSE = "Not Substantially Equivalent"

IFU = "Indications For Use"

# Classes of Medical Devices – Class III

- General controls are insufficient and there is not enough information to show that any special controls will ensure safety and effectiveness of the device.
- These devices usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury. Examples of Class III devices include implantable pacemakers, breast implants, and overnight wear contact lenses.
  - 10% of medical devices fall under this category.
  - Highest regulatory control.
  - Requires pre-market approval (PMA).

# Pre-Market Approval

- Premarket approval (PMA) is the FDA process of **scientific and regulatory review** to evaluate the **safety and effectiveness** of Class III medical devices.
- PMA is the most stringent type of device marketing application required by FDA.
- The applicant must receive FDA approval of its PMA application prior to marketing the device.
- PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s).
  - FDA says, “good science and scientific writing is a key to the approval of PMA application.”

# Currently FDA Approved Class III Ortho-K GP Lenses

Establishment Name		Registration Number	Current Registration Yr
<a href="#">BAUSCH &amp; LOMB, INC.</a>	NY/USA	1313525	2019
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight</a></li> </ul>			Complaint File Establishment
<a href="#">BAUSCH &amp; LOMB, INC.</a>	MA/USA	1281950	2019
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight</a></li> </ul>			Manufacturer; Specification Developer
<a href="#">BLANCHARD CONTACT LENS, INC.</a>	NH/USA	1223801	2019
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - DreamLens; Equalens II(Ortho-K Overnight Waer)</a></li> </ul>			Contract Manufacturer
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - FluoroPerm 30/60/151; FluoroPerm 92; HDS / HDS UV / HDS 100; Paraqon Thin / PVS Basics</a></li> </ul>			Contract Manufacturer
<a href="#">C &amp; E GP SPECIALISTS, INC.</a>	CA/USA	2032336	2019
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - Fargo</a></li> </ul>			Manufacturer
<a href="#">CONTEX, INCORPORATED</a>	CA/USA	2031102	2019
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - Contex OK Lens</a></li> </ul>			Manufacturer
<a href="#">E &amp; E OPTICS INC</a>	CA/USA	3003900215	2019
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - Fluoroperm 151; Fluoroperm 92; Paraqon HDS</a></li> </ul>			Contract Manufacturer
<a href="#">EUCLID SYSTEMS CORPORATION</a>	VA/USA	3002652243	2019
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - EMERALD; JADE; SmartLens</a></li> </ul>			Manufacturer
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - Emerald; Jade; Sapphire; SmartLens; Topaz</a></li> </ul>			Manufacturer
<a href="#">EUCLID SYSTEMS CORPORATION</a>	VA/USA	3014175039	2019
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - Emerald; Euclid Systems Orthokeratology (Oprifocon A) Contact Lenses For Overnight Wear; Euclid Systems Orthokeratology (Tisilfocon A) Contact Lens For Overnight Wear; Jade; Sapphire; SmartLens; Topaz</a></li> </ul>			Manufacturer
<a href="#">LES LABORATOIRES BLANCHARD</a>	CANADA	9612500	2019
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - Dreamlens; Eqaulens II (Ortho-K Overnight Wear)</a></li> </ul>			Contract Manufacturer
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - Fluoroperm 30/60/92/151; HDS/HDS UV/HDS 100; Paraqon Thin/PVS Basics</a></li> </ul>			Contract Manufacturer
<a href="#">Paragon Vision Sciences</a>	AZ/USA	2020433	2019
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - Paraqon Z CRT</a></li> </ul>			Manufacturer
<ul style="list-style-type: none"> <li>• <a href="#">Lens, Contact, Orthokeratology, Overnight - Normaleyes 15.5; Paraqon CRT Dual Axis Contact Lens</a></li> </ul>			Manufacturer

# Summary: How to Study and Market a Device

# Establishment Registration

- Owners or operators of places of business (also called establishments or facilities) that are involved in the production and distribution of medical devices intended for use in the United States (U.S.) are required to register annually with the FDA.
- Payment of fees (\$5,326 for FY2020)

# Pre-Market Requirement Steps

- Classify your device
- Choose the Correct Premarket Submission
  - 501(k) – Premarket Notification
  - PMA – Premarket Approval
  - De Novo
- Prepare appropriate information for the premarket submission to the FDA
- Send your premarket submission to the FDA and interact with the FDA staff during review
- Complete the registration and device listing

# The Device Maker's Rule

Medical devices can only be marketed or promoted for purposes reflected on the device's FDA approved **labeling**.

# What is a “Label” or “Labeling?”

- Display of written, printed, or graphic matter upon the **immediate container** of any article...
  - The term 'immediate container' does not include package liners.
- Any word, statement, or other information appearing on the immediate container must also appear 'on the outside container or wrapper, if any there be, or the retail package of such article, or is easily legible through the outside container of wrapper.'

# What is a “Label” or “Labeling?”

- 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 at any time while a device is held for sale after shipment or delivery for shipment
- The term ‘accompanying’ is interpreted liberally and extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc.
  - ‘Accompanying’ also includes labeling that is brought together with the device after shipment or delivery for shipment.
- Advertising is generally deemed “labeling.”

# Off-Label Marketing and Promotion

# What is “Off-Label” Use?

- Off-label use as applied to medical devices is the application (use) of the device for a purpose that is not included as an indication in the FDA approved device labeling.
  - Such applications are also called unapproved or new uses.
- Beyond a use not being indicated, some off-label uses may be expressly contraindicated as well as explicitly warned against.

# Examples of “Off-Label” CL Use

- Using an Approved Contact Lens in an Unapproved Way
  - Reuse of contact lenses labeled single use only
  - Use of frequent replacement at longer than approved intervals
  - Use of daily wear CL for extended/overnight wear
  - Use of GP lenses for orthokeratology/myopia reduction not expressly approved for orthokeratology
  - Use of SCL not approved as a bandage lens as a “bandage” lens
  - Use of Scleral lenses to “treat” DED/OSC

# Legal “Promotions” of Off-Label Use

## TWO EXCEPTIONS TO THE RULE AGAINST PROMOTING OFF-LABEL USE

- Communications to Payors and Similar Entities
- Communications “Consistent With the FDA-Required Labeling”

# Communications to Payors and Similar Entities

- May provide “Health Care Economic Information”
- Permitted because payors are “sophisticated” and need to know in advance of approval
- Communications must be “truthful and non-misleading” with appropriate background
- Also applies to unapproved devices:
  - Product information (description and features)
  - Information about the indications sought and patient utilization projections
  - Anticipated timeline for FDA approval
  - Product pricing
  - Factual presentation of study results

# Communications “Consistent With the FDA-Required Labeling”

- Information not contained in the FDA-required labeling for the product but that may be consistent with it
  - **Limited to information about the approved or cleared uses of a product**
- Product communications that are consistent with a product’s FDA-required labeling but are false or misleading may subject a firm to enforcement action
- Factors the FDA Considers in assessing if it is “consistent”:
  - 1. How the information compares as to indication, patients, limitations/directions, and use
  - 2. Does the information increase the potential for harm (risk vs. benefit)
  - 3. Can the product be safely and effectively used under conditions in the communication
- Information about different use regimen or for different disease is not “consistent”
- <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-product-communications-are-consistent-fda-required-labeling-questions-and-answers>

# Responding to “Unsolicited Requests” for Off-Label Information

- Unsolicited requests are those initiated by persons or entities that are completely independent of the relevant firm.
  - This may include many health care professionals, health care organizations, members of the academic community, and formulary committees, as well as consumers such as patients and caregivers).
- Requests that are prompted in any way by a manufacturer or its representatives are not unsolicited requests, they are “solicited requests.”

# Responding to “Unsolicited Requests” for Off-Label Information

- Solicited Requests

- FDA considers requests for off-label information that are prompted in any way by a manufacturer or its representatives to be solicited.
- Such solicited requests may be considered evidence of a firm’s intent that a drug or medical device be used for a use other than that specifically approved or cleared by FDA.
- *Example:* A firm’s sales representative mentions a use of a product that is not reflected in the product’s approved labeling and invites a health care professional to request more information. Resulting requests would be considered solicited requests.
- *Example:* A representative of a firm, such as a medical science liaison or paid speaker (e.g., key opinion leader), presents off-label use data at a company-sponsored promotional event (e.g., a dinner) and attendees then ask or submit requests for more information, these requests would be considered solicited requests.

# Responding to “Unsolicited Requests” for Off-Label Information

- Non-public Unsolicited Requests

- A non-public unsolicited request is an unsolicited request that is directed privately to a firm using a one-on-one communication approach.
- *Example:* An individual calls or e-mails the medical information staff at a firm seeking information about an off-label use. In this case, neither the request nor the response would be visible to the public.

- Public Unsolicited Requests

- A public unsolicited request is an unsolicited request made in a public forum, whether directed to a firm specifically or to a forum at large.
- *Example:* During a live presentation, an individual asks a question, directed to a firm’s representative but heard by other attendees, regarding off-label use of a specific product. This request is a public request. Similarly, a response by the firm that is conveyed to the same audience as the original question would be considered a *public response*.

# Responding to “Unsolicited Requests” for Off-Label Information

- Responding to a Non-Public Unsolicited Request:
  - Firms can respond to **unsolicited requests** for information about FDA-regulated medical products by providing truthful, balanced, non-misleading, and non promotional scientific or medical information that is responsive to the specific request, even if responding to the request requires a firm to provide information on unapproved or uncleared indications or conditions of use.
  - Regardless of whether the initial unsolicited request for off-label information was made in a non-public or public forum, a firm that chooses to respond should provide the final response containing the requested off-label information about its product only to the specific individual who requested the information as a private, one-on-one communication.
  - Information distributed in response to an unsolicited request should be tailored to answer only the specific question(s) asked.
  - Information should NOT be provided by sales and marketing personnel

# Responding to “Unsolicited Requests” for Off-Label Information

- Responding to a Public Unsolicited Request:
  - If a firm chooses to respond to public unsolicited requests for off-label information, the firm should respond only when the request pertains specifically to its own named product (and is not solely about a competitor’s product).
  - A firm’s public response to public unsolicited requests for off-label information about its named product should be limited to providing the firm’s contact information and should not include any off-label information.
  - The firm’s public response should convey that the question pertains to an unapproved or uncleared use of the product and state that individuals can contact the medical/scientific representative or medical affairs department with the specific unsolicited request to obtain more information.
  - The firm’s public response should provide specific contact information for the medical or scientific personnel or department (e.g., e-mail address, telephone number) so that individuals can follow up with the firm to obtain specific information about the off-label use of the product through a non-public, one-on-one communication.

# Why Legal Considerations Matter

# FDA Enforcement

# Compliance Steps (Before an Inspection)

- Establish procedures for preventive and correction actions (21 CFR 820.100)
- Establish a clearly document complaint procedure (21 CFR 820.198)
  - Be able to show what the complaints were and how they were resolved
- Establish a written medical device reporting (MDR) procedure (21 CFR 803.17)
- Establish procedures for nonconforming products (identify and segregate) (21 CFR 820.90)

# FDA Enforcement Options

- **Inspections**
- “Form 483” (After inspection)
- FDA Warning Letter
  - Cease and Desist
  - Requires response describing corrective action
- Seizure of misbranded products
- Injunctions
- Criminal Prosecution
  - Misdemeanor does not require proof of intent
  - Civil fines up to \$500,000
  - Potential for imprisonment

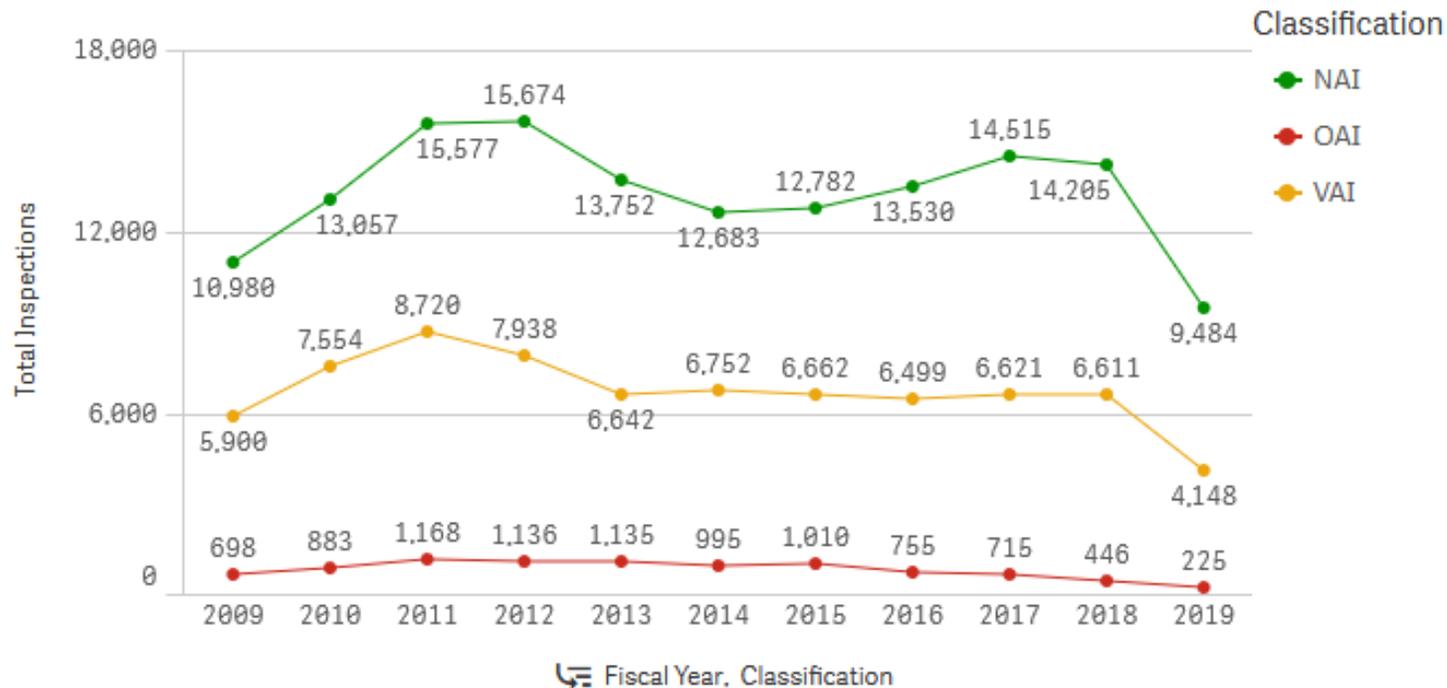
# FDA Inspections

- Filthy, putrid, or decomposed substance, or prepared, packed, or held under unsanitary conditions.
- Its container is composed, in whole or part, of any poisonous or deleterious substance;
- It contains, for the purposes of coloring only, an unsafe color additive;
- Its strength differs from, or its purity or quality falls below, that which it claims to represent.
- It is subject to a performance standard and does not comply with all the requirements of the standard;
- It is a Class III device and fails to conform to the requirements for an approved premarket approval application or a notice of completion of a product development protocol;
- It is a banned device;
- Violation of good manufacturing practice requirements; or
- Failure to comply with an Investigational Device Exemption (IDE).

# Inspections

## Inspections Classification by Fiscal Year

Fiscal Years: 2009 - 2019

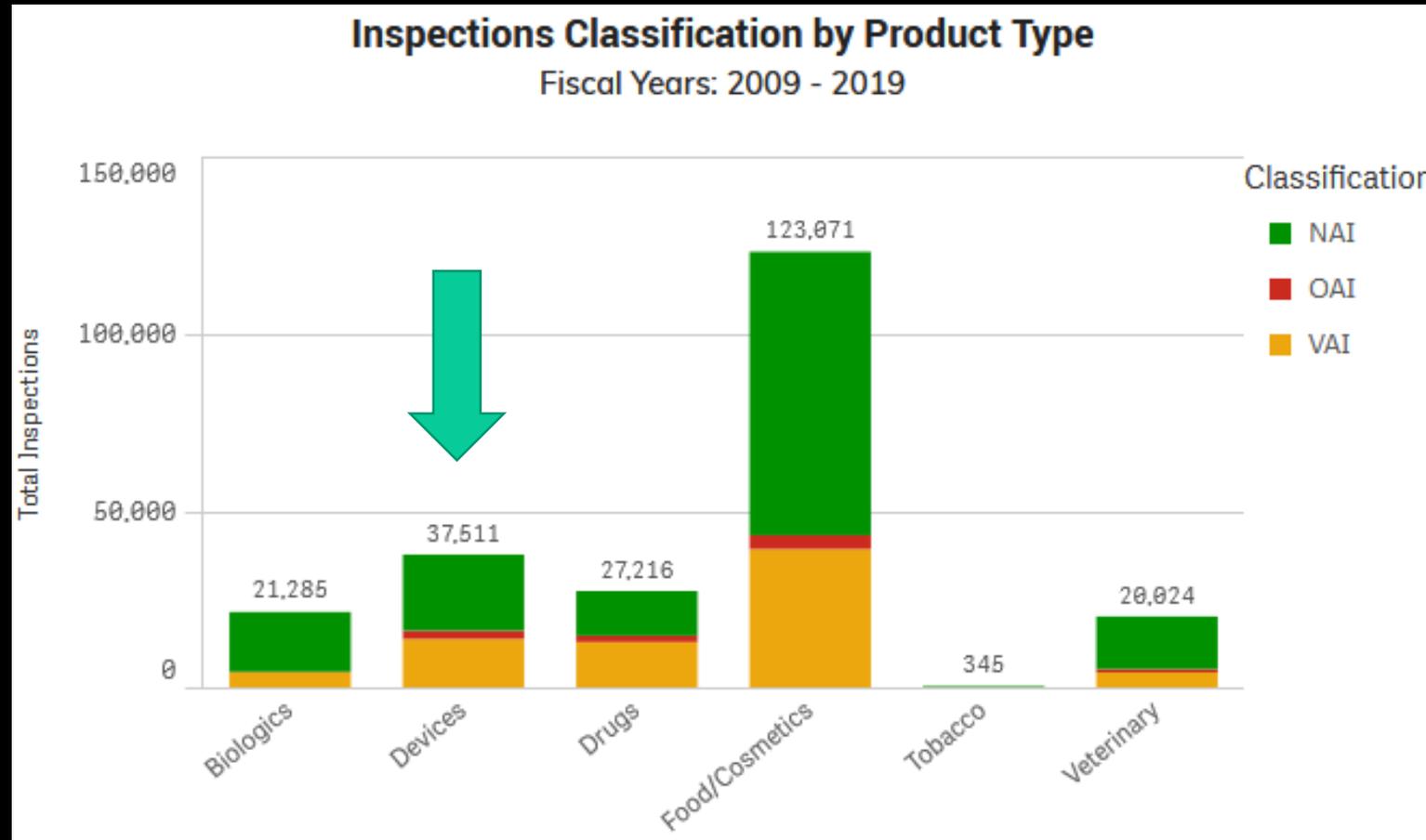


NAI – No action indicated

OAI – Official action indicated

VAI – Voluntary action indicated

# FDA Inspections by Product Type



# FDA Enforcement Options

- Inspections
- “Form 483” (After inspection)
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  - Cease and Desist
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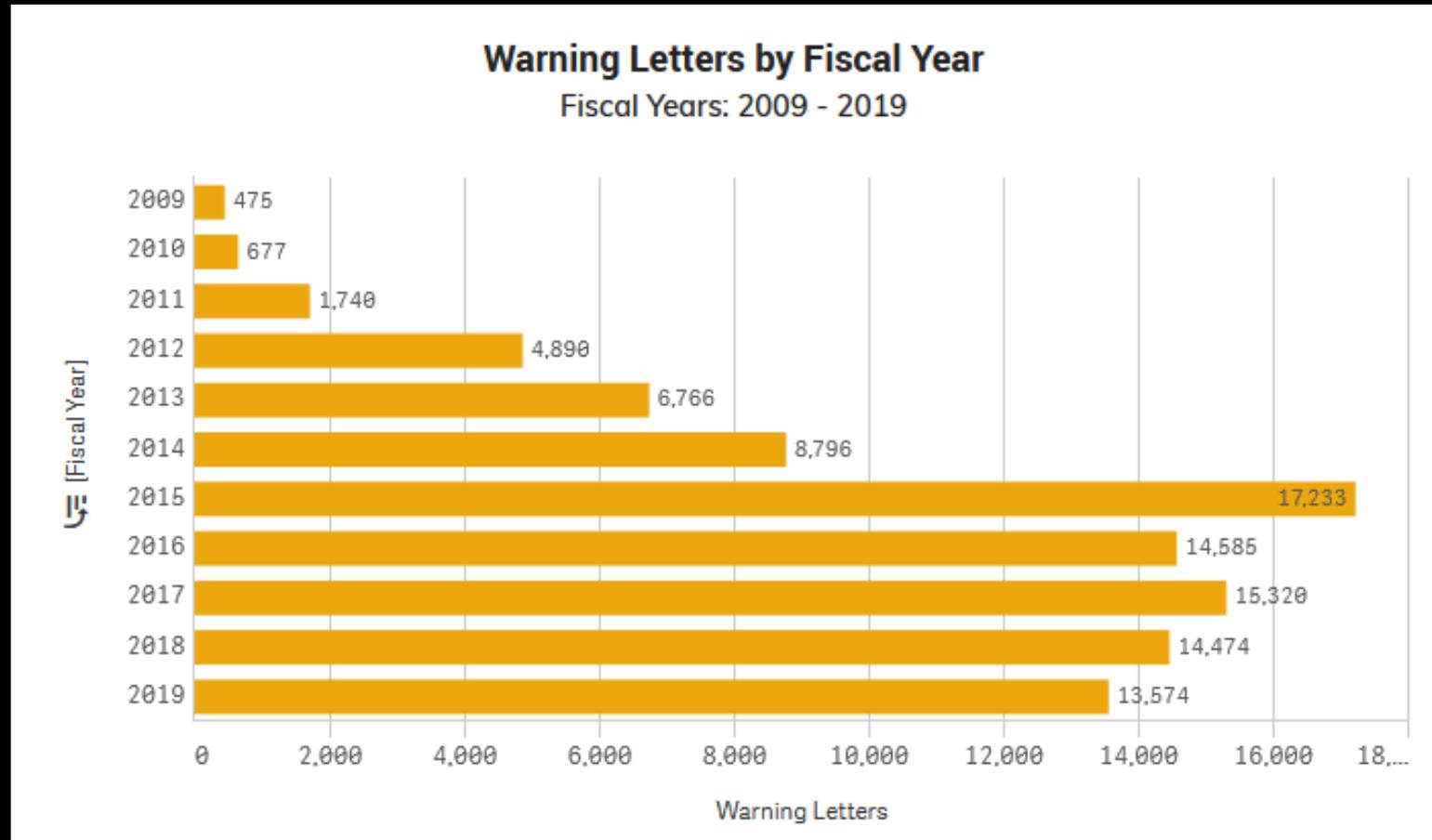
# FDA Form 483

- Issued After an Inspection
  - An FDA Form 483 is issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts.
  - At the conclusion of an inspection, the FDA Form 483 is presented and discussed with the company's senior management.
  - Companies are encouraged to respond to the FDA Form 483 in writing with their corrective action plan and then implement that corrective action plan expeditiously.
- <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions>

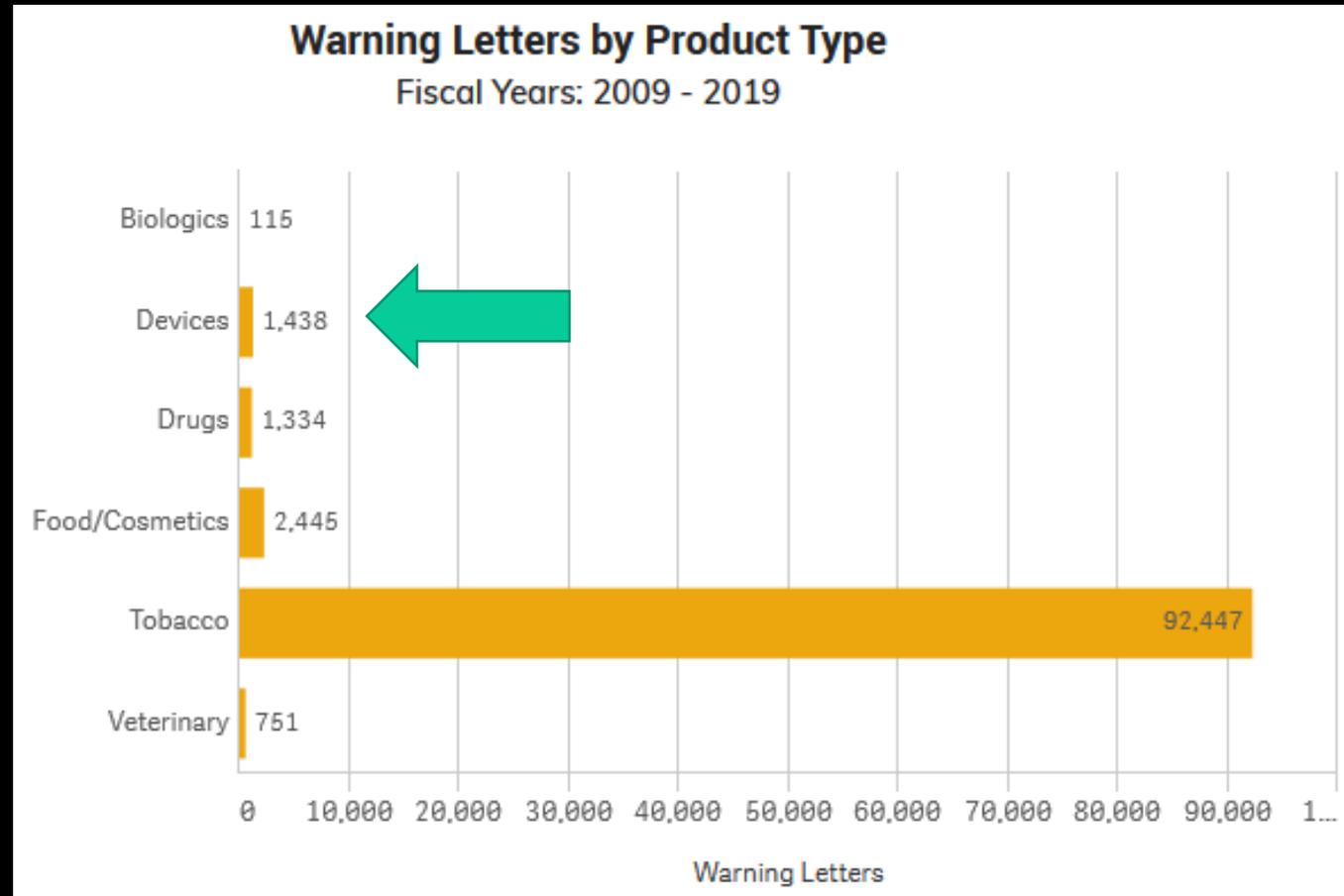
# FDA Enforcement Options

- “Form 483” (After inspection)
- Corrective and Preventative Action
- **FDA Warning Letter**
  - **Cease and Desist**
  - **Requires response describing corrective action**
- Seizure of misbranded products
- Injunctions
- Criminal Prosecution
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# FDA Warning Letters by Year



# FDA Warning Letters by Product Type



# Consumer Enforcement

# Consumer Civil Action for Product Liability

## STRICT LIABILITY

One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused to the ultimate user or consumer, or to his property, if

- (a) the seller is engaged in the business of selling such a product and
- (b) it is expected to and does reach the user or consumer without substantial change in the condition in which it is sold.

The rules apply although (a) the seller has exercised all possible care in the preparation and sale of his product, and (b) the user or consumer has not bought the product from or entered into any contractual relation with the seller.

# Consumer Civil Action for Deceptive Advertising

- **FTC: “Truth In Advertising.”**
  - When consumers see or hear an advertisement, whether it’s on the Internet, radio or television, or anywhere else, federal law says that ad must be truthful, not misleading, and, when appropriate, backed by scientific evidence.”
  - Advertising that makes the purchaser believe that the product or service they are buying performs better than it actually does.
- **Misleading by Omission.** Claims may be true, but the you do not include information that a reasonable person would consider relevant.
- **Caution with Price Advertising**
- **Under Promise – Over Deliver!**

# How to Safely Market and Advertise

# Don't Draw Attention and Don't Mislead!

- Know What the Label Says
  - Approved Uses
  - Approved Methods
- Make Sure Sales Staff Knows What the Label Says
- Keep Marketing and Promotion “general” and not “specific” if you are veering away from the precise language in the label (approved uses)
- Don't advise doctors on off-label use or procedures beyond that it is up to the discretion of the doctor
- Don't make promises about results

# If You Are Inspected or Receive a Notice

- Don't panic! Cooperate.
- Do NOT ignore any FDA notice, respond promptly
- Do NOT “lose” (destroy) any records
  - Consider backing up media and email immediately
- Make notes to yourself, labeled “For Attorney” because your memory will fade
  - Retain an attorney to interview any relevant parties/witnesses to retain privilege
- Contact your insurance
  - If insured, they will appoint an attorney
  - If not insured, seek legal counsel before any response to the complainant or FDA

# Questions?

The FDA and Off-Label Use  
Of Medical Devices

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