Introduction to FDA for Health Care Providers: Opportunities and Obligations when Providers Collaborate with the Life Sciences Industry

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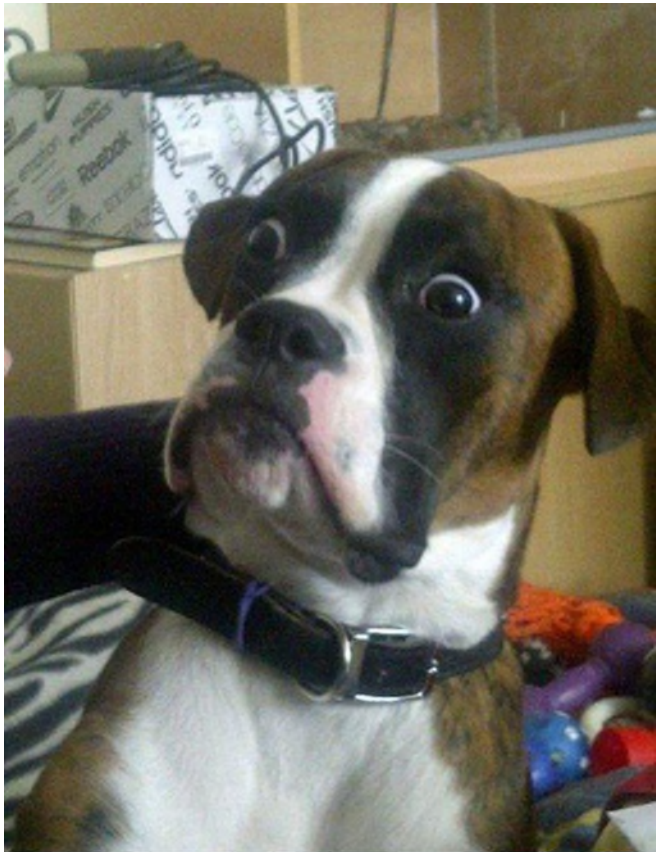
Agenda

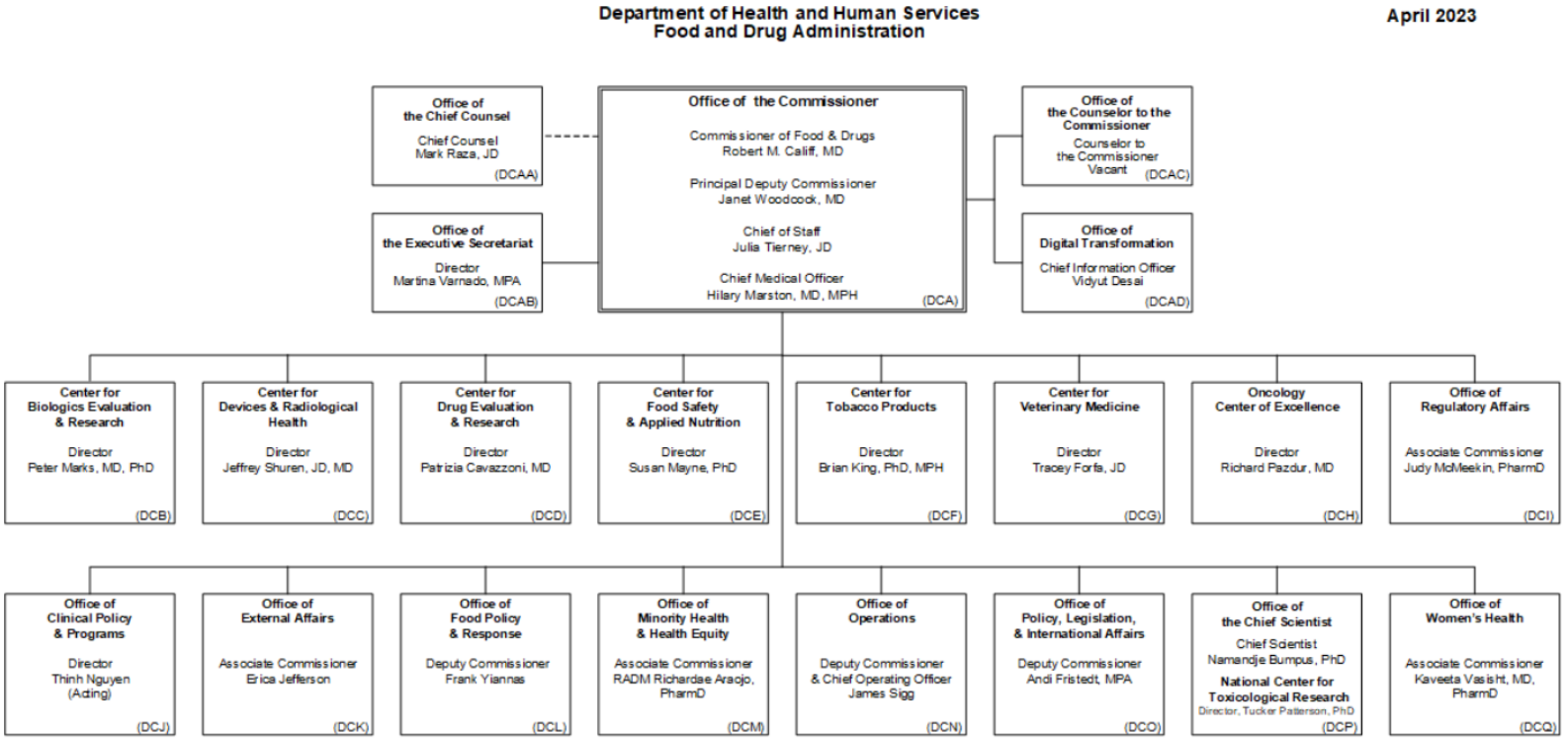
- Overview of FDA: How is it organized, what does it do and what doesn't it do?
- What kinds of FDA issues do health care providers generally confront?
- Q: How to try and cover the vast array of FDA requirements in less than 60 minutes! A: Focus on select examples: 3D printing of medical devices, lab developed tests and clinical trials and what FDA requirements in those areas might mean for providers
- Touch on some of the foundational health care regulatory issues that arise in arrangements between providers and life sciences industry
- All as told through cute and sort of surprised looking animals



FDA Overview and Organization

- FDA functions as both a consumer protection agency and regulatory agency
- Agency within HHS consisting of 9 Center-level organizations and 13 Headquarter Offices:
  - Center for Biologics Evaluation and Research
  - Center for Devices and Radiological Health
  - Center for Drug Evaluation and Research
  - Center for Food Safety and Applied Nutrition
  - Center for Tobacco Products
  - Center for Veterinary Medicine
  - National Center for Toxicological Research
  - Office of Regulatory Affairs
  - Office of Operations
- Very large and very smart: in 2018, FDA had approximately 18,000 FTEs (11,000 science degreed individuals)

FDA Overview and Organization



Key FDA Centers in Health Care

- Scope of FDA regulation includes:
  - Biologics Evaluation and Research—regulates biological products for human use under applicable federal laws, including the Public Health Service Act and the Federal FD&C Act.
  - Devices and Radiological Health—oversees medical devices and radiology producing products, primarily under the Medical Device Amendments to the FD&C Act; manages regulatory pathways for devices; responsible for premarket approval, as well as oversight of the manufacturing, performance and safety of medical devices.
  - Drug Evaluation and Research—regulates over-the-counter and prescription drugs, including generics and items made for human use such as toothpaste, deodorant and sunscreen.

Background: Important Points in FDA Legislative History

- 1906 Pure Food and Drug Act
  - Have you read The Jungle?
- 1938 Federal Food, Drug and Cosmetic Act
  - Passed after legally marketed toxic elixir killed 107 people
  - FD&C Act overhauled public health system, authorizing FDA to demand evidence of safety for new drugs
- 1962 Drug Effectiveness Amendments
  - Strengthened rules for drug safety and required manufacturers to prove drugs' effectiveness
- 1968 Radiation Control for Health and Safety Act
- 1976 Medical Device Amendments
  - Arose from US Senate study that faulty devices killed 731 people and injured 10,000. Applied safety and effectiveness standards to devices.

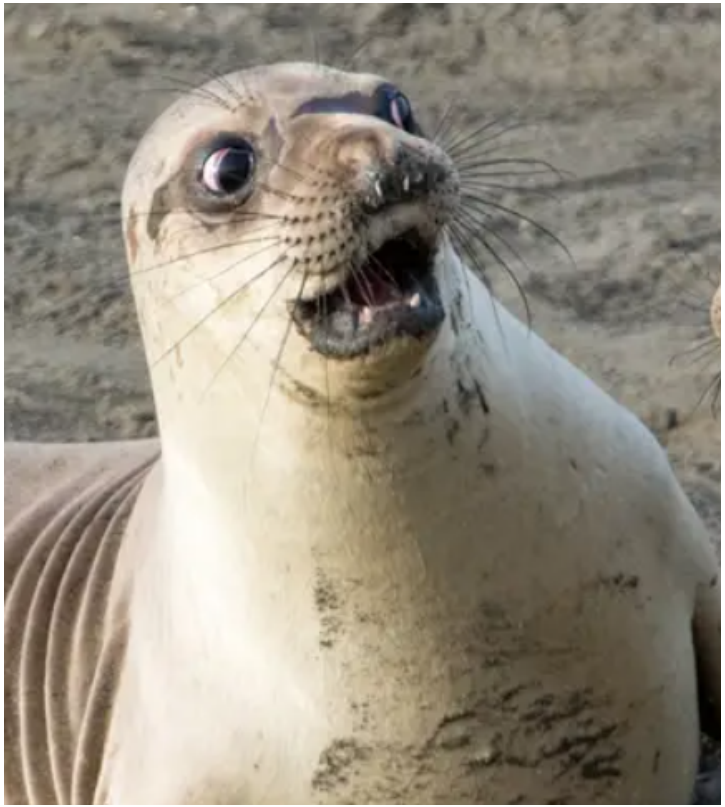
What Does FDA Regulate?

- Scope of FDA regulation includes
  - Drugs (prescription drugs, both brand-name and generic)
  - Medical devices (e.g., simple items like tongue depressors and bedpans; complex technologies such as heart pacemakers; dental devices, surgical implants and prosthetics)
  - Biologics (vaccines for humans, blood and blood products, cellular and gene therapy products, tissue and tissue products, allergenics)
  - Foods (e.g., dietary supplements, bottled water, food additives, infant formulas)
  - Electronic products that generate radiation (e.g., x-ray equipment, ultrasonic therapy equipment, laser products, microwave ovens, sunlamps)
  - Veterinary products (e.g., livestock feeds, pet foods, veterinary drugs and devices)
  - Cosmetics (e.g., skin moisturizers and cleansers, nail polish and perfume)
  - Tobacco products (cigarettes, smokeless tobacco, cigars, e-cigarettes)

What is a “Medical Device”?

- The term “device” … means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is –
  - recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
  - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.
- Examples: tongue depressors, hospital gowns, contact lenses, wheelchairs, programmable pacemakers and robotic surgical systems, pregnancy tests, blood glucose monitors, ultrasound machines, X-ray machines, medical lasers, smart watch that monitors heart rhythm and mobile apps that provide therapy for mood disorders.

What Does FDA Do?



- Approves new drugs and biological products
- Applies risk-based, tiered approach for regulating medical devices for human use
- Applies risk-based approach for human cells and tissues
- Reviews drugs, devices and biological products for safety, effectiveness and quality
- Inspects manufacturing facilities to help ensure product quality
- Conducts surveillance of products currently available on the market to mitigate risks to patients
- Takes action to remove products from the market

What Does FDA Not Do?

- Approve compounding pharmacies / compounded pharmaceuticals
- Approve health care facilities, providers, clinical labs
  - Exceptions exist
  - And the curious case of “Lab Developed Tests”
- Approve medical foods (enteral nutrition)
- Approve dietary supplements
- Dictate medical practice, medical services, the price of medical products or whether government or commercial payors reimburse services / products
- Develop medical products
- Approve medical product companies (FDA reviews and approves medical products for intended uses)

Where Does FDA Regulation Sit?

		Part / Section
▼ **Title 21**	Food and Drugs	
▼ **Chapter I**	Food and Drug Administration, Department of Health and Human Services	1 – 1299
Subchapter A	General	1 – 99
Subchapter B	Food for Human Consumption	100 – 199
Subchapter C	Drugs: General	200 – 299
Subchapter D	Drugs for Human Use	300 – 499
Subchapter E	Animal Drugs, Feeds, and Related Products	500 – 599
Subchapter F	Biologics	600 – 680
Subchapter G	Cosmetics	700 – 799
Subchapter H	Medical Devices	800 – 898
Subchapter I	Mammography Quality Standards Act	900
Subchapter J	Radiological Health	1000 – 1040
Subchapter K	Tobacco Products	1100 – 1150
Subchapter L	Regulations Under Certain Other Acts Administered by the Food and Drug Administration	1210 – 1299

Application of FDA Principles to Providers

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Depending on Context, Providers Might Feel Like This

Access to Investigational Devices: Options

- Clinical Trials (will come back to this)
- Emergency Use
  - Deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Deviation must be reported to FDA within 5-working days after the sponsor learns of it.
- Treatment Use
  - Option that recognizes it may be appropriate during the clinical trial or prior to final action on the marketing application, to use an investigational device in the treatment of patients not in the trial under the provisions of a treatment investigational device exemption (IDE).
  - FDA will consider the use of an investigational device under a treatment IDE if:
    - Device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
    - No comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;
    - Device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and
    - Sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence. Application must be made to FDA for treatment use.

Access to Investigational Devices: Compassionate Use

- Expanded Access (EA) (a/k/a compassionate use) started in the 1990s as a method for patients to access investigational drugs to treat HIV if they had exhausted all approved treatment options and did not qualify for a clinical trial.
- FDA has made improvements over the years, streamlining and improving the process by which patients can access a drug through an application (Form FDA 3926). EA requires the physician to complete and submit the form that is then reviewed and approved by an IRB.
- Physician treating the patient seeking EA must first determine there are no available clinical trials for the patient and that their condition qualifies as serious.
- Physician must reach out to the manufacturer of the investigational product and file paperwork with the FDA and IRB. IRB and FDA must approve the request. If granted for the individual patient, the EA may be within an existing investigational new drug application (IND) protocol or a single patient protocol.

Access to Investigational Devices: Right to Try

- Federal Right to Try Act was passed in 2018 to create an additional pathway for patients to access investigational, non-FDA approved drugs or biological products.
- Right to Try (“RTT”) is similar to EA as the patient must have a serious condition and not be eligible for a clinical trial.
- Process of approval completely bypasses the FDA and instead lies directly with the manufacturer or sponsor of the investigational product.
- Permits direct access to investigational drugs that are not yet approved by the FDA, under certain circumstances. Drug manufacturers or sponsors may decide they will not provide an investigational drug for use outside of a clinical trial because of supply issues or the patient's clinical presentation. May also refuse to provide access for no reason at all.

Access to Investigational Devices: Right to Try

- Right to Try (cont.)
  - For a patient to request use of an investigational drug through RTT, it must have passed through Phase I Clinical Trials.
    - Drugs that have passed this process are known as "eligible investigational drugs."
  - Providers who wish to assist a patient in accessing an investigational drug consult with the sponsor of the drug or biological product, as they are in the best position to provide information about whether it meets criteria and is eligible under the Act.
  - If the investigational drug is determined to be an eligible investigational drug, the manufacturer or sponsor has approved access, and the provider has certified that the patient has a serious disease or condition, then the patient may be granted access to the drug.

Expanded Access v. Right to Try

- Expanded Access
- Access – access to investigational products when clinical trials inaccessible
- Risk – may not be effective
- Process – Providers submit requests via Form FDA 3926 (30-day waiting period)
- Approval – Physician and manufacturer; then IRB and FDA
- Oversight – IRB / FDA
- Reimbursement – Govt. & commercial payors not required to cover; manufacturers cannot profit; patients may be required to pay for IRB costs

- Right to Try
- Access – same, but product must have completed / in ongoing clinical trial or in development
- Risk – same
- Process – Providers work directly with manufacturers
- Approval – Physician and manufacturer
- Oversight – Physician / manufacturer
- Reimbursement – Govt. & commercial payors not required to cover; manufacturers cannot profit from unapproved treatments

Other Ways Providers Become Subject to Direct FDA Regulation

- Mammography suppliers (diagnostic or screening)
  - Medicare will reimburse diagnostic and screening mammograms only if performed by supplier of diagnostic mammography/supplier of screening mammography.
  - Requires meeting Mammography Quality Standards Act ("MQSA"). MQSA requires that mammography facilities must be FDA-certified.
  - FDA provides CMS with list of all facilities that have been issued certificates to provide mammography services.
- Dental Labs
  - May be exempt from FDA registration / listing requirements under specific exception
  - Remain subject to QSR
- Orthotic & prosthetic facilities
  - Exceptions to registration / listing requirements may be available
  - Remain subject to QSR

Clinical Trial Arrangements

- What is a clinical trial?
- Who are the typical parties?
  - Subject—individuals who participate in clinical trials. Many people participate because the standard treatment options have nor worked.
  - Sponsor—party that initiates, funds and is responsible overall for the clinical trial but does not actually conduct the investigation.
  - Investigator—party that actually carries out the clinical trial pursuant to the protocol.
  - IRB—board, committee or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. Primary purpose of the IRB is to assure the protection of the rights and welfare of the human subjects.
- Significant Risk Studies v. Nonsignificant Risk Studies v. Exempt Studies

Clinical Trial Arrangements: Investigator-Sponsored

- Investigator-sponsored clinical trials:
  - Investigator has dual responsibilities: both initiates and conducts the investigation and serves as the party under whose immediate direction the investigational drug / investigational device is administered, dispensed or used
  - Requirements that apply vary based on a number of factors—for example, whether drugs or devices are at issue. E.g., if drugs involved:
    - If a sponsor-investigator determines that an IND needs to be submitted to the FDA, they would be the party that acquires the relevant information for the IND related to the proposed trial. Would be responsible for complying with Content and Format regulation
      - Addressing things like table of contents, introductory statement and general investigational plan, investigator's brochure, protocols, chemistry, manufacturing and control information, pharmacology and toxicology information and other requirements
    - Responsible for Form FDA 1571
      - Documents sponsor-investigator's agreement to refrain from beginning trial until 30 days after FDA receives the IND (or unless the sponsor-investigator receives earlier notification from the FDA that the trial may begin), to refrain from beginning or continuing a trial covered by the IND if that trial is placed on clinical hold, to ensure that an IRB in compliance with FDA regulations will be responsible for the initial and continuing review and approval of each proposed trial, and to conduct the trial in accordance with all other applicable regulations.

Clinical Trial Arrangements: Investigator-Sponsored (cont.)

- Sponsor-investigators conducting trials under an IND must comply with both the sponsor and investigator responsibilities specified in 21 C.F.R. parts 312, 50, and 56. This includes:
  - Good Clinical Practice, including human subject protection and IRB review and approval.
    - Good Clinical Practice ("GCP") includes human subject protection as afforded by adherence to requirements for review and approval of the trial by an IRB and requirements to obtain informed consent from each clinical trial subject. Sponsor-investigators must conduct trials in compliance with FDA regulations about the protection of human subjects and about IRB review and approval of studies.
  - Sponsor-investigators are responsible for ensuring proper monitoring of the investigation.
  - Compliance with restrictions on promotion of, or charging for, an investigational drug. Promoting the investigational drug is not permitted. Charging for the investigational drug is only permitted in rare circumstances, and then only with prior written approval by the FDA.

Clinical Trial Arrangements: Investigator-Sponsored (cont.)

- Sponsor-investigators obligations (cont.):
  - Maintain adequate and accurate case histories, adequate records showing the receipt, shipment, or other disposition of the investigational drugs.
  - Various notification requirements, including:
    - Notifying FDA of any unexpected fatal or life threatening suspected adverse reaction as soon as possible (no later than 7 calendar days after receipt of the information).
    - Notify FDA (and sponsors must notify all participating investigators) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible (no later than 15 calendar days after the sponsor determines that the information qualifies for reporting).
    - Promptly notifying the IRB of all unanticipated problems involving risk to human subjects or others.

Clinical Trial Arrangements: Investigator-Sponsored (cont.)

- Sponsor-investigators obligations (cont.):
  - Within 60 days of the anniversary date that an IND went into effect, must submit a brief annual report of the progress of the trial. Report must contain certain information:
    - Individual trial progress (i.e., enrollment, dropouts) with results, if the trial has been completed or if interim results are known;
    - Summary showing the most frequent and most serious adverse events by body system;
    - Summary of all IND safety reports submitted during the previous year;
    - List of subjects who dropped out because of adverse events / description of adverse events;
    - New information regarding the investigational drug's actions (e.g., dose response), completed nonclinical studies, and any CMC changes, if available;
    - General investigational plan for the coming year.

Clinical Trial Arrangements: Registration

- FDA Amendments Act of 2007 requires that the “Responsible Party” for certain clinical trials to register with, and submit the results of some trials to, the ClinicalTrials.gov databank.
- Registration within 21 days after first subject enrolls
- Registration required for “applicable” clinical trials, such as:
  - Investigational New Drug Application (IND)
  - New Clinical Protocol Submitted to an IND
  - New Drug Application (NDA)
  - Efficacy Supplement to an Approved NDA
  - Biologics License Application (BLA)
  - Efficacy Supplement to an Approved BLA
  - Abbreviated New Drug Application (ANDA)
  - Premarket Approval Application (PMA)
  - PMA Panel Track Supplement
  - Humanitarian Device Exemption (HDE)
  - 510(k) submissions that refer to, relate to, or include information on a clinical trial

Clinical Trial Arrangements: Consent and Confidentiality

- Several frameworks can apply:
  - Research on drugs, devices, biologics subject to FDA requirements (21 C.F.R. Parts 50, 56).
  - Health care providers subject to HIPAA (45 C.F.R. Parts 160—164) and state law as relates to use of patient information for research.
  - HHS' Common Rule (45 C.F.R. Part 46) applies to research conducted with federal funds or conducted, supported or otherwise subject to regulation by federal agencies
- Many changes in regulatory frameworks in recent years:
  - 21st Century Cures Act mandated HHS revise Common Rule. Final rule published in Jan. 2017 (effective in 2018).
  - FDA issued proposed regulations in Sept. 2022 (comment period through Nov. 28, 2022)
  - Intended to "harmonize" FDA and Common Rule requirements. Would add new informed consent elements and expectations on how information is presented / organized.

Clinical Trial Arrangements: Informed Consent

- Investigators are not permitted to involve human beings in research subject to the Protection of Human Subject regulations without obtaining the legally effective informed consent of the subject (or his / her legally authorized representative).
- No informed consent may include exculpatory language through which the subject may appear to waive any of the subject's legal rights or release, or appear to release, the investigator, sponsor, institution or agents from liability for negligence.
- Studies that are subject to FDA regulations should have informed consent that:
  - Meets requirements of 21 C.F.R. 50.20
  - Contains the 8 basic elements of 21 C.F.R. 50.25(a)
  - Contains each of the 6 elements of 21 C.F.R. 50.25(b) appropriate to the study

Basic Elements of Informed Consent

- Include the following:
  - Statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
  - Description of any reasonably foreseeable risks or discomforts to the subject.
  - Any benefits to the subject or to others which may reasonably be expected from the research.
  - Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
  - Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that FDA may inspect the records.
  - For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
  - Explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
  - Statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Clinical Trial Arrangements: Informed Consent (cont.)

- Additional elements—When appropriate, one or more of the following elements of information shall also be provided to each subject:
  - Statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
  - Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
  - Any additional costs to the subject that may result from participation in the research.
  - The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
  - Statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
  - Approximate number of subjects involved in the study.

Clinical Trial Arrangements: Informed Consent (cont.)

- HHS Policy for Protection of Human Research Subjects (2018 changes).
  - Significant revamping of numerous Common Rule requirements, not just informed consent (45 C.F.R. 46.101—46.124)
  - Informed consent regulations include 46.116 (general requirements for informed consent) and 46.117 (documentation of informed consent).
  - Changes from prior version of Common Rule include:
    - Informed consent must give prospective subjects the information that a reasonable person would want to have in order to make an informed decision about whether to participate.
    - Information needs to be presented in sufficient detail and organized and presented in a way that facilitates an understanding of why one might, or might not, want to participate.
    - Key information about the study must be provided at the beginning.
    - One new element that has been added to the basic elements of informed consent (notice about whether participants' information or biospecimens collected as part of the current research might be stripped of identifiers and used for other research in the future).
    - Three new additional elements of informed consent. Only required if relevant to the study.
      - Notice about possible commercial profit
      - Notice about whether clinically relevant research results will be returned to the subjects
      - Notice about whether research activities will or might include whole genome sequencing

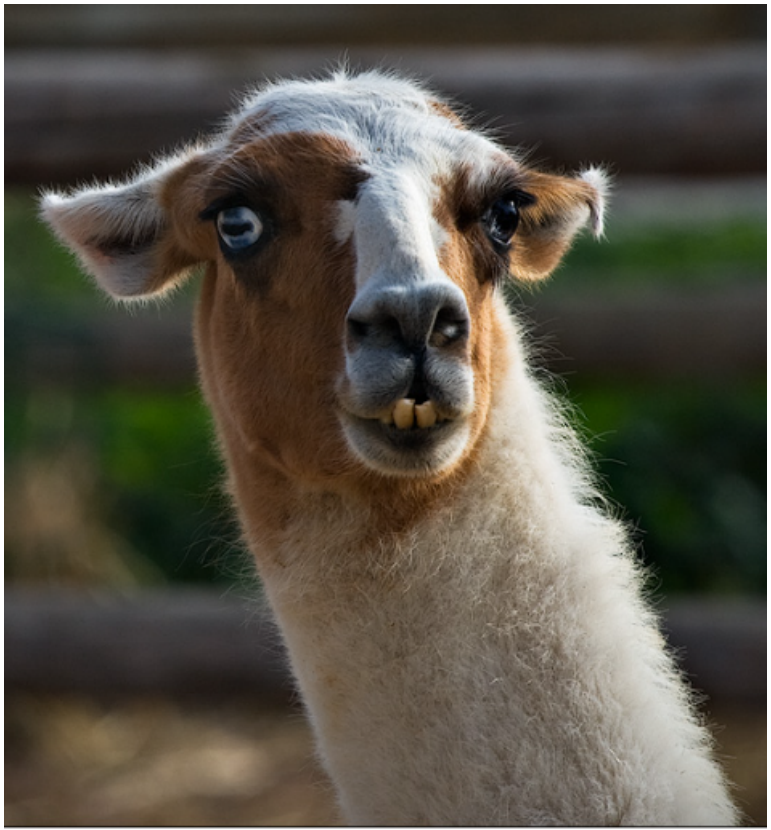
Clinical Trial Arrangements: HIPAA

- Various methods for covered entities to use / disclose PHI for research purposes. Options include:
  - Use or disclosure of “de-identified” information.
  - Individual authorization for the research.
  - Documentation that an alteration or waiver of research participants’ authorization for use/disclosure of information about them for research purposes has been approved by an IRB or a Privacy Board.
  - Representations from the researcher that the use or disclosure of the PHI is solely to prepare a research protocol or for similar purposes preparatory to research, that the researcher will not remove any PHI from the covered entity, and representation that PHI for which access is sought is necessary for the research purpose.
  - Research on PHI of decedents in certain circumstances.
  - Involving a “limited data set” and pursuant to a “data use agreement”

Clinical Trial Arrangements: Other HIPAA Considerations

- Research “accounting of disclosures”
- Covered entities may disclose PHI without an individual’s authorization to an entity or person subject to the jurisdiction of the FDA for purposes related to the quality, safety or effectiveness of a FDA regulated product or activity.
  - Qualifying purposes for disclosure include collecting or reporting adverse events, defects or problems with a device, or biological product deviations.
  - It also includes tracking FDA regulated products, enabling product recalls, repairs or replacement, or lookback, which includes locating and notifying individuals who have received products that have been recalled, withdrawn, or are the subject of a lookback and conducting post marketing surveillance.
- Disclosures under this public health exception are still subject to the minimum necessary standard.

Clinical Trial Arrangements: The Contract



- Clinical Trial Agreements
- Key Provisions
  - Intellectual property
  - Compensation
  - Publication rights
  - Indemnification
  - Privacy
- Other Provisions
  - Conduct of Trial
  - Reps / warranties
  - Monitoring / inspection
  - Subject injuries
  - Etc.

Clinical Trial Arrangements: Financial Conflicts

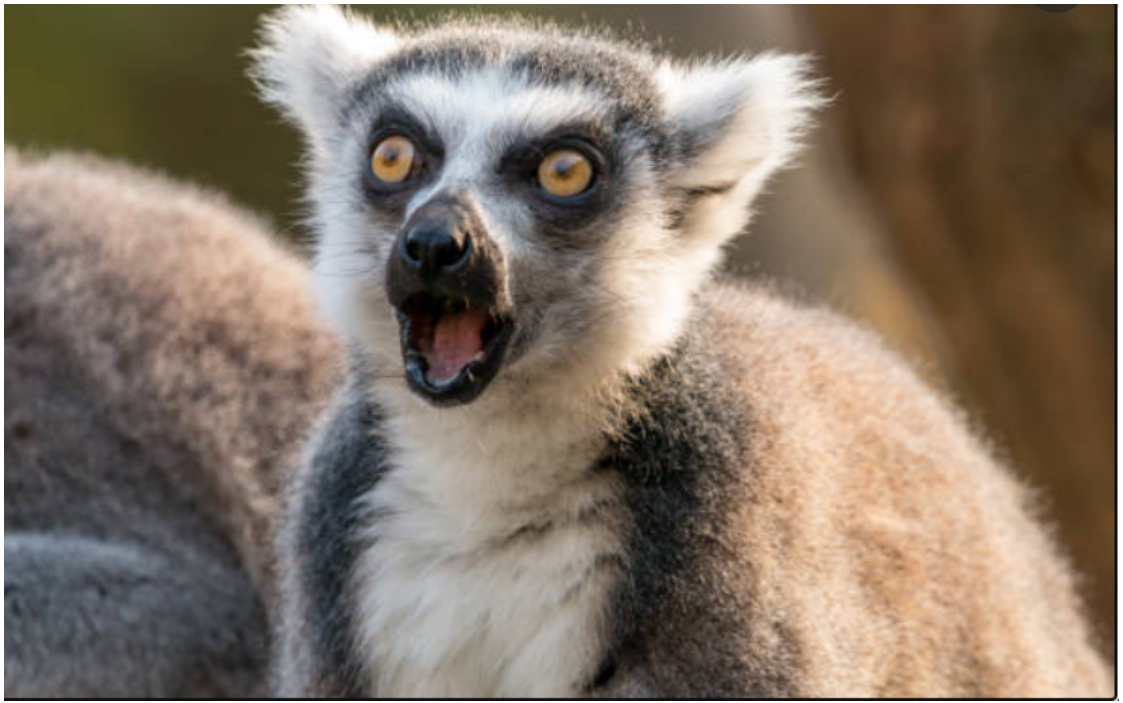
- Disclosure of financial interests—applicants who submit marketing application required to submit information concerning financial interests
- Applicants can certify to the absence of certain financial interests that could affect the reliability of data submitted to FDA, or to disclose those financial interests and arrangements to the agency and identify steps taken to minimize the potential for bias
- FDA can refuse to file marketing application that lacks appropriate disclosures.

Clinical Trial Arrangements: Financial Conflicts

- Financial interests that must be disclosed include:
  - Any compensation made to the investigator by any sponsor of the covered clinical study in which the value of compensation could be affected by study outcome.
  - A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.
  - Certain equity interests in sponsor of covered study
  - “Significant payments of other sorts”
- If FDA determines financial interests raise serious question regarding data integrity, can take steps including:
  - Initiating agency audits of the data derived from the clinical investigator in question;
  - Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect o the clinical investigator's data on the overall study outcome;
  - Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and
  - Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

Clinical Trial Arrangements

- FDA Approval (Drugs / Devices)
  - Applicable regulations outline a process governing the use of investigational new drugs or devices in clinical trials.
  - Investigational new drugs or devices for which an IND or investigational new device exemption (“IDE”) are in effect are exempt from otherwise applicable premarket approval requirements.
  - May be shipped lawfully for purposes of conducting clinical investigations of the drug or device



Clinical Trial Arrangements: Drugs

- INDs may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap.
- Three phases of an investigation:
  - Phase 1 includes the initial introduction of an investigational new drug into humans.
  - Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug.
  - Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information about effectiveness and safety necessary to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.
- The IDE regulation describes three types of device studies: significant risk (SR), nonsignificant risk (NSR), and exempt studies. IDE requirements depend on how devices are categorized within these studies.

Clinical Trial Arrangements: Level of Risk

- Significant Risk (SR) v. Nonsignificant Risk (NSR) v. Exempt
  - SR device means an investigational device that
    - Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
    - Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
    - Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
    - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
  - NSR device study is one that does not meet the definition of an SR device study.
  - Sponsors are responsible for making the initial risk determination and presenting it to the IRB. Unless FDA has already made a risk determination for the study, the IRB must review the sponsor's SR or NSR determination for every investigational medical device study reviewed and modify the determination if the IRB disagrees with the sponsor.
  - FDA is the final arbiter as to whether a device study is SR or NSR and makes the determination when an IDE is submitted to FDA or if asked by the sponsor, clinical investigator, or IRB.

Clinical Trial Arrangements: Level of Risk

- Differences between SR and NSR studies, include:
  - SR device studies must follow all the IDE regulations at 21 C.F.R. 812.
  - SR device studies must have an IDE application approved by FDA before they may proceed.
- Examples of SR devices include:
  - Epidural and Spinal Catheters,
  - Epidural and Spinal Needles,
  - Respiratory Ventilators,
  - Cardiac Assist Devices:
  - Artificial hearts,
  - ventricular assist devices,
  - Temporomandibular Joint (TMJ) Prostheses,
  - Injectable Collagen and Implantable Craniofacial Prostheses.

Clinical Trial Arrangements: Level of Risk

- NSR device studies must follow the abbreviated requirements at 21 C.F.R. 812.2(b).
- Requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion. However, there is no need to make progress reports or final reports to FDA.
- NSR device studies do not have to have an IDE application approved by FDA. Sponsors and IRBs do not have to report the IRB approval of an NSR device study to FDA. A NSR device study may start at the institution as soon as the IRB reviews and approves the study and without prior approval by FDA.

Clinical Trial Arrangements: Level of Risk

- Examples of NSR devices include:
  - contact lens solution,
  - denture repair kits and realigners,
  - digital mammography,
  - magnetic resonance imaging (MRI) Devices within FDA specified parameters,
  - Ob/Gyn diagnostic ultrasound within FDA approved parameters,
  - Ureteral Stents

Clinical Trial Arrangements: Level of Risk

- Certain devices are exempt from these requirements under 21 C.F.R. § 812.2
- For example, the following devices are exempt:
  - Devices undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
  - Diagnostic devices, if the sponsor complies with applicable requirements in § 809.10(c) and if the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk, (does not by design or intention introduce energy into a subject, and Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
  - Custom devices (as defined under § 812.3(b) unless device used to determine safety or effectiveness for commercial distribution.
  - Devices intended solely for veterinary use.

Application of FDA Principles to Providers: 3D Printing

Overview of 3D Printing and Medical Device Regulation

- Health care providers usually not subject to FDA obligations applicable to “manufacturers”
- What is 3D printing and how might it be used in health care delivery?
- Recall the definition of “medical device”
- Medical devices classified by risk into 3 categories
- Level of risk and regulatory controls attaches based on classification
- Class I
  - Lowest levels of control
  - Generally exempt from premarket review, unless Class I reserved
  - Subject to most postmarket control

Overview of Medical Device Regulation: Class II and III

- Class II
  - Moderate risk devices
  - Generally subject to premarket review process (510(k))
  - May be required to comply with certain special controls
- Class III devices
  - Highest risk devices, highest level of controls
  - Must comply with premarket approval requirements
  - Subject to postmarket general controls
  - May also be required to comply with conditions of approval from PMA approval letter

Establishment Registration

- Establishment registration
  - Owners / operators of “establishments” involved in the production and distribution of devices intended for commercial distribution are required to register their establishments.
  - What is an “establishment”?
    - Place f business under one management at one general physical location at which a device is manufactured, assembled or otherwise processed
  - Variety of domestic establishments to which requirement applies
    - Manufacturers, which are establishments that make by chemical, physical, biological or other procedures, any article that meets the definition of ‘device’” under the FD&C Act.
    - Kit assemblers (examples include firms that assemble first aid kits and general surgery trays).
    - Remanufacturers, which are establishments that “[p]rocesses, conditions, renovates, restores or does any other act to a finished device that significantly changes the finished device’s performance or safety specifications, or in any way changes the intended use”.

Establishment Registration (cont.)

- Additional examples of “Establishments” include:
  - Manufacturers of accessories or components that are packaged or labeled for commercial distribution for health-related purposes to an end user.
  - Custom device manufacturers.
  - Reprocessors of single use devices (meaning an establishment that performs remanufacturing operations on a single use device).
  - Number of other categories of businesses that also would require registration.
    - E.g., an entity that “Acts as an initial importer as defined in § 807.3(g)” (subject to limited exceptions

Establishment Registration & Exceptions

- Number of exceptions to registration requirement. For example:
  - Wholesale distributor exception exempts entities that distribute a device from the original place of manufacturer to the person who makes the final delivery or sale of the device to the ultimate consumer or user.
  - “Refurbishers or remarketers of used devices already in commercial distribution in the United States do not need to register.”
  - Distributors that distribute directly to consumers including “pharmacies, surgical supply outlets, or other similar retail establishments making final delivery or sale to the ultimate user…”
  - Providers may be able to qualify for the “practitioner exception” to the registration requirements.

Practitioner Exception

- Practitioner exception to registration requirements
  - Licensed practitioners, including physicians, who manufacture or otherwise alter devices solely for use in their own practice are exempt from the registration requirements
  - Scope of practitioner exception—is it just registration and listing?
- Have been enforcement actions where providers tried to assert that exemption from registration and listing meant that they were exempt from all FDA requirements.
  - In 1977 preamble, FDA explained that, “exemption from registration does not relieve [licensed providers] from their obligation to comply with other provisions of the [FDA Act] or regulations”.

Practitioner Exception (cont.)

- Strategies for interpretation?
- FDA commentary from related guidance: Policy for Device Software Functions and Mobile Medical Applications
- Gives examples of parties that would qualify as mobile medical app manufacturers and those who would not
  - Licensed practitioners, including physicians, dentists, and optometrists, who manufacture a mobile medical app or alter a mobile medical app solely for use in their professional practice and do not label or promote their mobile medical apps to be generally used by other licensed practitioners or other individuals.

Practitioner Exception (cont.)

- Gives examples of parties that would qualify as mobile medical app manufacturers and those who would not (cont.):
  - For example, if Dr. XYZ, a licensed practitioner, creates a mobile medical app called the "XYZ-recorder" that enables attaching an ECG electrode to a smartphone, and provides the "XYZ-recorder" to his/her patient to use it to record the patient's electrocardiographic readings for 24 hours, Dr. XYZ is not considered a mobile medical app manufacturer. If Dr. XYZ is in a group practice (including a telehealth network) and permits other physicians in the practice to provide the XYZ-recorder to their patients, Dr. XYZ is not considered a mobile medical apps manufacturer. However, if Dr. XYZ, the licensed practitioner, distributes the "XYZ-recorder" and, through labeling or promotion intends to make it generally available to or to be generally used by other physicians (or other specially qualified persons), Dr. XYZ would be considered a mobile medical app manufacturer.

Practitioner Exception (cont.)

- Enforcement under practitioner exception
  - Distinction between the classes of “person” who become exempt from registration / listing and the “devices” manufactured by those persons, which remain subject to the regulatory requirements that would otherwise apply.
  - E.g., 2011 enforcement action against the Judge Rotenberg Center, FDA asserted that while licensed practitioners can be exempt from the 510(k) requirements under certain circumstances, the exception only applies to specific classes of persons and does not exempt devices from applicable clearance and approval requirements.
  - E.g., in 2014 FDA responded to a citizen petition from an anaplastologist who failed to register her practice as an establishment. Anaplastologist argued that she was exempt from the registration requirements under the Practitioner Exception. FDA believed that because the anaplastologist distributes the devices to her own patients “for use outside of your medical practice” the provider could not qualify for the relevant registration exception (and the agency felt that none of the other exceptions were available either). FDA informed the provider she was required to register as a device manufacturer and to list the devices she manufactured in-house with the FDA.

Device Listing Requirements

- Device Listing
  - Most establishments that are required to register must also list their devices through the FDA's device listing process.
  - Must happen within 30 days of entering into any activity that requires registration.
- If health care provider is exempt from registration under the practitioner exception the provider would also be exempt from the listing requirements.
- If provider is not exempt under that exception (because, for example, it is sending manufactured devices outside of the provider)—or exempt for some other reason—it would be subject to the listing requirements.

Good Manufacturing Practices

- Background on GMP
- Quality System Regulations (QSR)
  - 21 C.F.R. Part 820
  - QSRs apply to manufacturers of finished devices.
  - A “manufacturer” is any person who designs, manufacturers, fabricates, assembles or processes a finished device.
  - A “finished device” is any device or accessory to any device that is suitable for use of capable of functioning, whether or not it is packaged, labeled or sterilized”.
  - Manufacturers of device components are exempted from the QSRs, but are encouraged to follow its requirements.
  - A “device component” is any raw material, substance, piece, part, software, firmware, labeling or assembly which is intended to be included as part of the finished, packaged and labeled device”.

Overview of QSR

- QSR has requirements in 14 different areas.
  - Quality System Requirements
    - Develop and maintain a quality system appropriate for the devices manufactured and that meets any requirements specified under the QSR
    - Specific standards applicable to standards
    - Requirements for periodic audits
  - Design Controls
    - Applicability depends on whether devices are Class I, II or III
    - Goal is to ensure manufacturers control activities so that design controls re met
    - All Class II and III devices are subject to design control QSRs
  - Purchasing Controls
    - Policies / procedures to ensure purchased products / services meet manufacturer's requirements
    - Must be met by vendors, suppliers, contractors, consultants
  - Document Controls
    - Must follow specific processes for document approval, modification, distribution

Overview of QSR (cont.)

- QSR (cont.)
  - Identification and Traceability
    - Must have processes for identifying product during all stages of receipt, production, distribution and installation.
    - Applies to manufacturers of surgical implants or life-supporting / life-sustaining medical devices where failure to use properly would be expected to result in significant injury.
    - Must use system that permits tracking devices by control number
  - Production and Process Controls
    - Developing, conducting, controlling and monitoring production processes to ensure that devices meet design specifications.
  - Acceptance Activities
    - Must establish / maintain procedures for acceptance activities (e.g., tests, inspections and other verification activities designed to ensure that the manufacturer's specified requirements are met) over incoming product.

Overview of QSR (cont.)

- QSR (cont.)
  - Nonconforming Product
    - Must have procedures for controlling product that does not meet specified requirements with the goal of ensuring that nonconforming materials are not used.
    - Among other things, these procedures must address identification, segregation and disposition of conforming product.
  - Corrective and Preventive Action
    - Must be procedures for implementing corrective and preventive actions to address suspected nonconformities.
  - Labeling and Packaging Controls
    - Must develop procedures to control their labeling activities, along with design of packaging / shipping containers to ensure the device's effectiveness is not harmed during processing, storage, handling or distribution.

Overview of QSR (cont.)

- QSR (cont.)
  - Records
    - Requirements apply to four different types of records: device master record (addressing device specifications, production process specifications, quality assurance procedures, packaging and labeling and installation, maintenance and servicing procedures); device history records; quality system records; and complaint files.
    - Timeframe for recordkeeping depends on expected life of device
  - Servicing
    - Manufacturers that service devices are required to have procedures for performing servicing and verifying that servicing meets specified requirements.
  - Statistical Techniques
    - Manufacturers that use statistical techniques must have procedures for identifying valid statistical techniques.

Medical Device Reporting

- Medical device reporting ("MDR") regulations require specific parties to report various device-related adverse events on a timely basis so as to prevent problems.
  - Began in 1984
  - 21 C.F.R. Part 803
- 1990 Safe Medical Devices Act ("SMDA") (regulations became effective in 1996)
  - Driven by postmarket safety concerns
  - Goal: to strengthen postmarket controls for devices
  - Added substantial postmarket authorities
  - Above and beyond what existed for drugs
- 1990 SMDA: added postmarket authorities
  - User Reporting
  - Reports of Removals and Corrections
  - Mandatory Recalls
  - Temporary Suspension of a PMA
  - Device Tracking

Medical Device Reporting Basic Facts

- Sources of safety concerns
  - Complaints to firms or FDA from hospitals, doctors, patients, consumers, competitors
  - FDA inspection results
  - FDA analysis of adverse event reports
  - Research and medical literature
  - Other governments
- Manufacturer and User Facility Device Experience (MAUDE) database
  - Contains all mandatory reports filed by manufacturers and importers from 8/96 to present; all mandatory user facility reports from 1991 to present and voluntary reports filed after 1993
- Enforcement authority
  - Inspections: JC / FDA
  - Civil injunction/criminal prosecution
    - Failure to report
    - False or misleading report
  - Monetary penalties ($15,000/$1,000,000)

Medical Device Reporting (cont.)

- Different requirements that apply depending on whether an organization is a “device user facility” or “device manufacturer”.
  - Reporting requirements more extensive for manufacturers
- The SMDA requires “User Facilities” to report incidents involving medical devices that are reasonably believed to have caused or contributed to the serious injury or death of a patient or employee (21 U.S.C. Section 360i (b) and 21 C.F.R. part 803)
- Definition of “User Facility”
  - Hospital
  - Ambulatory Surgery Center
  - Nursing Home
  - Outpatient Treatment Facility
  - Outpatient Diagnostic Facility
  - Not a Physician’s Office

Medical Device Reporting (cont.)

- FDA has created specific definitions that need to be used in applying the MDR requirements
  - For example, the terms “caused or contributed” and “serious injury”.
- SMDA’s definition of “serious injury”—an injury that is:
  - Life threatening;
  - Results in permanent impairment of a body function or permanent damage to a body structure; or
  - Necessitates medical or surgical intervention to preclude permanent damage or impairment
- Definition of “reasonably suggests”:
  - Any information such as professional, scientific, or medical facts and observations or opinions that a medical device has caused or may have caused or contributed to a reportable event. This includes but is not limited to:
    - Equipment malfunction/failure;
    - Improper design;
    - Malfunction error;
    - Manufacturer error;
    - Labeling error; and
    - User error

MDR: User Facility Responsibilities

- User facilities required to report suspected medical-device death to both FDA and manufacturer
- User facilities must report medical device-related serious injuries to manufacturer (or FDA if manufacturer is unknown)
- User facilities also required to submit annual reports

REPORTER	WHAT TO REPORT	REPORT FORM #	TO WHOM	WHEN
User Facility	Device-related Death	Form FDA 3500A	FDA & Manufacturer	Within 10 work days of becoming aware
User Facility	Device-related Serious injury	Form FDA 3500A	Manufacturer. FDA only if manufacturer unknown	Within 10 work days of becoming aware
User Facility	Annual summary of death & serious injury reports	Form FDA 3419	FDA	January 1 for the preceding year

MDR: Distributors

- “Distributor” defined:
  - Any person (other than the manufacturer or importer) who furthers the marketing of a device from the original place of manufacture to the person who makes final delivery or sale to the ultimate user, but who does not repackage or otherwise change the container, wrapper or labeling of the device or device package
- Distributors must
  - Maintain device compliance records, including records of incident reports reported to or generated by the distributor, and records of complaints received about devices it distributes; or
  - Report to a manufacturer or importer information about a potential device adulteration or misbranding that may result in the voluntary recall of a device by the manufacturer or importer.

MDR: Manufacturers / Importers

- Manufacturers and importers must:
  - Establish and maintain MDR files with information about adverse events and documentation of organizational deliberations and decisions made when notified of an issue and determining if an issue is serious enough to be reported to the FDA;
  - Make a report to FDA of any correction or removal of a medical device(s) if the correction or removal was initiated to reduce a risk to health posed by the device or to remedy a violation of the act caused by the device;
  - Initiate voluntary recall of a device when it determines that the device presents a risk of illness or injury because it is adulterated or misbranded; or
  - Comply with an FDA recall order when the FDA determines that the device may cause adverse health consequences or death and the manufacturer has not voluntarily recalled the device.

Corrections, Removals, Recalls

- Corrections and Removals
  - Various parties required to take certain actions in event devices do not perform as expected
  - Obligations include reporting, and maintaining reports, of adverse events, correction or removal of a device (for the purpose of repair, modification, adjustment, or inspection), or the recall of a device either voluntarily or by FDA order
  - Obligations depend on the role – manufacturer/importer or distributor – of the entity
- FDA regulations set forth specific definitions that govern the recall analysis, implementation and reporting process.
  - Exceptions from the reporting requirements that are intended to accommodate performance improvement, routine servicing and similar types of activities.
  - Recordkeeping requirements that apply to all corrections and removals and regardless of whether the correction or removal at issue gave rise to an actual report to FDA.

Tracking

- The Food and Drug Administration Modernization Act (FDAMA) requires that manufacturers, refurbishers, and remanufacturers track certain FDA-approved devices. Class II or III devices.
  - 21 C.F.R. Part 821
- FDA publishes specific list of devices that must be tracked by manufacturers. Tracking is intended to facilitate notification and recall in the event a device presents a serious risk to health that requires prompt attention.
- When they do apply, the tracking obligations are intended to help FDA facilitate the recall of a device where (1) failure of the device could lead to serious adverse health consequences or (2) where the device is implanted into the body. If tracking requirements apply, manufacturers must maintain certain information about the location of the device and the patient who uses the device.
- While the obligations to track are imposed primarily on manufacturers, manufacturers may use third parties to assist in the meeting any tracking obligations including by contract or other arrangement.

Tracking (cont.)

- Distributors are required to assist in the tracking of the device by providing specified information to the manufacturer so that that the manufacturer may meet its obligations.
  - Includes information about the movement of the device facilitated by the distributor and identifying information about the patient who uses the device.

V. Medical Devices Requiring Tracking

FDA has issued tracking orders to manufacturers of the following devices, listed in alphabetical order according to the product code – preferred name:

Product Code - Preferred Name	*Procode*
Aortic valve prosthesis, percutaneously delivered	NPT
Breast prosthesis, non-inflatable, internal, silicone gel filled	FTR
Defibrillator, auxiliary power supply (AC OR DC) for low energy DC defibrillator	MPD
Defibrillator, automated, external, wearable	MVK
Defibrillator, automatic, implantable, cardioverter, with cardiac resynchronization (CRT-D)	NIK
Defibrillator, DC, high energy (including paddles)	DRK

Labeling

- FDA regulations outline comprehensive guidelines for the labeling of medical devices.
- Generally, the label on a medical device must provide information identifying the manufacturer, packer, or distributor of the device; describe the intended use of the device; and include adequate directions for use of the device.
- Specific device labeling requirements vary depending on the intended use of a product and the customary conditions of purchase and use.
- Requirements that apply to the “label” (what is affixed to the actual container) and to “labeling” (additional written material that explains or supplements the product).

Labeling (cont.)

- Labeling obligations are likely to be the primary responsibility of the manufacturer
- Specific requirements apply to subsequent distributors that may require modification or supplemental notices on the device label.
  - E.g., where device not manufactured by the entity whose name appears on the label, the label shall be qualified by a phrase that reveals the connection such entity has with such device such as "Distributed by _____."
- Distribution of device that fails to meet the labeling requirements (or where the labeling has been altered or modified and no longer meets the labeling requirements) would subject a distributor to FDA enforcement action.
- Compliance issues can arise where provider procures products and then seeks to resell them
- Exceptions to labeling requirements may be available in some cases

Noncompliance and Penalties

- Variety of conduct can lead to penalties
  - E.g., failing to comply with MDR requirements, failure to file a 510(k) where required, interstate shipment of adulterated or misbranded devices, refusing to permit inspections, submitting false or misleading reports and numerous other types of conduct.
- Device adulteration
  - Device is treated as adulterated if there is or may be something wrong with it that makes or could make it unsafe or ineffective.
  - FD&C Act provides multiple examples of “adulteration” including:
    - Device includes any filthy, putrid, or decomposed substance,
    - It is prepared, packed, or held under unsanitary conditions, or
    - Its strength differs from, or its purity or quality falls below, that which it claims to represent.

Noncompliance and Penalties (cont.)

- If device is adulterated, is a violation of federal law to deliver, proffer, or introduce such a device into interstate commerce
  - First time violators may be subject to fines up to $1,000 and prison sentences up to one year.
  - Additional penalties ($10,000 fines and up to three years in prison) for subsequent convictions or convictions with the intent to defraud or mislead
- Misbranding of devices can occur in a variety of ways, including if the labeling is false or misleading. FD&C Act outlines numerous other ways misbranding can occur.
- Penalties can arise in a variety of ways, including as a result of inspections.
- Enforcement actions often begin with the issuance of a warning letter,
  - Communication explaining that FDA believes it has discovered one or more violations of the FD&C Act and informing the recipient that failure to address the matter within a (relatively short) specific time frame can result in an enforcement action (without further notice).
- Potential penalties for noncompliance with FDA requirements include product seizure, injunctions, criminal prosecution, civil penalties along with a range of other administrative actions.

Potential Regulatory Framework

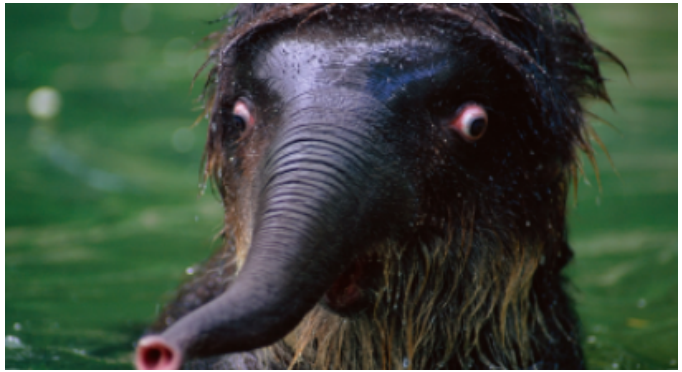
- Dec. 2021 “discussion paper”, 3D Printing Medical Devices at the Point of Care
- Not “guidance document”, but discussion paper outlining potential approach
- FDA describes 3 different approaches to regulation:
  - (i) where a health care facility uses a 3D medical device production system (“MDPS”), with the manufacturer of the MDPS assuming responsibility for compliance with FDA requirements;
  - (ii) co-location of a traditional manufacturer at or near the health care facility (with the manufacturer responsible for compliance with FDA requirements); or
  - (iii) a health care facility that “would not use an MDPS, and would not work with a traditional manufacturer to print devices”; rather, the “health care facility has chosen to engage in the activities of a traditional manufacturer” in the facility’s 3D printing site.

Potential Regulatory Framework

- Several examples given by FDA of how the approach being considered might apply:
  - Example 1—A health care facility's 3D printing facility already owns a 3D printer that is part of, and uses the same raw materials as specified by, a 510(k) cleared-MDPS manufactured by a traditional manufacturer for 3D printing of polymer-based cranioplasty plates made at the point of care. The 510(k)-cleared device includes or specifies in the labeling the validated software, materials, printer settings and directions for additional processing to be compatible with special locking screws.
  - Generally, in a situation like this, the responsibility for FDA compliance lies with the manufacturer of the MDPS, and the point of care 3D printing facility within the health care facility is the user of the MDPS.

Potential Regulatory Framework

- FDA Discussion Paper (cont.)
  - Example 2—a health care facility decides to 3D print patient matched titanium cranioplasty plates within their point of care 3D printing facility. In this situation, the point of care 3D printing facility within the health care facility would not work with an MDPS and would not work with a traditional manufacturer to 3D print devices. Rather, the health care facility has chosen to engage in the activities of a traditional manufacturer in their 3D printing facility.
  - As such, the health care facility would be responsible for complying with FDA requirements applicable to device manufacturers.



Potential Regulatory Framework

- FDA also considering excluding “very low risk devices” from regulation in this area.
  - Posed a number of questions to industry about how it might categorize some devices as “very low risk”, but it did not outline a proposed approach or any examples of what it had in mind.
- FDA will at some point likely be proposing guidance (in draft format, prior to finalization if that were to ever happen) related to how it would regulate 3D printing at the point of care.
  - Unknown how closely any approach will be to what is articulated in Discussion Paper
- In past, FDA has in the past issued various types of discussion materials intended to seek feedback from industry and ended up producing regulatory positions that are very different from the approach summarized in the relevant discussion document.

Lab Developed Tests (f/k/a “homebrew”)

What is a Lab Developed Test?

- One definition:
  - In vitro diagnostic test that is intended designed, manufactured and used within a single site CLIA-certified laboratory that meets the requirements for high complexity testing
- Compared to commercially marketed lab tests (manufactured by medical device companies and sold to providers)
  - Need to be cleared by FDA through premarket notification / premarket approval process
- 1976 Medical Device Amendments Act granted FDA jurisdiction over commercially distributed test kits as in-vitro diagnostic devices
- FDA has claimed that statute gives agency jurisdiction over LDTs
- Agency has historically exercised enforcement discretion over LDTs
- Some labs and various other parties have asserted LDTs are clinical services (not medical products) and thus not within scope of FDA authority

Why are LDTs Important?

- Often developed in response to the lack of an FDA cleared or approved assay, lack of available tests compatible with lab instrumentation or lack of tests that meet performance goals
  - As of Dec. 31, 2019 there were no FDA approved/cleared tests available that could detect or diagnose the active 2019-Novel Coronavirus (2019-nCov) clinical specimens in the United States.
- LDTs developed, validated and used for in house pathology and diagnostic purposes and are intended only for use by the lab that developed them.
- Labs may create necessary reagents themselves or purchase from vendors, but the tests are not to be sold to other labs, hospitals, doctors, etc.
- If tests developed and used as LDT are marketed in any way or distributed, FDA could consider it outside the scope of an LDT and regulate accordingly.

How Are LDTs Regulated?

- Potential role of CMS and FDA as relates to LDTs
  - CMS regulates quality of testing labs and analytical validity and ability to provide accurate / reliable testing results
  - FDA review includes analysis of clinical validity of tests, accuracy with which it identifies measures or predicts absence / presence of condition
- Regulation of LDTs?
  - 2014 Draft Guidance
  - 2017 FDA "Discussion Paper on Laboratory Developed Tests"
  - April 2019, FDA issues warning letter to Inova Genomics Laboratory for marketing genetic tests that have not been reviewed for safety / effectiveness
    - Tests claimed to predict patient responses to specific medications based on genetic variants, reducing side effects and other benefits
  - Follows Oct. 31, 2018 FDA Safety Communication discussing changing patient medication regimens based on genetic testing and making recommendations to providers and patients
- Previous legislative efforts (e.g., 2018's DAIA)
- FDA warning letters related to LDTs

LDTs & Covid-19

- HHS declaration of PHE triggered FDA authority under various sections of FD&C Act
- Sec. 564 allows FDA to grant “emergency use authorization” for medical products agency has not cleared / approved
- EUAs have been in use since 2009
- In Feb. 2020, FDA issued Policy for Coronavirus Disease-2019 During the Public Health Emergency detailing the process for obtaining EUAs for Covid-19 tests.
  - Seven editions of this guidance have been issued
  - Most recent edition is from Jan. 12, 2023 (renamed, Policy for Coronavirus Disease-2019 Tests (Revised))
- During PHE, hundreds of EUAs issued for diagnostic and serology or other immune response tests
- Importance of EUAs amplified issues around LDT regulation

LDTs & Covid-19

- FDA policy on EUAs for Covid-19 tests evolved during PHE and reflected changing landscape of pandemic
- Early versions of guidance created two policies (later expanded) for accelerating development of lab tests:
  - One leading to EUA
  - The other not leading to EUA where test was developed under authority of state in which lab resides and state takes responsibility for testing performed by state labs
  - Third policy was created for commercial manufacturers to more rapidly distribute diagnostics to labs for specimen testing after validation but while EUA application is being prepared for submission
  - Fourth policy created regarding serological testing
- Mar. 10, 2020 PREP Act immunity declaration for covered countermeasures, including EUA products
  - PREP Act immunity does not end at end of PHE.
  - Will continue to earlier of Oct. 1, 2024 or HHS revokes immunity

LDTs & Covid-19

- Aug. 2020 HHS published “Recession of Guidance and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests”
  - FDA would not require premarket review of LDTs absent notice and comment rulemaking
  - Change applied to all LDTs, not just Covid-19 tests
- HHS followed up with FAQs on LDTs
- Oct. 2020, FDA statement in town hall: no longer reviewing SARS-CoV-2 LDTs EUAs
- Nov. 2020, HHS directed to review voluntary EUA submissions for LDTs. Overflow to NCI
- FDA had FAQ on its website indicating it was “declining to review EUA requests for LDTs at this time”
- Guidance later updated indicating FDA has “hundreds of pre-EUA and EUA requests … under review” and receives new submissions daily. Reviewing requests “as quickly as we can”
- HHS (Aug. 2020) policy subsequently removed from website without public notice

LDTs & Covid-19

- Nov. 2021, HHS formally announced that it would withdraw previous policy that prevented FDA from requiring premarket review of LDTs absent formal rulemaking
  - "HHS no longer has a policy on LDTs that is separate from FDA's longstanding approach in this area"
- Nov. 2021, FDA released 5th version of Policy; addressed how HHS change affected review of LDTs
  - Newly offered Covid-19 tests (including LDTs) expected to have EUA or traditional authorization such as granted De Novo or 510(k) prior to clinical use
  - FDA to focus review on EUA requests for following tests
    - At-home / POC, with or without prescription that can be made in high volumes
    - Certain high-volume, lab-based molecular diagnostics that can detect multiple respiratory viruses at once
    - Certain lab-based / POC tests for fully quantitative antibody / neutralizing antibodies
    - Tests supported by certain agencies (e.g., NIH)

LDTs & Covid-19

- Jan. 2023 version of Policy (seventh edition)
- FDA intends to review EUA requests for a small subset of tests based on specific review priorities
  - Prioritize the review of EUA requests and supplemental EUA requests from experienced developers for diagnostic tests that are likely to have a significant public health benefit (e.g., employ innovative technology) or are likely to fulfill an unmet need (e.g., diagnosing infection with a new variant or subvariant
  - Review EUA requests from / supported by experienced US government stakeholders
- Confirmation of Nov. 15, 2021 change no longer applying policy on state authorization (of labs within the state to develop their own Covid-19 tests and perform testing) going forward
- Addresses distribution and offering of diagnostic and serology tests during FDA review
- FDA "believes that the number of EUA requests that fall withing FDA's current review priorities described in this guidance are likely limited and generally encourages developers to submit Covid-19 tests through traditional premarket review pathways".

LDTs & Covid-19

- End of PHE raised issue of what happens with various flexibilities
  - EUAs not directly affected by end of PHE (remain in effect for duration of relevant EUA declaration)
  - Termination of EUA declaration requires separate determination
  - When EUA declaration terminates, all EUAs issued under that declaration also terminate
- Dec. 2021, FDA issued two pieces of draft guidance intended to address potential end of PHE and implications for EUAs:
  - Transition Plan for Medical Devices Issued Emergency Use Authorizations During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency
  - Transition Plan for Medical Devices that Fall Within Enforcement Policies Issued During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency
- Transition plans address many items provided during PHE
- Both were open for comment through Mar. 23, 2022
- Final guidance released on Mar. 27, 2023. Final guidance largely consistent with drafts

Highlights of Transition Plan (EUA)

- Advance notice of termination of each EUA to be published in Federal Register 180 days before date on which EUA is terminated
- During period between EUA termination date and date of advance notice, manufacturers must continue to comply with terms of existing EUA
- At EUA termination date, EUA-authorized devices to be discontinued unless manufacturer has submitted marketing submission that has been accepted for substantive review. Ok if review still in process
- Commercial distribution may continue, but must stop if manufacturer receives negative decision (FDA final action), withdraws submission or fails to respond
- Manufacturers required to comply with general controls (e.g., QSR, MDR, establishment, listing; not necessary to comply with UDI)
- Allows exceptions to rule that normally requires manufacturers to dispose of devices after EUA termination date (where manufacturer does not intend to continue distribution)

Highlights of Transition Plan (EUA): Clinical Lab & LDTs

- FDA explained approach for categorizing IVDs (authorized under EUA) under CLIA will be based on marketing submission.
  - E.g., waived complexity, moderate complexity, high complexity
- Recommends submitting marketing application as soon as possible
- FDA will treat LDTs developed under EUA in response to Covid-19 the same as other LDTs

Highlights of Transition Plan (Devices)

- Addresses device guidance documents only intended to be in effect during PHE
- Applicable to certain lab devices (e.g., Remote Digital Pathology Devices, Modifications to FDA Cleared Molecular Influenza and RSV Tests)
- FDA outlined three-phase approach (occurring over 180-days) beginning on May 11, 2023
- Phase 1
  - Begins on 5/11/23. Manufacturers to follow adverse event reporting requirements (21 CFR Part 803), begin preparation of marketing submissions
- Phase 2
  - Begins 8/9/23. Before phase 2, manufacturers should submit reports of corrections / removals (21 CFR 806), register establishments and list devices, submit marketing application and have it accepted before Phase 3
- Phase 3
  - Begins 11/7/23. If application accepted, continued distribution is permitted. Manufacturers must comply with QSR and other applicable requirements
- FDA outlines process for manufacturers who do not intend to distribute

Future of LDT Regulation?

- Verifying Accurate, Leading-edge IVCT Development ("VALID") Act
  - Introduced in 2020 and 2021. Included in legislation reauthorizing FDA user fee program, but stripped from bill in Sept. 2022.
  - Would create new test product category, in vitro clinical tests ("IVCTs") and give FDA authority to approve IVCTs. Risk-based framework for IVCT regulation.

Test Category	Summary of Definition	Approval Process
High-Risk Tests	Inaccurate results likely to cause death, serious harm, other serious negative outcomes; no sufficient mitigating measures	Subject to FDA premarket review
Moderate-Risk Tests	Inaccurate results cause non-life threatening or medically reversible injury or treatment delay (or qualifies as high-risk but sufficient mitigating measures exist)	Brought to market through voluntary technology certification program requiring companies to demonstrate appropriate internal test validation processes
Low-Risk Test	Inaccurate result cause minimal or immediately reversible harm (or sufficient mitigating measures exist so that test meets above standard)	Exempt from premarket review

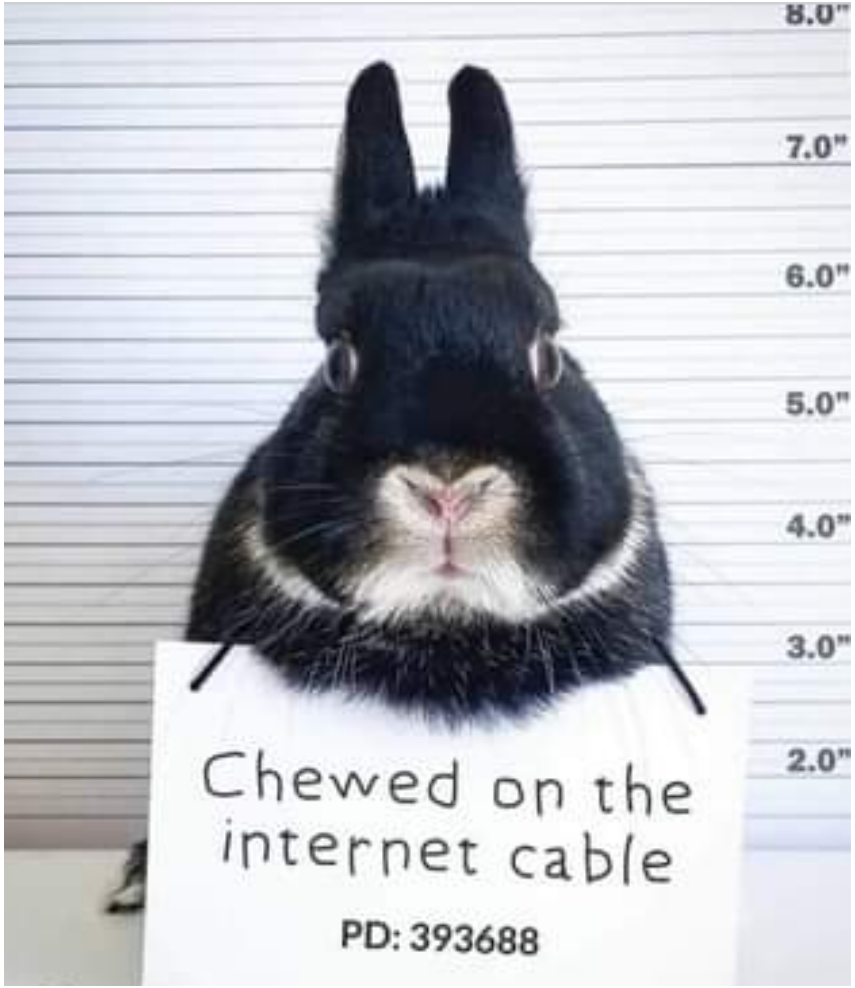
VALID Act (cont.)

- Existing LDTs are grandfathered (no review required)
- Use of “mitigating measures” to move tests into lower tiers of regulation (e.g., appropriate labeling, performance testing, submission of clinical data, clinical studies, etc.)
- Other exemptions from premarket review for low-volume tests, modified tests, manual interpretation tests, humanitarian tests
- FDA prohibited from infringing on practice of medicine
- FDA directed to issue regulations (cannot be duplicative of CLIA)
- Effective date 5 years after passage
- Public hearings to occur related to LDT oversight
- Bipartisan support in House & Senate

Another Approach to LDT Regulation

- 2021 VITAL Act (S.1666)
  - Verified Innovative Testing in American Laboratories Act of 2021
  - Would transfer all aspects of regulation over LDTs to HHS / CLIA
  - Specifically removes authority from FDA
  - CMS directed to hold hearings (within 90 days of legislation passing) related to updating CLIA regulations to reflect new oversight over LDTs
  - HHS directed to issue report to Congress within 6 months of passage
  - One sponsor (Rand Paul, R-KY)
  - No progress on legislation in 2022
  - Will VITAL Act be reintroduced in 2023?

Fraud & Abuse



Anti-kickback Statute

- Anti-kickback Statute
  - Prohibits knowing and willful offer, payment, solicitation or receipt of “remuneration” to induce or reward referral of items or services reimbursable by federal health care programs
  - “Remuneration” includes anything of value
    - Examples: Money, rebates, free services, computers, tickets, jewelry, etc.
- Penalties
  - Criminal Penalties
    - Maximum fine of $100,000; or
    - Imprisonment up to 10 years; or
    - Both
  - Possible CMP penalties
    - Up to $100,000 per kickback; and
    - 3x the amount of the remuneration
    - Exclusion from Federal health care programs
    - Violation of the False Claims Act (triple damages and minimum fines of about $22,000 per claim!)

Anti-kickback Statute

- Intent
  - OIG—AKS applies if one purpose of the remuneration is to induce or reward referrals, even if it is not the primary purpose of the arrangement
  - “One purpose” test or…
- Safe Harbors
  - Certain exceptions (called “safe harbors”) may be available to ensure AKS compliance
  - Arrangements that meet safe harbor will not be subject to criminal prosecution under the statute.
  - Examples:
    - Personal Services and Management Contracts
    - Bona Fide Employee
    - Discounts
    - Group purchasing organizations
- Why not meet a safe harbor?

Anti-kickback Statute

- If safe harbor cannot be met, facts and circumstances analysis is required
- Arrangements that do not meet safe harbor are analyzed under following factors:
  - Potential for the arrangement to result in overutilization, improper utilization or increased costs to federal programs
  - Potential effect on quality of care
  - Potential impact on access to services
  - Potential impact on competition
  - Intent of the parties
  - Degree to which key safe harbor standards are otherwise met
- Strategies for interpreting AKS:
  - OIG guidance: Compliance Guidance, Special Fraud Alerts, Special Advisory Bulletins, Letters to Industry, Advisory Opinions
  - Often identify areas of concern and help suggest strategies for mitigating risk

Background on OIG Interest: 1992 OIG Report and Investigation

- "Promotion of Prescription Drugs Through Payments and Gifts"—concluded that gifts and offers of value to physicians appear to affect physicians' prescribing decisions.
  - Companies improperly offered payments to physicians, including sponsorship of drug studies, speaking engagements and payments for program attendance including travel arrangements for spouses to luxurious resorts.
- Investigation into drug company promotional practices.
  - Random sample of 1,000 physicians to inquire about items of value offered by drug companies.
  - Found that companies were more likely to offer gifts to physicians who were frequent prescribers of those companies' products than to those who were infrequent prescribers.

1994 OIG Special Fraud Alert

- Addressed marketing initiatives offered to physicians by drug companies
- Because marketing practices may interfere with judgment, if one purpose of the activity was to induce provision of a prescription drug item reimbursable by federal programs, then AKS was implicated and no safe harbor would protect the conduct.
- Generally, payments or gifts improper if:
  - Made to person in position to generate business for paying party;
  - Related to volume of business generated; and
  - More than nominal in value or exceeds FMV of any legitimate service rendered to payer or is unrelated to any service at all other than patient referrals.

1994 OIG Special Fraud Alert (cont.)

- Identified specific arrangements that are problematic if any one purpose was to induce provision of specific drug:
  - Fee-per-switch: manufacturer offered cash award to pharmacies each time pharmacy persuaded prescriber to change from competitor's product to manufacturer's product
  - Frequent flier: physicians given credit toward airline frequent flier mileage each time new patient placed on company's product
  - Bogus "research" grants: physicians given big payments for minimal recordkeeping tasks, such as administering company's products to patients and making brief notes about treatment outcomes, sometimes a single word.

1994 OIG Special Fraud Alert (cont.)

- Other problematic relationships:
  - Any prize, gift, cash payment, coupon or bonus given in exchange for prescribing specific drugs.
  - Materials which offer cash or other benefits to pharmacists (or others in position to recommend drugs) in exchange for performing marketing tasks related to Medicare, including sales-oriented “educational” or “counseling” contacts, or physician/patient outreach.
  - Grants to physicians for studies of drugs that are of questionable scientific value and require little or no actual work.
  - Any payments given to patients or physicians for changing a prescription, or recommending or requesting such a change, from one product to another.

2003 OIG Compliance Program Guidance for Pharmaceutical Manufacturers

- Remuneration from a manufacturer provided to a purchaser that is expressly or impliedly related to a sale should be reviewed.
- Identifies a number of practices that could result in illegal remuneration. OIG highlighted 3 risk areas:
  - integrity of data used by state and federal government;
  - kickbacks and other illegal remuneration;
  - compliance with laws regulating drug samples.
- Manufacturers should examine whether they are providing valuable tangible benefits to the physician with the intent to induce or reward referrals from physician.

2003 OIG Compliance Program Guidance for Pharmaceutical Manufacturers

- Manufacturers should review all arrangements for physician services to ensure that:
  - the arrangement is set out in writing;
  - there is a legitimate need for the services;
  - the services are provided;
  - compensation is at fair market value; and
  - all of the preceding facts are documented prior to payment.
- If meeting safe harbor is not possible, manufacturers should review arrangement considering the following factors:
  - Nature of relationship between parties
  - Manner in which remuneration is determined
  - Value of remuneration
  - Potential federal program impact of remuneration
  - Potential conflicts of interest
- While focused on pharmaceutical industry, guidance is applicable to other types of manufacturers and vendors.

Risk Areas Identified by OIG

- Areas of concern identified by OIG include:
  - Research funding
  - Speaking engagements
  - Consulting and advisory payments
  - Detailing" arrangements
  - Business courtesies and other gratuities
  - Educational and promotional activities
  - Switching arrangements
  - Drug samples
  - Others

Key Risk Areas Identified by OIG

- Research Funding
  - Manufacturers contract with physicians on a fee-for-service basis to provide research services. Companies offer a wide variety of payments for physician involvement in studies of drugs and medical devices, including per-patient cash reimbursement, medical equipment, large grants and trips.
  - Companies also conduct post-marketing research to discover scientifically relevant information.
    - Some studies are intended to promote the sponsor company's drug and only tangentially include methods designed to capture or discover scientifically relevant results.
    - Other studies may provide scientific data, but also promote the company's drug.
- OIG: funding that is conditioned, in whole or in part, on the purchase of products implicates the AKS, even if the educational or research purpose is legitimate.
- OIG: try to meet personal services safe harbor.

Key Risk Areas Identified by OIG

- Research Funding:
  - Grant-funding for educational and research implicate the AKS if funding is based on the physician's referral of the manufacturer's product. Questionable research arrangements include:
    - Research initiated or directed by marketers or sales agents
    - Research that is not transmitted to, or reviewed by, a manufacturer's science component
    - Research that is unnecessarily duplicative or is not needed by the manufacturer for any purpose other than generating business
    - Post-marketing research used as a pretense to promote product
  - Post marketing research activities should be scrutinized to ensure that they are legitimate and not a pretext to generate business.
  - OIG recommends that manufactures develop contracting procedures that clearly separate the awarding of research contracts from marketing or promotion of their products.

Key Risk Areas Identified by OIG

- Speaking engagements:
  - Drug companies and other manufacturers often use speakers for promotional purposes:
    - Companies provide slides, notes, and a full text of a speech, which are slanted toward the companies' products.
    - In return, speakers are usually paid compensation directly in the form of honoraria and travel expenses or money is contributed to the speaker's healthcare institution or organization's education fund.
  - OIG: to the extent manufacturer has any influence over substance of an educational program or the presenter, there is a risk that the educational program may be used for inappropriate marketing purposes.

Key Risk Areas Identified by OIG

- Consulting and advisory payments:
  - Manufacturers often engage physicians to furnish services as consultants or advisers to the manufacturer.
    - OIG: indicated that fair market payments to a small number of physicians for bona fide consulting or advisory services are unlikely to raise any significant AKS concerns.
  - Certain things are suspect and pose AKS risks:
    - Payments made to physicians as “consultants” to attend meetings in a passive capacity.
    - Payments related to manufacturer’s marketing and sales activities, such as speaking, certain research or preceptor or “shadowing” services, and ghost-writing of papers or speeches.

Key Risk Areas Identified by OIG

- "Detailing" Arrangements:
  - Highly suspect under AKS.
  - Involves paying physicians for time spent listening to sales representatives as they market products.
  - Payments characterized as "consulting fees" and may require participating physicians to complete minimal paperwork.
  - Related "detailing" practices include companies that pay physicians for time spent accessing web sites to view or listen to marketing information, otherwise characterized as "educational."

Key Risk Areas Identified by OIG

- Educational and Promotional Activities
  - Draw line between genuine education programs and cases where benefits to attendees are inherently promotional and intended to influence their purchasing decisions.
  - OIG: while commercial sources of information have benefits and are often legitimate, support can be more promotional than educational, including when:
    - Discussions focused mainly on sponsoring company's products as opposed to a particular medical issues;
    - Programs held in resort locations;
    - Topics, speakers, and attendees are all chosen by the sponsoring company;
    - High ratio of free time and organized recreational activity to lecture and discussion time; or
    - Additional guests are invited to attend.

Key Risk Areas Identified by OIG

- Business courtesies and other gratuities:
  - Implicate the AKS if any one purpose of the arrangement is to generate business for the company.
  - Provided in variety of ways:
    - Vendors supply meals in connection with hospital and physician meetings and provide receptions and meals at large regional or national medical organization conferences.
    - Special outings, babysitting services, transportation, and trinkets were offered at these meetings.
    - Sponsors of educational programs sometimes pay for all expenses incurred by the attendee, including airfare, hotel accommodations, meals, and entertainment and recreational activities.
    - Pay all or some of the expenses for a spouse or guest to attend the conference.
  - OIG: compliance with PhRMA Code helps reduce risk in this area

Key Risk Areas Identified by OIG

- Switching arrangements
  - Typically involve manufacturers offering physicians cash payments or other benefits each time a patient's prescription is changed to the manufacturer's product from a competing product.
  - Implicates the AKS because this type of arrangement appears to diminish the objectivity of professional judgment.
  - Physicians should avoid any relationship in which a pharmaceutical manufacturer offers payment in any form or kind in return for changing a patient's prescription from one drug to another.
  - Programs may be permissible in certain managed care arrangements, but, where products involve federal health program reimbursement, AKS issues need to be considered.

AKS Enforcement

AKS Enforcement: “Traditional” Themes

- Sep. 2022—Bayer agreed to pay $40 million to resolve alleged FCA violations involving its drugs Trasylol, Avelox and Baycol. Case brought by former employee who worked in marketing department (who will receive $11 million from the settlement). Alleged that Bayer paid kickbacks to physicians to induce them to utilize Trasylol and Avelox and also marketed these drugs for off-label uses that were not reasonable and necessary. Bayer allegedly also downplayed the safety risks of Trasylol.
- Aug. 2022, Essillor International and affiliated companies agreed to pay $16.4 million to resolve allegations that it violated FCA by causing claims to be submitted to Medicare / Medicaid that resulted from violations of AKS. Essillor entered into 5-year CIA, obligated it to hire an independent review organization to review its processes for ensuring that any discounts, rebates or other reductions in price offered to providers comply with AKS. Required to implement a new review and approval process to ensure all existing and new discount arrangements comply with AKS.

Special Fraud Alert: Speaker Programs

- Problematic conduct cited in older guidance noted as genesis for new Alert
- OIG identified certain characteristics of “suspect” speaker programs:
  - Sponsoring speaker programs where little or no substantive information is actually provided.
  - Alcohol is available or a meal exceeding modest value is provided to program attendees (concerns are heightened when alcohol is free).
  - Program is held at locations that are not conducive to the exchange of educational information (e.g., restaurants or sports venues).
  - Sponsoring a large number of programs on the same / substantially the same topic or product, especially in situations involving no recent substantive change in relevant information.
  - There has been a significant period of time with no new medical or scientific information not a new FDA-approved or cleared indication for the product(s) at issue.

Special Fraud Alert: Speaker Programs

- Suspect characteristics (cont.):
  - Physicians attend programs on the same or substantially the same topics more than once (as either a repeat attendee or as an attendee after being a speaker on the same or substantially the same topic).
  - Attendees include individuals who don't have a legitimate business reason to attend the program
    - For example, friends, significant others or family members of the speaker or physician attendee; employees or medical professionals who are members of the speaker's own medical practice; staff of facilities for which the speaker is a medical director; and other individuals with no use for the information.
  - Sales or marketing business units (of the sponsoring company) influence the selection of speakers or the company selects physician speakers or attendees based on past or expected revenue that speakers / attendees have or will generate by prescribing or ordering the company's products (e.g., a return on investment analysis is considered in identifying participants).
  - Paying physician speakers more than FMV for the speaking or paying compensation that takes into account the volume or value of past business generated or potential future business generated by the physicians.

Physician-Owned Distributors

- In 2013, OIG issued a Special Fraud Alert on Physician-Owned Entities
- Identified specific concerns with PODs:
  - Selecting investors because they are in a position to generate substantial business for the entity
  - Requiring investors who cease practicing in the service area to divest their ownership
  - Distributing extraordinary returns on investment compared to the level of risk involved.
- OIG was “particularly concerned about the presence of such financial incentives in the implantable medical device context because such devices typically are ‘physician preference items’, meaning that both the choice of brand and the type of device may be made or strongly influenced by the physician, rather than being controlled by the hospital or ASC where the procedure is performed.”

Physician-Owned Distributors

- OIG is “particularly concerned” with PODs (or their physician owners) where the following characteristics are present:
  - The size of the investment offered to each physician varies with the expected or actual volume or value of devices used by the physician.
  - Distributions are not made in proportion to ownership interests, or physician-owners pay different prices for their ownership interests, because of the expected or actual volume or value of devices used by the physicians.
  - Physician -owners condition their referrals to hospitals or ASCs on their purchase of the POD’s devices through coercion or promises, for example, by stating or implying they will perform surgeries or refer patients elsewhere if a hospital or an ASC does not purchase devices from the POD, by promising or implying they will move surgeries to the hospital or ASC if it purchases devices from the POD, or by requiring a hospital or an ASC to enter into an exclusive purchase arrangement with the POD.

Physician-Owned Distributors

- Suspect characteristics of PODs (cont.):
  - Physician-owners are required, pressured, or actively encouraged to refer, recommend, or arrange for the purchase of the devices sold by the POD or, conversely, are threatened with, or experience, negative repercussions (e.g., decreased distributions, required divestiture) for failing to use the POD's devices for their patients.
  - The POD retains the right to repurchase a physician-owner's interest for the physician's failure or inability (through relocation, retirement, or otherwise) to refer, recommend, or arrange for the purchase of the POD's devices.
  - The POD is a shell entity that does not conduct appropriate product evaluations, maintain or manage sufficient inventory in its own facility, or employ or otherwise contract with personnel necessary for operations.
  - The POD does not maintain continuous oversight of all distribution functions.
  - When a hospital or an ASC requires physicians to disclose conflicts of interest, the POD's physician-owners either fail to inform the hospital or ASC of, or actively conceal through misrepresentations, their ownership interest in the POD.

A New Perspective on PODs? OIG Adv. Op. 22-07

- OIG approves arrangement involving physician-owned manufacturer that sells devices that physician owners (family members) order for their patients.
  - Orthopedic surgical procedures at hospitals and ASCs
- First time OIG has approved of physician POD ownership since publication of 2013 Special Fraud Alert.
- Three physician members of same medical group; medical device company formed by one of the physicians (has majority ownership). Two physicians (daughter of founder and her husband) have ownership through trust. Founder and wife also have ownership through trust. Non-provider minority owners. Founder owns all of the device company's intellectual property and serves as the device company's chief scientific officer but does not participate in the device company's day-to-day activities.

OIG Adv. Op. 22-07 (cont.)

- Potential AKS risks include:
  - Physicians are either beneficiaries of, or the spouse of a beneficiary of, the Trusts, which hold an ownership interest in the Company, and the Physicians order products from the Company that may be reimbursable by Federal health care programs and may recommend the Company's products to others.
  - Arrangement could not meet relevant safe harbor (small entity investments).
  - Regulatory concerns could arise if physicians:
    - State or imply they will perform surgeries or refer patients elsewhere if a hospital or an ASC does not purchase devices from the physician-owned entity;
    - Promise or imply they will move surgeries to a hospital or an ASC if it purchases devices from the physician-owned entity;
    - Require a hospital or an ASC to enter into an exclusive-purchase arrangement with the physician-owned entity.

OIG Adv. Op. 22-07 (cont.)

- OIG approved of arrangement because it did not present types of risks described in 2013 Special Fraud Alert. For example:
  - Does not exhibit the suspect characteristics sometimes associated with physician-owned entities related to the legitimacy of the entity as a business from the perspective of AKS.
  - Manner in which the Company would make future profit distributions reduces the risk of harms that the Federal anti-kickback statute is designed to prevent.
  - Unlike physician-owned entities where physician owners are the sole, or primary, users of (and sources of business for) the devices sold or manufactured by their physician-owned entities, the physicians and other medical group members generate a very limited amount of business for the Company.

OIG Adv. Op. 22-07 (cont.)

- Other factors leading to OIG approval of arrangement:
  - Arrangement differed from other physician-owned entity arrangements that select or retain physician investors in suspect ways (e.g., by retaining the right to repurchase physicians' ownership interests or requiring physician owners to divest their interests if the physicians cease practicing medicine or refer less business to the physician-owned entity).
  - Requestors certified that, although they may recommend company products and order company products for surgeries they personally perform at hospitals and ASCs, the physicians will not otherwise attempt to influence hospitals or ASCs to purchase the company's products.
  - Physicians and their medical group partners are transparent about the Trusts' ownership interest in the Company.
- Does Adv. Op. 22-07 harken new point of view on PODs?

Recent Enforcement Actions Involving PODs

- July 2022—Reliance Medical Systems settlement. Spinal implant manufacturer and two physician-owned distributorships agreed to pay $1 million to resolve case alleging they violated the FCA and AKS by paying kickbacks to physicians. Alleged physicians were paid to use Reliance medical devices in spinal surgeries on their own patients. DOJ also alleged that POD terminated physicians from participating if they did make sufficient volumes of referrals.
- May 2021—South Dakota Neurosurgeon William Asfora and two medical device distributors that he owns (Medical Designs LLC and Sicage LLC) agreed to pay $4.4 million to resolve FCA allegations involving kickbacks paid to Asfora to induce him to use medical devices and to perform medically unnecessary surgeries. Distributors allegedly paid physician profit distributions in exchange for his use of their devices in his spine surgeries. Medical Designs LLC also acted as a distributor, reselling other manufacturers' spinal devices and splitting the profits with the physician when he used those devices in surgeries. Case also alleged that the physician solicited and received kickbacks from Medtronic in exchange for using its SynchroMed II infusion pumps.

State Laws

- Many states have anti-kickback laws that extend to these relationships.
- Physician-vendor conflicts of interest. Maine, Vermont, West Virginia, and the District of Columbia - requiring gift reporting by drug companies.
- E.g., Minnesota law prohibits drug manufacturers and distributors from offering or giving gifts to practitioners.
- But Minnesota law permits:
  - Drug samples for distribution to patients
  - Items valued under $50 (in one year)
  - Payments to sponsors of medical conferences
  - Reasonable honoraria and expenses
  - Compensation for genuine research consulting
  - Publications / educational materials
  - Salaries / benefits paid to employees

Beneficiary Inducement CMP

- Beneficiary Inducement CMP prohibits any person or entity from offering remuneration to a Medicare or Medicaid beneficiary if that remuneration is likely to influence the beneficiary's selection of a provider
- Remuneration:
  - "transfers of items or services for free or for other than fair market value" §1128A(i)(6)
- Penalties include fines of up to $15,270 per item/service provided
- Definition of remuneration amended to include exceptions which went into effect in 2017. New exceptions include:
  - Copayment reductions for certain hospital outpatient department services;
  - Certain remuneration that poses a low risk of harm and promotes access to care;
  - Coupons, rebates, or other retailer reward programs that meet specified requirements;
  - Certain remuneration to financially needy individuals; and
  - Copayment waivers for the first fill of generic drugs.

Enforcement of Beneficiary Inducement CMP

- October 2022—DermaTran and 3 other pharmacies pay almost $6.9 million to resolve allegations they violated FCA by waiving copays, charging the government higher prices than permitted and trading federal healthcare business with other pharmacies.
- Allegedly created copay waiver program where patients would have copays waived based on brief, unverified statement of economic need. Companies misled government programs about prices being charged to uninsured, cash-paying patients by falsely stating that prices where high when they were much lower. For example, some veterans were charged $600 for compounded pain creams while uninsured patients were charged only $30.
- Case also alleged that the compounding pharmacy sold its out-of-network prescriptions to other pharmacies after it was removed by some networks and received a portion of proceeds back.
- FCA action; relator (former accountant of the compounding pharmacy) will receive about $1.4 million.

False Claims Act

- More than $72 billion has been recovered since 1986 amendments.
- $2.2 billion was recovered during FY 2022 (ending 9/30/22). This is the fourteenth straight year where recoveries exceeded $2 billion.
- More than $1.9 billion came from qui tam lawsuits. Whistleblowers filed 652 qui tam suits in 2022.
- 2022 had the second-highest number of FCA settlements in history (351 settlements).
- More new FCA filed in 2022 than in any other year (948 new cases).
- 2022 had the greatest number ever of FCA cases brought by DOJ outside of qui tam context (296 cases).
- 80% of the total recoveries (or $1.7 billion) comes from cases in the health care industry.

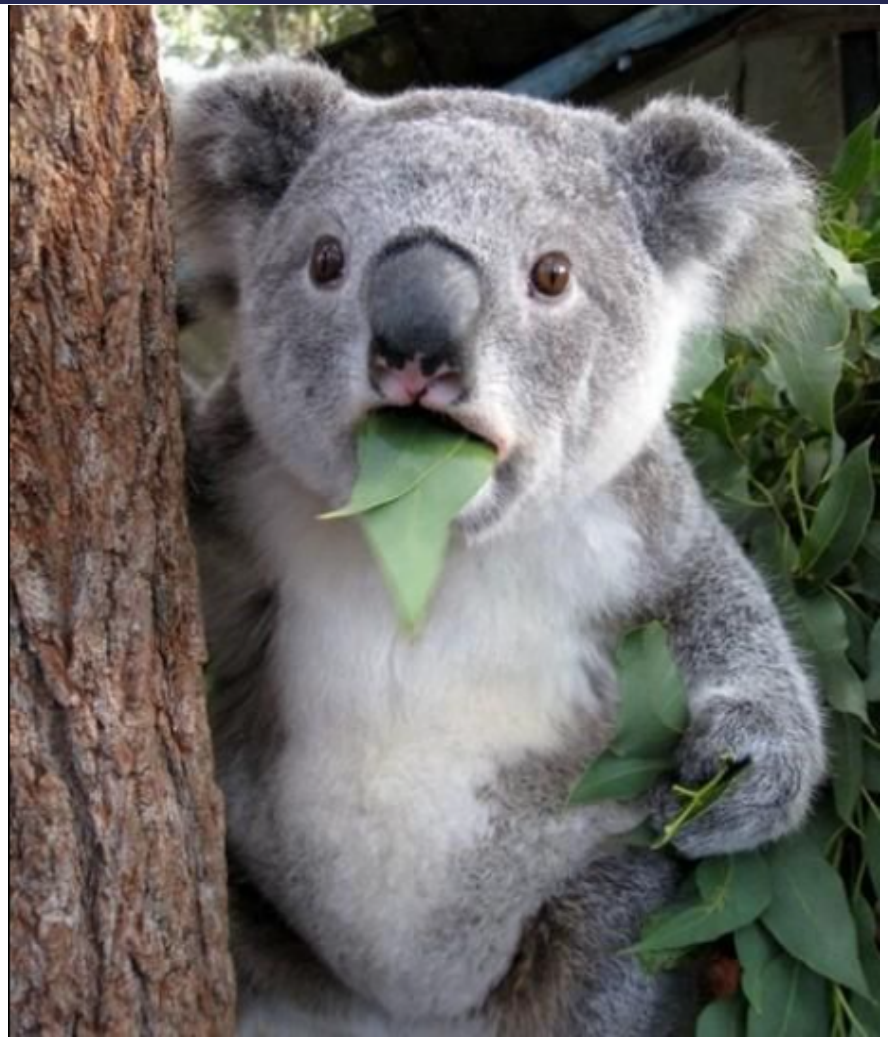
Examples of FCA in Drug / Device Space

- Biogen Settlement (Sep. 2022)
- Agreed to pay $900 million to resolve FCA action based on allegations of AKS violations
- Filed as qui tam by former employee; DOJ did not intervene
- Biogen allegedly paid kickbacks in the form of speaker honoraria, speaker training fees, consulting fees and meals to physicians
- Allegedly done to induce physicians to order drugs Avonex, Tysabri and Tecfidera in violation of AKS.
- Whistleblower received approximately $266 million

Examples of FCA in Drug / Device Space

- July 2022—Biotronik settlement. Medical device manufacturer agreed to pay $12.95 million to resolve allegations that it violated FCA by causing submission of false claims to Medicare / Medicaid through kickbacks paid to physicians to induce them to use Biotronik's implantable cardiac devices, such as pacemakers and defibrillators.
- Manufacturer allegedly made excessive payments to physicians to train new employees, including for "training events that either never occurred or were of little or no value to the trainees".
- Allegedly paid kickbacks in the form of "holiday parties, winery tours, lavish meals with no legitimate business purpose and international business class airfare and honoraria in exchange for making brief appearances at international conferences".
- Payments were made despite concerns raised by the company compliance department, which warned against the conduct. The case arose from a qui tam filed by two of the manufacturer's former sales representatives who received $2.1 million of the recovery.

Open Payments Program



AMERICAN HEALTH LAW ASSOCIATION

Open Payments Program: The Basics

- Who must report?
  - Applicable manufacturers of drugs, devices, biologicals and medical supplies covered by Medicare, Medicaid or CHIP are required to report annually to HHS most payments, transfers of value, physician ownership, investment interest that are provide to physicians or teaching hospitals.
  - Applicable manufacturer is one engaged in the production, preparation, propagation, compounding, or conversion of a covered drug, device, biological, or medical supply for sale or distribution in the United States or any entity under common ownership with such entity.
  - Applicable GPO: Purchases, arranges or negotiates the purchases of a covered drug, device, biological or medical supply for resale or distribution in the United States or, a territory, commonwealth or entity in possession in the United States.

Open Payments Program: The Basics

- Who is a covered recipient?
  - All physicians, physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists or certified nurse midwifes who are not bona fide employees of the applicable manufacturer reporting the payment.
  - Does not need to be enrolled in Medicare / Medicaid.
  - Covered recipients include teaching hospitals that receive GME or IME payments during the most recent year.
- Name of Applicable Manufacturer, GPO
- Covered Recipient's:
  - Name (NPPES), including middle initial
  - Specialty (physician only)
  - Primary business street address (practice location)
  - NPI #
  - State professional license number

Open Payments Program: What is Reported (cont.)?

- Amount of payment or other transfer of value
- Nature of payment/transfer of value
- Form of payment/transfer of value
- Date of payment/transfer of value
- Name of the related drug, device, biological or supply:
  - NDC of related covered drug/biological (if any)
  - For devices/medical supplies, need either the name under which it's marketed or therapeutic area or product category
  - "Non-covered product" (if appropriate)
  - "None" (if appropriate)

Open Payments Program: What is Reported (cont.)?

- Eligibility for delayed publication (research)
- Name of entity that received payment or transfer if not provided to CR directly (indirect payments)
  - Payment to third party at request of; or
  - Designated on behalf of, the CR
- Payments/transfers of value to physician owners
- “Context” statement (optional)
- Ownership treated slightly differently
- Covered drug, device, biological or medical supply includes:
  - Those for which payment is made under Medicare, Medicaid or CHIP:
  - Requires a physician prescription to be dispensed,
  - Pre-market approval by or notification to the FDA.
  - Over the counter drug manufacturers are excluded

Open Payments Program: Payments

- Amount of payment / transfer of value:
  - Payments are to be reported at fair market value:
  - Should not be specific to recipient
  - Include tax and shipping
  - Good faith effort
  - Importance of assumptions document
- Form of payment:
  - Each payment needs to be classified as being in one of several “forms” of payment:
    - Cash or Cash Equivalents
    - In Kind Items or Services
    - Ownership or Investment Interests
    - Dividend, Profit or other Return on Investment

Open Payments Program: Payments (cont.)

- Nature of payment—each payment must be classified into one of several “nature of payment” categories
  - If no one category clearly applies, must choose the closest one:
    - Consulting fee.
    - Compensation for services other than consulting, including serving as faculty or as a speaker at an event other than a continuing education program.
    - Honoraria.
    - Gift.
    - Entertainment.
    - Food and beverage.
    - Travel and lodging (including the specified destinations).
    - Education.
    - Research.
    - Charitable contribution.

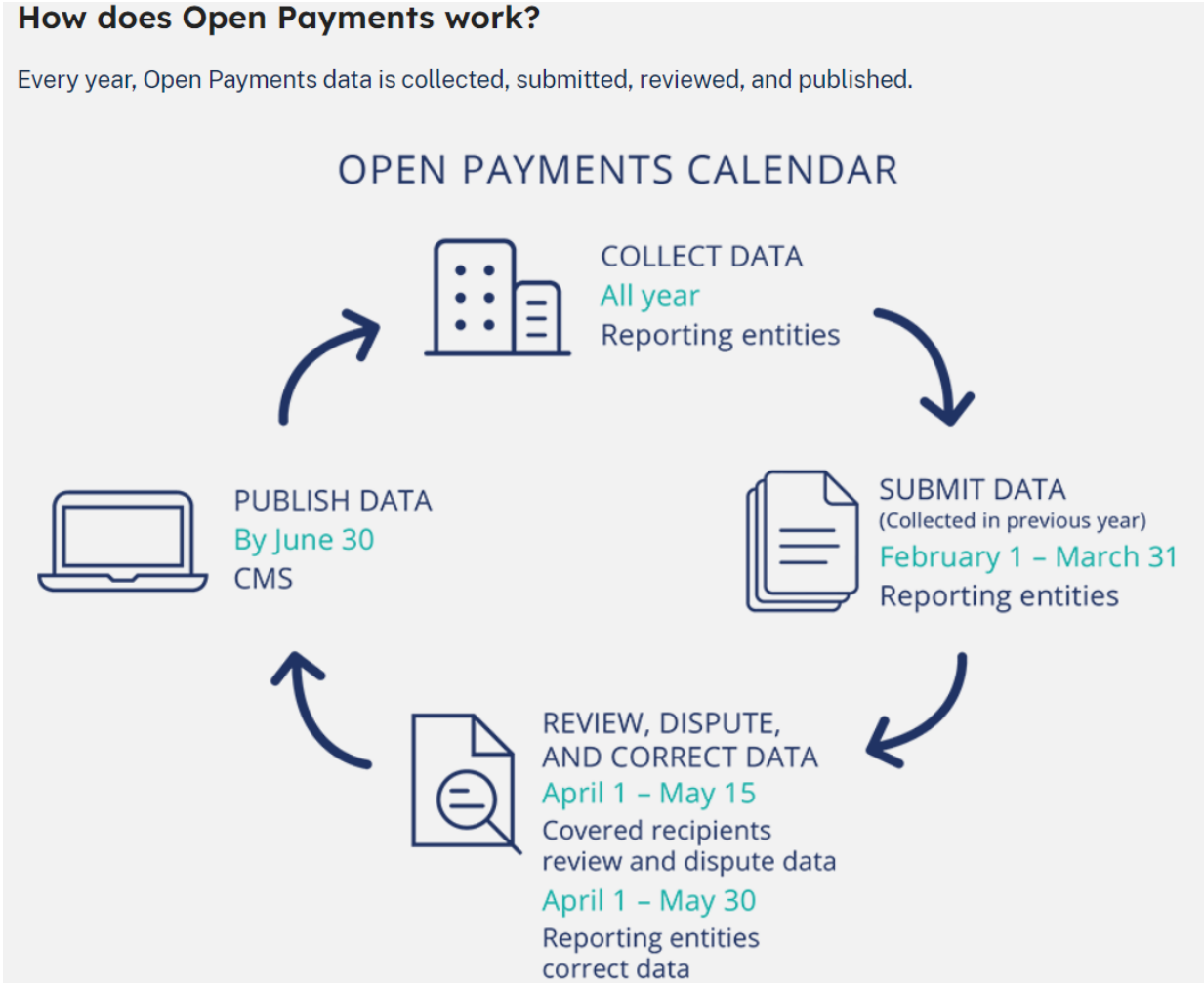
Open Payments Program: Payments (cont.)

- Nature of payment categories (cont.)
  - Debt forgiveness.
  - Royalty or license.
  - Current or prospective ownership or investment interest.
  - Compensation for serving as faculty or as a speaker for a medical education program.
  - Long term medical supply or device loan.
  - Grant.
  - Space rental or facility fees (teaching hospital only).
  - Acquisitions.
- Numerous “special rules” apply to various categories of transfers
  - Research, CME, food & beverage
  - Attribution rules apply to certain transfers

Open Payments Program: The Results

- Penalties for noncompliance:
  - Manufacturer or group purchasing organization that fails to report may be subject to civil monetary penalty of $1,000 to $10,000 for each payment, transfer of value, or ownership or investment interest not reported, up to $150,000 annually.
  - Knowing failure to report can increase the penalties to $10,000 to $100,000 for each payment, transfer of value or ownership or investment interest not reported up to $1,000,000 annually. Penalty amounts are adjusted for inflation.
- What have the results been?
  - In program year 2020, reporting entities reported $9.12 billion in publishable payments and ownership and investment interests.
  - These payments were comprised of 6.38 million payment records attributable to 487,152 physicians and 1,213 teaching hospitals.
  - Since the inception of the Open Payments Program in 2014, CMS has published over 78 million records totaling more than $59 billion.

Open Payments Program: Timing



Open Payments Program: Enforcement

- On October 29, 2020, DOJ announced a settlement with Medtronic that resolved allegations it made improper payments to a neurosurgeon and failed to accurately report payments in violation of OPP. Medtronic settled for a total of $9.2 million dollars, $1.11 of which was specifically to resolve the OPP claims.
- Medtronic allegedly made payments that benefitted Dr. Wilson Asfora, the owner of medical device distributor, in order to induce Dr. Asfora to use Medtronic's SynchroMed II intrathecal infusion pumps. Government alleged that Medtronic sponsored over 100 events at a restaurant owned by Dr. Asfora and spent approximately $87,000 on meals and drinks for the doctor's referral sources and business partners.
- In reports to CMS, Medtronic only listed the value of the food and drinks consumed by individual physicians, rather than reporting the total amount paid to the restaurant as a transfer of value to the physician owner.

Open Payments Program: Enforcement

- May 2021, DOJ entered into a settlement with Dr. Asfora and his two medical device distributorships to resolve alleged violations of the FCA, AKS and OPP.
- Dr. Asfora agreed to pay $4.4 million for accepting illegal kickbacks allegedly intended to induce his use of certain devices and performing unnecessary procedures.
- Two device distribution companies, Medical Designs, LLC and Sicage, LLC, paid an additional $100,000 in penalties to settle allegations they violated the OPP by failing to report Dr. Asfora's ownership interests in Carnaval Brazilian Grill and accepting payments to the restaurant the doctor requested in order to benefit his friends and colleagues.

Open Payments Program: Enforcement

- May 2021, Medicrea International, a French manufacturer, and its American affiliate Medicrea USA agreed to pay $1 million to resolve AKS violations and an additional $1 million to resolve OPP violations.
- Alleged to have provided items of value in the form of meals, alcoholic beverages, entertainment and travel expenses to U.S. based physicians at events surrounding the Scoliosis Research Society's September 2013 Congress in Lyon, France.
- Government alleged Medicrea provided the benefits in an effort to induce the physicians to purchase or order Medicrea's spinal devices, resulting in false claims to federal healthcare programs. Medicrea did not fully report the physician-entertainment expenses to CMS. The settlement came after Medtronic bought Medicrea in November, 2020.

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