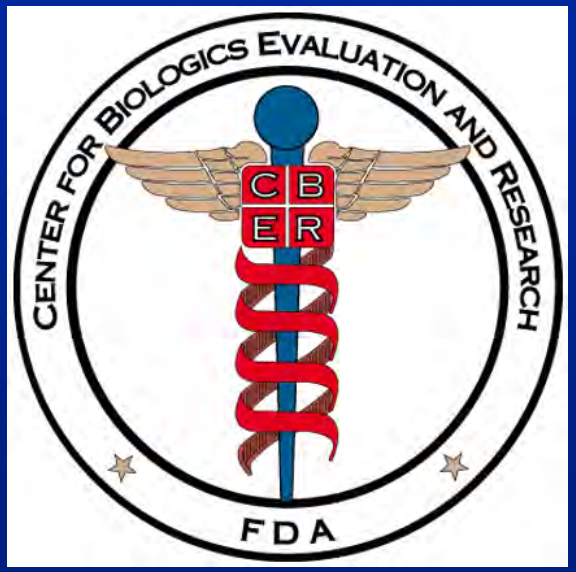
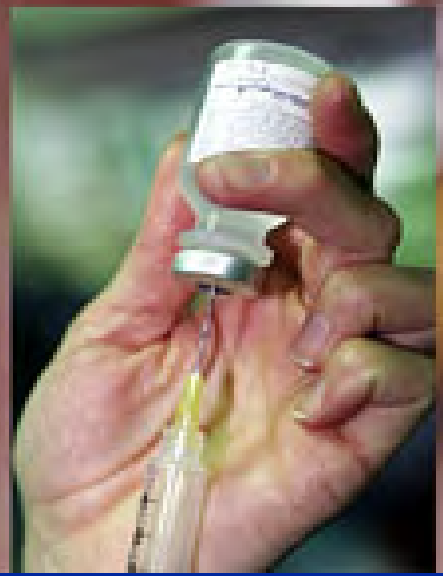


Regulation of Biological Products – Review

Food and Drug Administration

Judy Ciaraldi
Linda Mattingly
Armando Zamora
Sharon O'Callaghan
Laura St. Martin, MD

Safe And Effective



Medicines

Biologics

Medical Devices

FDA

Five Layers of Blood Safety

- Selection of suitable donors
  - Donor education and risk factor screening
  - Medical interview and limited physical examination
- Use of deferral registries to identify unsuitable donors
- Infectious disease testing (HIV, HCV, HBV, HTLV, STS, WNV)
- Quarantining blood while verifying suitability and doing tests
- Monitoring, investigating and taking corrective actions to address manufacturing problems and adverse reactions

FDA History

- 1902 Biologics Control Act
  - Statutory authority to regulate products
  - Labeling, inspections, penalties
- 1938 Federal Food, Drug and Cosmetic Act
  - Drugs must be safe before marketing
  - Registration, inspections, penalties
- 1944 Public Health Safety Act
  - Need license to distribute product in interstate commerce
  - Regulate blood and blood components like drugs
  - Sections 351 and 361

Regulated Blood Components

- **Blood components for transfusion**
  - **Whole Blood, Red Blood Cells**
  - **Platelets, Platelets Pheresis**
  - **Fresh Frozen Plasma, Plasma Cryoprecipitate Reduced**
  - **Cryoprecipitated AHF**
  - **Irradiated, leukocyte reduced, divided, washed, frozen, deglycerolized, rejuvenated**
- **Blood components for further manufacturing**
  - **Source Plasma**
  - **Source Leukocytes**
  - **Recovered plasma**

Regulated Blood Establishments

- Hospital/Community Blood Banks/Collection Centers/Plasmapheresis Centers
- Product Testing Laboratories
- Hospital Transfusion Services
- Component Preparation Facilities
- Distribution Centers
- Brokers
- Tissue Collection and Preparation Facilities

Regulatory Process

- **Regulations**
  - Required standard or conduct; found in CFR
- **Guidance**
  - Recommended procedures, new policies; found in GGP guidance documents
- **Registration**
  - Required if perform manufacturing step on product
- **Licensure**
  - Must be a registered manufacturer
  - Required if product distributed in interstate commerce
  - 85 – 90% of transfused blood is prepared in licensed blood banks

Registration vs. Licensure

- **Blood establishment must register if it manufactures biological product or performs a manufacturing step**
  - **Register electronically on CBER website**
  - **Intrastate commerce only**
- **Applicant must also hold an approved, un-revoked U.S. license if it wants to distribute the biological product across state lines (interstate commerce)**
  - **Submit documents to CBER for review**
  - **Undergo FDA pre-license inspection**
  - **Approvals are specific for product and facility**
  - **FDA license number on label of approved products**

License Application

- **License submissions:**
  - **Application, Supplement, Amendment**
  - **BLA form – 356h**
- **Submission review includes:**
  - **Desk review of paperwork (always)**
  - **Observe product manufacture during pre-license/approval inspection (sometimes)**
- **Licensed applicants must report changes to an approved application**
  - **PAS, CBE30, CBE, AR**
  - **Comparability Protocol**

Licensure Review Procedure

- CBER reviews based on:
  - Regulations and Guidance Documents
  - Operator's Manuals and Package Inserts
- Submission should contain information for substantive review
  - Consult FDA regulations, guidance documents, and CBER review checklists
  - Consult operator's manuals and package inserts
- Some reviews may require platelet products sent to CBER for testing
- Facility inspections before approval

Manufacturing Processes

- **Labeling**
  - **No false or misleading claims = misbranding**
  - **Container label for transfusible products must contain machine readable information**
- **Cooperative manufacturing agreements allowed**
  - **Shared, Divided**
  - **Contract**
  - **Short Supply**
- **Variances submitted under 21 CFR 640.120**
  - **Only for regulations in 600s of CFR**
  - **Both licensed and unlicensed establishments**
  - **Case by case review and approval**

Unlicensed Facilities

- **Unlicensed, registered-only facilities**
  - **These facilities prepare 10-15% of transfused blood**
  - **Manufacturing activities observed during FDA (ORA) inspections**
- **Unregistered facilities**
  - **Exempt under 607.65**
  - **Still required to follow GMPs and regs**
  - **Inspections under authority of CMS**
- **CBER does not review submissions from unlicensed facilities unless they:**
  - **Request a variance**
  - **Apply for licensure**

Device Reviews

- CBER reviews biological devices
- Licensed devices
  - PHS Act
  - Must be approved before distributed in interstate commerce
- Cleared devices (510(k))
  - FD&C Act
  - Must be substantially equivalent to predicate device
- Device manufacturers are required to register with FDA and list products

FDA Perspective on Quality

- Who? – QC unit
- What? – Ensure cGMPs are met
- Why? – Assure product quality
- Where? – All manufacturing facilities
- When? – Ongoing basis
- How? – cGMP regulations and quality guidance documents

Responsibility or Activity	Licensed & Registered	Registered-Only	Unregistered
Interstate commerce	x		
Intrastate commerce	x	x	
Follow cGMPs	x	x	x
BPD reporting	x	x	x
Fatality reporting	x	x	x
Request variance	x	x	x
FDA inspection	x	x	X* [CMS]
Annual registration	x	x	
Report under 601.12	x		

Human Cells, Tissues and Cellular and Tissue-Based Products

(HCT/Ps = human cells/tissues intended for implantation, transplantation, infusion, or transfer to human recipient)

- **Musculoskeletal tissue**
- **Skin**
- **Ocular tissue**
- **Human heart valve**
- **Dura mater**
- **Reproductive tissue**
- **Hematopoietic stem/progenitor cells**
- **Other cellular therapies**
- **Tissue/device and other combination therapies**

Tissue Requirements

- Found in 21 CFR 1271
- Facilities engaging in tissue manufacturing must register separately
- Donor eligibility determined by screening and testing
  - Free from being able to transmit communicable diseases; negative test results
  - Screening may involve interview, review of medical records or coroner and autopsy reports
  - Some exceptions, e.g., autologous use, reproductive tissues from partner

Tissue Requirements

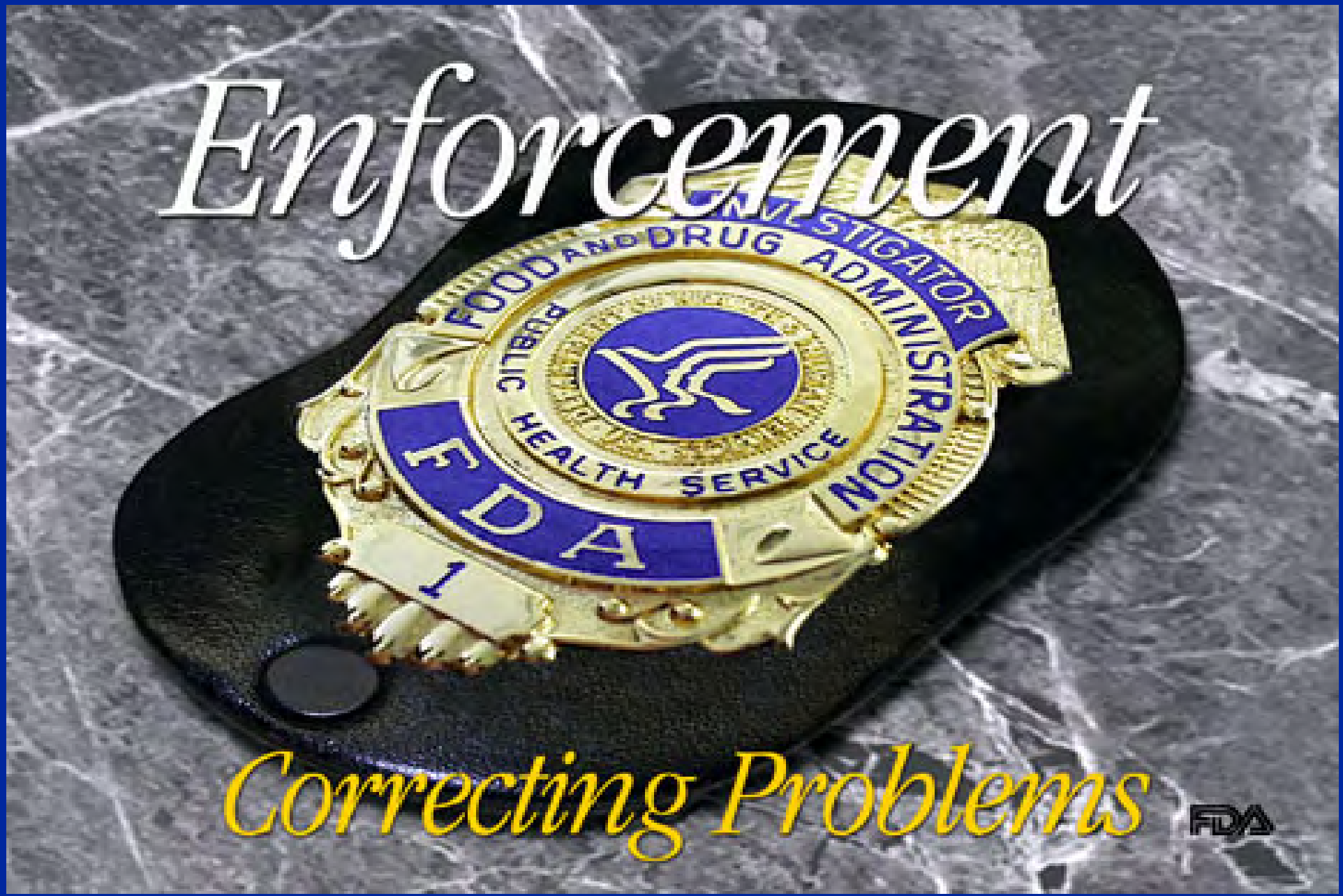
- **HCT/Ps from ineligible donors may be used with appropriate labeling, storage, and documentation**
  - **Allogeneic 1st or 2nd degree relative**
  - **Directed donor for reproductive HCT/P**
  - **Documented urgent medical need**
- **cGTPs, 210/211 Drug GMPs & 820 Device GMPs apply**
  - **Methods to control manufacturing and prevent disease transmission**
  - **Establishments determine how to meet GTPs/GMPs**
  - **Quality program to detect, correct and prevent deficiencies that could increase risk of transmitting diseases**

Current Good Tissue Practice Requirements

- Exemptions and Alternatives
- Quality Program
- Personnel
- Procedures
- Facilities
- Environmental Control and Monitoring
- Equipment
- Supplies and Reagents
- Recovery
- Processing and Process Controls
- Process Changes
- Process Validation
- Labeling Controls
- Storage
- Receipt, Pre-distribution, Shipment and Distribution
- Records
- Tracking
- Complaint File
- Donor Eligibility Determination

361 vs 351 HCT/Ps

- Sections 351 and 361 of the PHS Act
- Section 361
  - Focus on preventing transmission of communicable diseases; must meet all criteria in 21 CFR 1271.10
  - No application to FDA; compliance determined during FDA inspections
  - Ex. skin, cornea, reproductive tissue, related cell therapies, etc.
- Section 351
  - Must apply to FDA (IND+BLA or NDA, IDE+PMA)
  - May not meet all criteria in 21 CFR 1271.10
  - Pre-approval/pre-license inspections + FDA field inspections
  - Ex. unrelated cell therapies, more than minimally manipulated, etc.


Enforcement
INVESTIGATOR
FOOD AND DRUG ADMINISTRATION
PUBLIC HEALTH SERVICE
FDA
1
Correcting Problems
FDA

Types of ORA Inspections

- **Level 1 – covers critical areas of these systems:**
  - **Quality assurance**
  - **Donor eligibility**
  - **Product testing**
  - **Quarantine/Inventory Management**
  - **Product processing**
- **Level 2 – covers critical areas of these systems:**
  - **Quality assurance**
  - **Donor eligibility**
  - **One other system**
- **Directed, For cause – compliant, fatality, CBER requested**
- **Compliance follow-up – after violative inspection**

ORA Inspections

- Required and authorized under the FD&C and PHS Acts
- Check for compliance with Acts, regulations, GMPs, own standards
- Conducted by highly trained field investigators
- Performed initially and at least every 2 years
- ORA participates in CBER pre-license inspections
  - Level 1 inspections

ORA Inspections

- Scope of inspection includes all aspects of:
  - Product manufacturing
  - Donor safety
  - Quality oversight
- Observe practices, review procedures and records
- Deficiencies found in all areas
  - Listed on FDA-483
  - Must respond to violative FDA-483 in writing

Resources for B&P & Tissue Inspections

- **Compliance Program Guidance Manuals**
  - **Inspections of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories and Contractors (10/06)**
  - **Inspection of Source Plasma Establishments (10/06)**
  - **Inspection of Tissue Establishments (3/03)**
  - **Inspection of Human Cells, Tissues and Cellular and Tissue-based Products (HCT/Ps) (7/05)**
- **Inspection or compliance references:**

http://www.fda.gov/ora

http://www.fda.gov/cber/cpg/cpg.htm

Enforcement Actions

- **Regulatory tools used to bring manufacturers into compliance**
  - **Licensed Suspension – reinstatement, revocation, debar personnel, criminal prosecution**
  - **Licensed Revocation (NOIR, Direct) – cannot distribute in interstate commerce**
  - **Warning Letter – notification of violation of the law, opportunity to correct**
  - **Seizure – remove violative products**
  - **Injunction (Consent Decree) – stop/prevent violation of law, opportunity to correct**
  - **Prosecution – criminal court case**

Recalls

- **Types of Recall Actions**
  - **Recall – firm's removal or correction of distributed product that violates law; FDA can take legal action**
  - **Market Withdrawal – removal/correction of distributed product with minor violation**
  - **Correction (Field Correction) – product not removed to another location for correction**
- **Types of Recalls**
  - **Firm Initiated (Voluntary) – after informed by FDA product violates law**
  - **FDA Requested – urgent; risk of illness or injury**
  - **FDA Ordered**

Recalls

- **Recall Classifications**
  - **Class I – reasonable possibility violative product will cause serious adverse event**
  - **Class II – exposure may cause temporary or reversible medical event or serious event is remote**
  - **Class III – product not likely to cause serious event**

- **Recalls are posted on FDA & CBER websites**

http://www.fda.gov and http://www.fda.gov/cber

Recall Reasons

- Testing errors
- Ineligible donors
- Extend expiration date
- Improper component preparation
- Temperature deviations
- Processing/manufacturing errors
- Problems with reagents and supplies – loss of potency or contamination

Adverse Event Reporting

- **Adverse reactions related to collection or transfusion**
  - **Maintain records**
  - **Document investigation, conclusions and follow-up**
  - **Notify collection/manufacturing facility if product at fault**
  - **Currently these do not need to be sent to FDA unless they are part of a MDR**
- **Fatality related to collection or transfusion**
  - **All manufacturers (licensed, registered-only, unregistered) must report to FDA**

Fatality Reporting

- **Submit initial report within 7 days after fatality**
  - **Even if determine later product/collection was not the cause**
  - **Donor fatality reported by collecting facility**
  - **Transfusion fatality reported by transfusion/crossmatch facility**
- **Amend 7-day report with additional information**
  - **Conclusions of cause of fatality even if collection or product was not the cause**
- **Guidance document**

  http://www.fda.gov/cber/gdlns/bldfatal.htm

Biological Product Deviation (BPD) Reporting

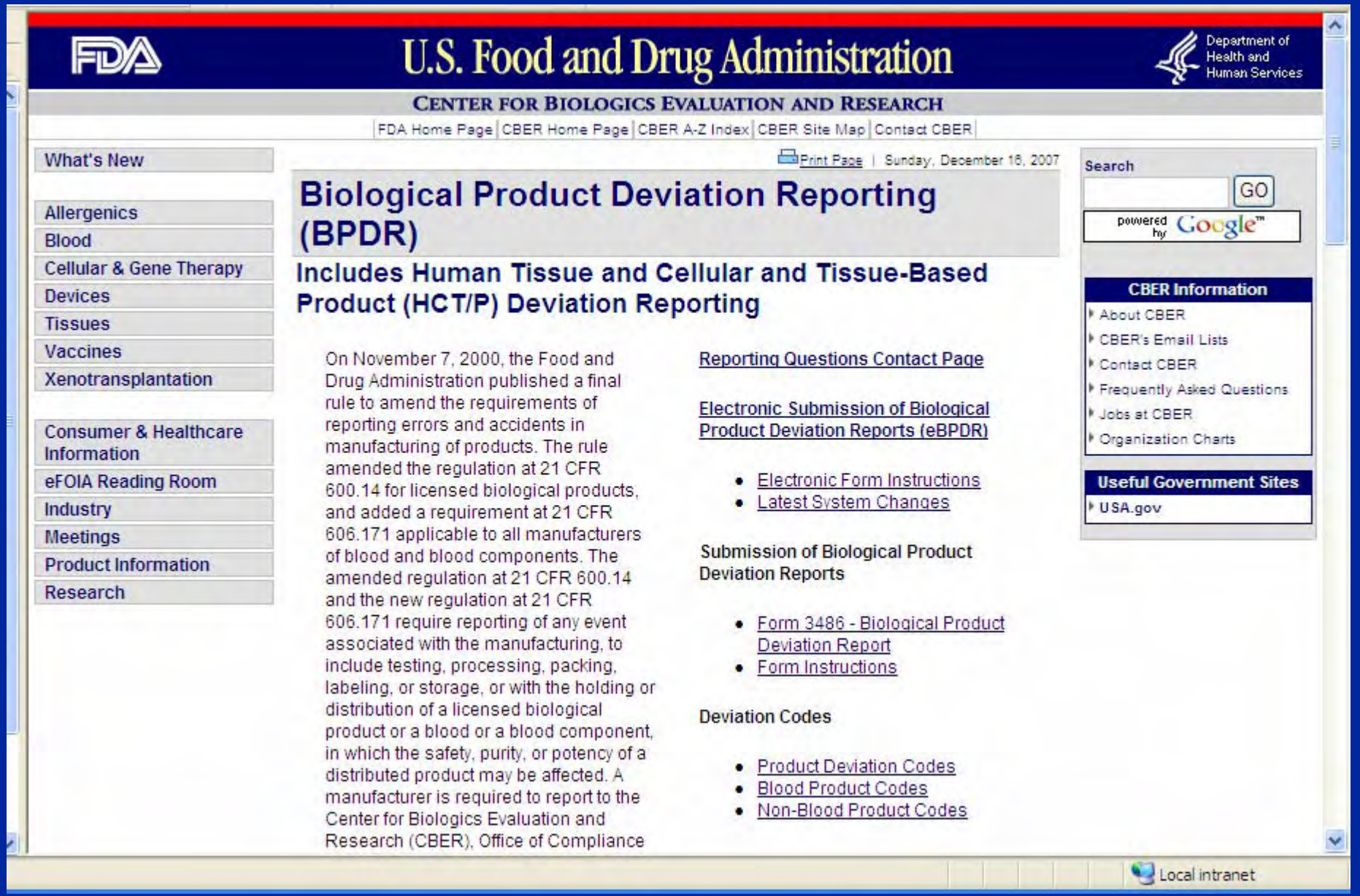
- **All manufacturers report to FDA any event associated with manufacturing a product that adversely affects safety, purity or potency of the product and product was distributed (21 CFR 606.171)**
- **Applies to all facilities (licensed, unlicensed, transfusion services)**
- **Guidance document**

  http://www.fda.gov/cber/gdlns/devbld.htm

Reportable BPDRs

- Event associated with manufacturing
- Event occurred while in the control of manufacturing facility or transfusion service
- Deviation or unexpected event that may affect safety, purity or potency of product
- Product was distributed
- Report within 45 days after acquiring info about event
- Report using form FDA-3486 or electronically

  http://www.fda.gov/cber/biodev/biodev.htm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Print Page | Sunday, December 16, 2007
Biological Product Deviation Reporting (BPDR)
Includes Human Tissue and Cellular and Tissue-Based Product (HCT/P) Deviation Reporting
On November 7, 2000, the Food and Drug Administration published a final rule to amend the requirements of reporting errors and accidents in manufacturing of products. The rule amended the regulation at 21 CFR 600.14 for licensed biological products, and added a requirement at 21 CFR 606.171 applicable to all manufacturers of blood and blood components. The amended regulation at 21 CFR 600.14 and the new regulation at 21 CFR 606.171 require reporting of any event associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution of a licensed biological product or a blood or a blood component, in which the safety, purity, or potency of a distributed product may be affected. A manufacturer is required to report to the Center for Biologics Evaluation and Research (CBER), Office of Compliance
Reporting Questions Contact Page
Electronic Submission of Biological Product Deviation Reports (eBPDR)
Electronic Form Instructions
Latest System Changes
Submission of Biological Product Deviation Reports
Form 3486 - Biological Product Deviation Report
Form Instructions
Deviation Codes
Product Deviation Codes
Blood Product Codes
Non-Blood Product Codes
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Local intranet

Our Challenges

- Scientific Breakthroughs
- More Sophisticated Products
- New Public Health Threats
- International Commerce
- Consumer Information

Where can I get more information?

Regulatory, Licensing, Blood Product Standards

- **Call Division of Blood Applications, OBRR at:**

  301-827-3543

- **Fax Division of Blood Applications at:**

  301-827-3534

- **Write Division of Blood Applications at:**

  FDA-CBER-OBRR-DBA (HFM-370)

  1401 Rockville Pike, Suite 400N

  Rockville, MD 20852-1448

Contact Information

- **Mailing Address**

  Director, Division of Blood Applications, OBRR, CBER, FDA
  HFM-370
  c/o Document Control Center, HFM-99
  1401 Rockville Pike, Suite 200N
  Rockville, MD 20852-1448
- **Telephone – (301) 827-3543**
- **Fax – (301) 827-3534**
- **Blood and Plasma Branch Consumer Safety Officers**

Regulatory, Licensing, Tissue, Cell, GT Standards

- **Call OCTGT at: 301-827-6106**
- **Fax OCTGT at: 301-827-2844**
- **Write OCTGT at:**

FDA-CBER-OCTGT (HFM-775)

1401 Rockville Pike

Rockville, MD 20852-1448

- **Tissue Info – http://www.fda.gov/cber/tiss.htm**
- **Cellular/Gene Therapy Info – http://www.fda.gov/gene.htm**

Inspections and Enforcement

- **Call Division of Case Management, OCBQ at: 301-827-6201**
- **Call Division of Field Investigations, ORA at: 301-827-5653**
- **Report Biological Product Deviations: 301-827-6220**

http://www.fda.gov/cber/biodev/biodev.htm

Helpful Website Addresses

- **General CBER information**
  http://www.fda.gov/cber/
- **Guidance Documents**
  http://www.fda.gov/cber/guidelines.htm
- **Other useful information**
  http://www.fda.gov/cber/reading.htm
- **Forms (356h, 2830, 2567)**
  http://forms.psc.gov/forms/FDA/fda.html

What's New
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Blood
Cellular & Gene Therapy
Devices
Tissues
Vaccines
Xenotransplantation
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Hot Topics

- Influenza Virus Vaccine 2006-2007 Season
- GARDASIL Approval
- Zostavax Approval
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- Contact CBER
- Frequently Asked Questions
- Jobs at CBER
- Organization Charts

Useful Government Sites
- CDC National Immunization Program
- FDA's Critical Path to New Medical Products
- FDA Centennial
- MedWatch
- Pandemic Flu
- Vaccine Adverse Event Reporting System (VAERS)
- FIRSTGOV

Updated: September 6, 2006

What's New

Allergenics
Blood
Cellular & Gene Therapy
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Tissues
Vaccines
Xenotransplantation

Consumer & Healthcare Information
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Product Information
Scientific Expertise & Research

Electronic Reading Room (eFOI)

The CBER Reading Room provides access to documents posted on the CBER website. These documents are ones frequently requested by the public through the Freedom of Information Act. Many documents are also available by e-mail and in printed copy.

Product Approval Information

- Licensed Products
- 510K Devices
- PMAs (Premarket Approval Devices)
- NDA (New Drug Applications)
- Postmarketing Study Commitments
- Transfer of Therapeutic Products to CDER (2003)

Compliance, Surveillance and Enforcement

- Clinical Investigator Inspection List
- Compliance Program Guides for CBER
- NIDPOE (Notice of Initiation of Disqualification Proceedings and Opportunity to Explain) Letters
- Recalls / Withdrawals
- Warning Letters
- Violative Advertising & Promotional Labeling for Approved Biological Products
- Other Compliance Actions

Product Safety & Availability

- Information Sheets
- Letters to Industry / Healthcare Providers / Clinical Investigators
- Safety Information
- Adverse Event Reporting System (AERS) - CDER
- Vaccine Adverse Event Report System (VAERS)
- Shortages

Meetings

- Advisory Committees
- Minutes from Workshops & Open Public Meetings
- Presentations

Talk Papers & Press Releases

Additional Documents Available from FDA

- FDA's Electronic Freedom of Information Reading Room
- Handbook for Requesting Information and Records from FDA
- Compliance Program Guidance Manual - Office of Regulatory Affairs
- Compliance Policy Guides Manual - Office of Regulatory Affairs
- Dockets Management - Official repository for the administrative proceedings and rule-making documents for FDA
- Inspection Guides - Office of Regulatory Affairs

Updated: August 16, 2006

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Useful Government Sites
- Public Health Service Act
- Federal Register
- FD&C Act
- Code of Federal Regulations
- International Conference on Harmonisation (ICH)
- CDC's MMWR
- FIRSTGOV

Email Subscriber Service

www.fda.gov/emaillist.html

- **Biologics information**
  - **www.fda.gov/emaillist.html#biologics**
  - **“What’s New at CBER”**
  - **Enter email address**
- **It’s free!!**

New items posted to FDA's Center for Veterinary Medicine (CVM) website

Biologics

Blood Guidances
Guidance documents related to blood products and blood establishments, links to information about blood publications and FDA's Blood Action Plan

Blood Products Advisory Committee
Information on current and past meetings of the Blood Products Advisory Committee

Cellular, Tissue and Gene Therapies Advisory Committee
Information on current and past meetings of the Cellular, Tissue and Gene Therapies Advisory Committee (Formerly Biological Response Modifiers Advisory Committee)

FDA Patient Safety News (video)
Broadcasts for hospitals and other medical facilities in the U.S. featuring information on new drugs, biologics and medical devices, FDA's safety notifications and product recalls, and protecting patients when using medical products

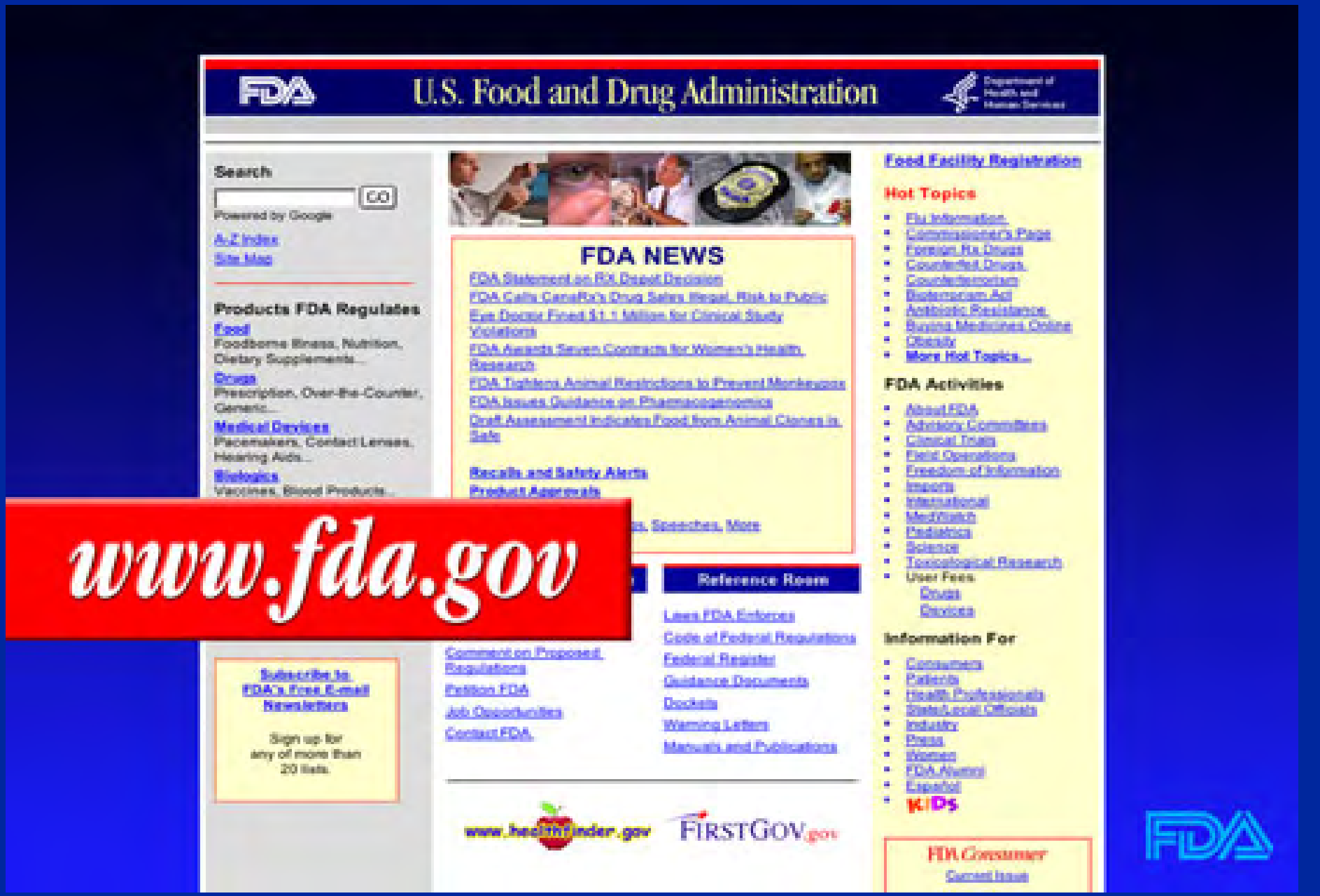
MedSun
Adverse event reporting program for the clinical community to identify, understand, and solve problems with the use of medical devices.

Tissue Related Documents
Guidance, rules and related documents on Human Cells, Tissues, and Cellular and Tissue Based-Products

What's New at CBER
New Items posted to the Center for Biologics Evaluation and Research website

Consumer Health Information

FDA & You
FDA newsletter on medical products and health topics for teens, parents and educators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FDA Calls CanaRx's Drug Sales Illegal, Risk to Public
Eye Doctor Fined $1.1 Million for Clinical Study Violations
FDA Awards Seven Contracts for Women's Health Research
FDA Tightens Animal Restrictions to Prevent Monkeypox
FDA Issues Guidance on Pharmacogenomics
Draft Assessment Indicates Food from Animal Clones is Safe
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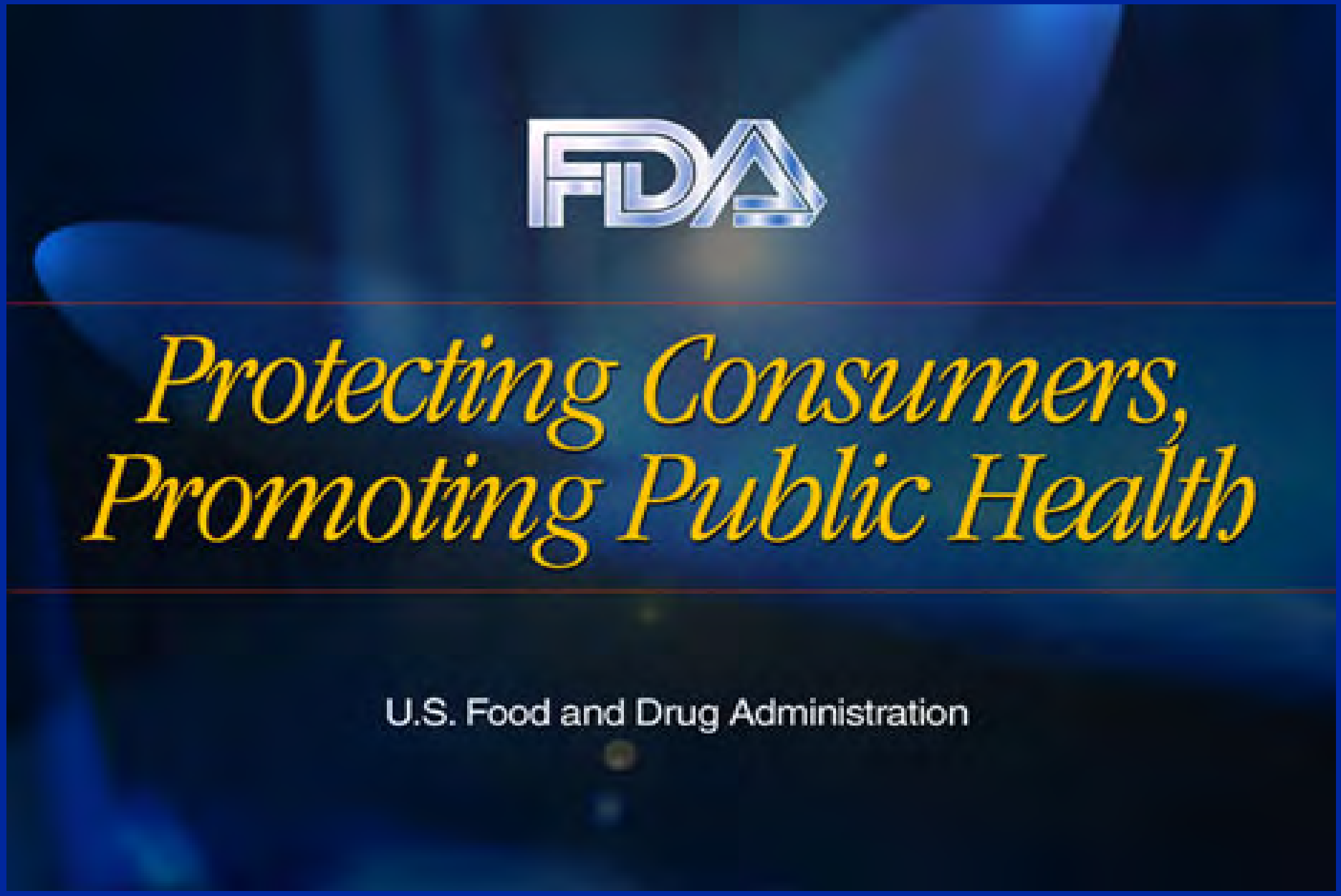
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