Center for Devices and Radiological Health

Food and Drug Administration
Centennial Celebration
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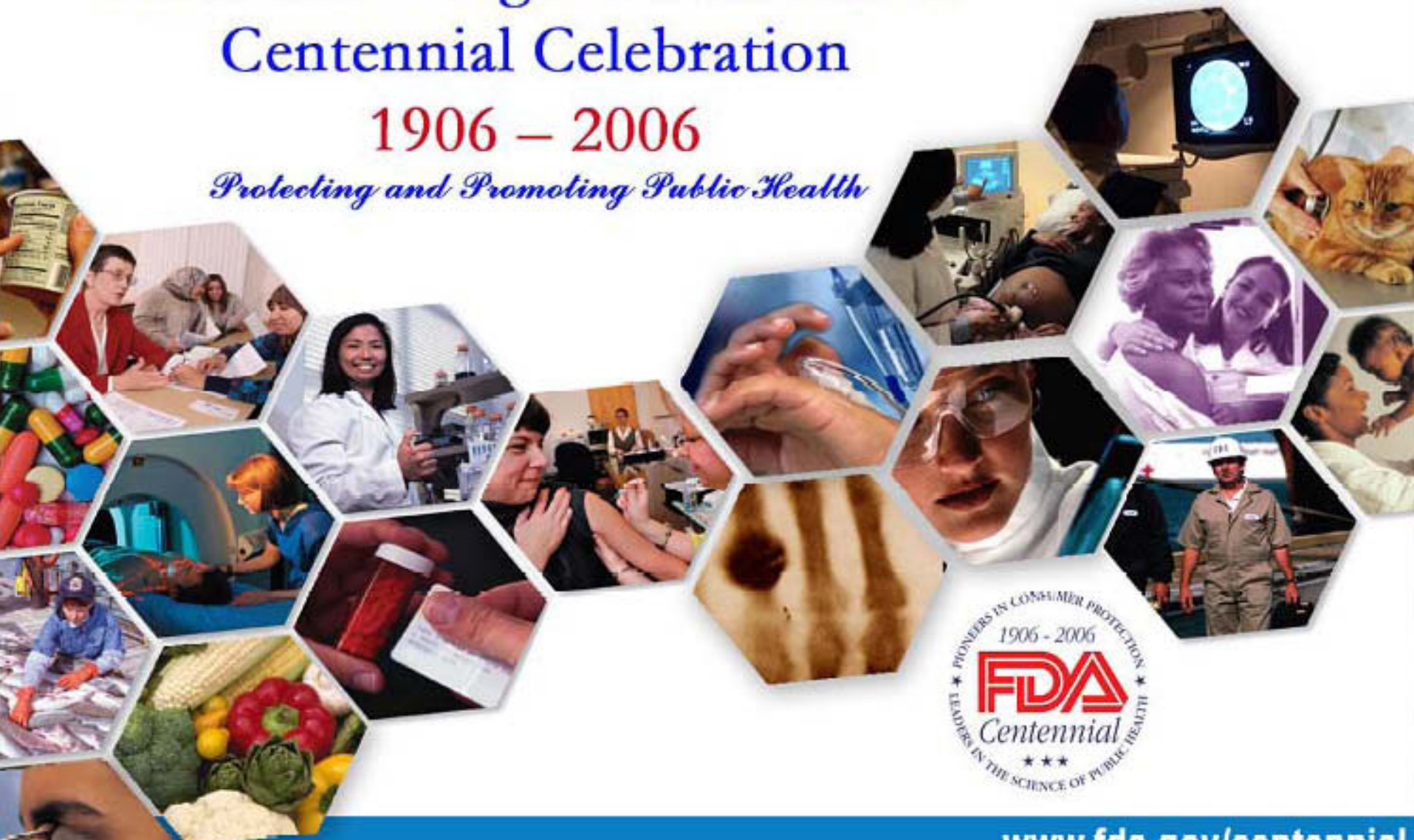
Protecting and Promoting Public Health



www.fda.gov/centennial

OIVD

The FDA Pre-Market Regulatory Process

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Overview

- Describe enabling legislation
- Define medical device
- Describe device classification
- Discuss pathways to market
  - Emphasis on Emergency Use Authorization
  - Premarket Approvals
- All opinions presented here are my own

CDRH Mission Statement

"Promotes and protects the health of the public by ensuring the safety and effectiveness of medical devices and the safety of radiological products."

Background

- Federal Food, Drug, and Cosmetic Act of 1938 (The Act)
- Medical Device Amendments of May 28, 1976
- Safe Medical Devices Act of 1990
- FDA Modernization Act (FDAMA) of 1997
- Medical Device User Fee and Modernization Act of 2002

What is a Device?

Medical Devices

Regulated under authority of Federal Food, Drug, and Cosmetic Act (by 1976 Device Amendments)

"… an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory … 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 …"

Medical Devices

- not technologies or methodologies alone
- not specific materials
- not processing techniques
- finished products for use in the diagnosis of disease, or other conditions, or the cure, mitigation, treatment, or prevention of disease

What is an IVD medical device?

"…those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body."

21 CFR Part 809.3

Recent New IVDs

510k: Redline Alert Test

Ampli Chip CYP450 Test

IDE (CDC):

SARS RT-P

510k: QuickELISA Anthrax-PA Kit

IDI-Group B Strep

510k de Novo: IgM West Nile Virus Capture ELISA

In vitro diagnostic (IVD) products

Traditionally used in clinical laboratories

- also other settings: point-of- care (e.g., ER, out-patient clinics), over-the-counter, prescription home use
- IVDs are not the only diagnostic devices – there are *in vivo* imaging and other diagnostic devices that don't use human specimens removed from the body (e.g., thermometers, implanted sensors)

Medical Devices, IVDs

May not necessarily include reagents/kits/systems for exclusive:

- forensic use
- custom use
- food/water use
- other environmental use

Caveat: Unless a claim is made to diagnose disease or other conditions, or cure, mitigate, treat or prevent disease, in man or other animals

Note: USDA regulates test systems exclusively for animal use

CLIA - Clinical Laboratory Improvement Amendments of 1988

- This law established quality standards for laboratory testing and an accreditation program for clinical laboratories
- Requirements vary according to the technical complexity in the testing process and risk of harm in reporting erroneous results

Regulatory requirements for IVDs

(Depend on classification, product type, and how used)

- Registration (facility) & Listing (product) (21 CFR 807)
- Quality Systems (GMPs and design controls) (21 CFR 820)
- Adverse Event Reporting (MDR, MedSun) (21 CFR 803)
- Restrictions (sale, distribution, and use)

Regulatory requirements for IVDs (cont'd)

- Informed consent (21 CFR 50)
- IRB approval (21 CFR 56)
- Investigational Device Exemption (21 CFR 812)
- Premarket notification (21 CFR 807 Subpart E) or Premarket approval application (21 CFR 814 Subparts A,B,C)
- Labeling (21 CFR 809.10, 809.30, 814.20, 814.104)
- Humanitarian Use Device (21 CFR 814 Subpart H)
- Analyte Specific Reagent (21 CFR 864.4020)

Labeling of IVDs (21 CFR 809.10(b))

- Proprietary and established names
- Intended use(s)
- Summary and explanation of test
- Principle of procedures
- Information on reagents and instruments
- Specimen collection and preparation
- Step-by-step recommended procedures
- Interpretation, expected values, performance
- Warnings and limitations

21 CFR 809.10(b)

Device Classification

- Intended Use
- Indications for Use

- Risk Based

- Three Classes

Device Classification (cont'd)

Class I

- devices needing the lowest level of regulation
- subject to General Controls
  - requirements sufficient to assure safety and effectiveness for their intended use

General Controls

- registration and listing
- Good Manufacturing Practices (GMPs)
- premarket notification (510(k))
- labeling
- prohibition of adulterated, misbranded, or banned devices
- record keeping
- reporting of device failures

Device Classification (cont'd)

Class II

- devices subject to special controls in addition to general control requirements

Special Controls (to minimize risk)

- special labeling requirements
- performance requirements
- postmarket surveillance
- patient registries
- guidelines/guidances
- design control
- tracking requirements

Device Classification (cont'd)

Class III

- devices with high risk
- no established predicates
- new intended use
- new device raises new types of questions about safety and effectiveness

Device Classification (cont'd)

Class III

Usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury

IVD may be exempt

- Unfinished device
- Finished device not sold in US
- General purpose reagents
- Analyte specific reagent - ASR
- Research use only - RUO
- Investigational use only - IUO
- "Home brew" – in house lab test
- Veterinary device
- Custom device
- Preamendment device

Pathways to Market

- Investigations
  - "significant risk" studies require an Investigational Device Exemption – IDE
  - "nonsignificant risk" studies and those exempt from part 812 must only be approved by an IRB
- Premarket approval - PMA
- Premarket notification - 510(k)
- Humanitarian device exemption – HDE
  - Humanitarian use device – HUD
- Emergency use authorization – EUA

510(k) Process

- Section 510(k) of the FD&C Act
- Called Premarket Notification
- Demonstrates "substantial equivalence"
  - same intended use AND
  - similar technological characteristics OR
  - does not raise new issues of safety and effectiveness
- 90-day review clock
- SE determination "cleared"

510(k) Process (cont'd)

- Based on evaluation of comparable performance of the new device with the predicate
- Uses clinical samples and sometimes artificial samples
- Prospective clinical studies rarely required for IVDs

510(k) Process (cont'd)

- Limitations to review:
  - No wet-lab product evaluation
  - Review based on data and information supplied by the sponsor
  - Few performance standards
- Optional approaches:
  - Special 510(k)
    - modifications
  - Abbreviated 510(k)
    - guidance documents or standards exist

De Novo Classification

- FDAMA provided new mechanism for classifying a new device for which a predicate does not exist
- Sponsor requests risk-based classification determination
- Allows a new device to be put into a class other than Class III

PMA Process

- Class III devices are subject to premarket approval requirements
- Reasonable assurance of safety and effectiveness
- 180 day review timeframe
- FDA finds product safe and effective for its intended use "approved"

Basic Premarket Review

- Assess safety for an IVD: Risk of misdiagnosis & epidemiological misinformation due to a false positive or a false negative result
- Evaluate effectiveness data
- Assess directions and conditions for use; adequate warnings against unsafe use
- For PMA devices, Review of manufacturing processes, inspection of facility, and bioresearch monitoring audit of clinical data sites

Safety

Reasonable assurance, based on valid scientific evidence, that the **probable benefits to health from use of the device** for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, **outweigh any probable risks**.

Effectiveness

Reasonable assurance, based on valid scientific evidence, that in a significant portion of the target population, the **use of the device for its intended use and conditions of use**, when accompanied by adequate directions for use and warnings against unsafe use, **will provide clinically significant results.**

IDE – Investigational Device Exemption

- Permits use in clinical studies to collect safety and effectiveness data
- Protects subjects participating in device investigations
- Assesses risks posed by use of a device
- Many IVD investigations exempted

Exempt from IDE

IVD exempt from IDE requirements if:

1. testing is non-invasive
2. does not require invasive sampling presenting significant risk
3. does not introduce energy into subject
4. is not used as a diagnostic procedure without confirmation by another, medically established product or procedure

Labeling requirements, informed consent, and IRB approval apply

Labeling

Investigational use only – IUO

"For investigational use only. The performance characteristics of this product have not been established."

Research use only - RUO

"For research use only. Not for use in diagnostic procedures."

Questions answered during review

- Do the benefits of using the results outweigh the risks of a false positive or false negative result?
- Is it necessary (to assure safety) to restrict use of the test system to certain types of laboratories?
- Can effectiveness of the test system for its recommended use be reliably predicted from data and information provided?
- What additional information should be included in the directions for use?

Other Information reviewed

- Interpretation of test system output:
  - the criteria used to call a test result positive or negative and how these results are to be reported
- Impact of a positive or negative result when applied to its intended use
  - and the impact of a false positive or negative result for the patient or the activity
- Limitations of the test system

HDEs – Humanitarian Device Exemption

- Similar to a PMA *except* exempt from effectiveness requirements
- Requires sufficient information
  - Device does not pose unreasonable risk
  - Probable benefits outweigh risk
- No comparable devices available
- Restricted use of humanitarian use device
  - IRB approval
  - Labeling that effectiveness has not been demonstrated

EUAs – Emergency Use Authorization

- Use of an unapproved product during a declared emergency
- Life-threatening or serious condition; no alternative available
- Prior FDA clearance, approval, or licensing under FD&C Act not obtained due to time constraints
- Request for EUA submitted to FDA Commissioner

http://www.fda.gov/oc/bioterrorism/emergency_use.html

Emergency

HHS Secretary must declare based on:

- Secretary of Homeland Security - domestic emergency or a significant potential for one
- Sec Def – military emergency
- HHS Secretary – public health emergency under section 319 of the PHS Act

FDA Commissioner issues EUA

- Serious of life-threatening disease or condition
- Reasonable to believe the product may be effective in diagnosing, treating, or preventing
- Known and potential benefits outweigh known and potential risks
- No adequate, approved, and available alternative

Pre-Emergency Activities

- For possible candidate products, now at advanced stage of development
- Contact CDRH for discussion on appropriate vehicle to use when submitting available safety and effectiveness information on the product
- Dr Claudia Gaffey
  claudia.gaffe@fda.hhs.gov

Pre-Emergency Activities (cont'd)

Prioritization of activities by FDA:

- For seriousness and incidence of the clinical condition
- The effect its use may have in ensuring national security
- Whether the product is included in US government stockpiles
- The adequacy of supporting clinical and non-clinical information

Pre-Emergency Activities (cont'd)

- FDA recommends that a pre-emergency submission be filed using existing process (IDE) to the extent feasible and appropriate
- Review timelines will be determined on a case-by-case basis
- Submissions for high priority activities may be reviewed in a matter of weeks

Emergency Activities

Once determination of an emergency has been made:

- Technical experts will identify products that may be eligible for an EUA in light of the circumstances
- HHS will facilitate timely submission of EUA request
- Emergency Use Authorization Working Group

Submitting an EUA Request for Consideration

- Description of the product and its intended use
- Identify what unmet needs would be addressed by issuance of the EUA
- Description of the product's approval or clearance status
- List each site where it would be manufactured and GMP status

Submitting an EUA Request for Consideration (cont'd)

- Identify any alternative approved products, including their availability and adequacy for the proposed use
- Provide all available safety and effectiveness information for the product
- Discuss risks and benefits
- Provide information on chemistry, manufacturing, and controls

Submitting an EUA Request for Consideration (cont'd)

- Describe the information to be provided to the authorized dispensers and users of the product
- … and the feasibility of providing such information
- Instructions for use, for example, if follow-up treatment is required
- Proposed labeling if applicable

Review Process for a Request for Consideration for an EUA

- Relevant FDA Center responsible for overall coordination
- Letter authorizing or not authorizing a specific emergency use or uses will be issued by the Office of the Commissioner
- Includes description of the intended use, indications and contraindications
- Federal Register notice will be drafted

EUA Conditions

- Unapproved product or Unapproved Use of an Approved Product
  - Information for Health Care Providers
  - Information for Recipients
  - Adverse Event Monitoring
  - Compliance with GMPs
  - Etc

fda.gov/oc/bioterrorism/emergency_use.html

EUA Conditions*

- Healthcare providers (doctors, pharmacists, nurses, etc.) and affected individuals are informed – NOT consented
- Informed about:
  - Risks & benefits
  - Alternative interventions
  - Option to accept or refuse product (HCP or patient)
    - Except Presidential waiver for DOD personnel

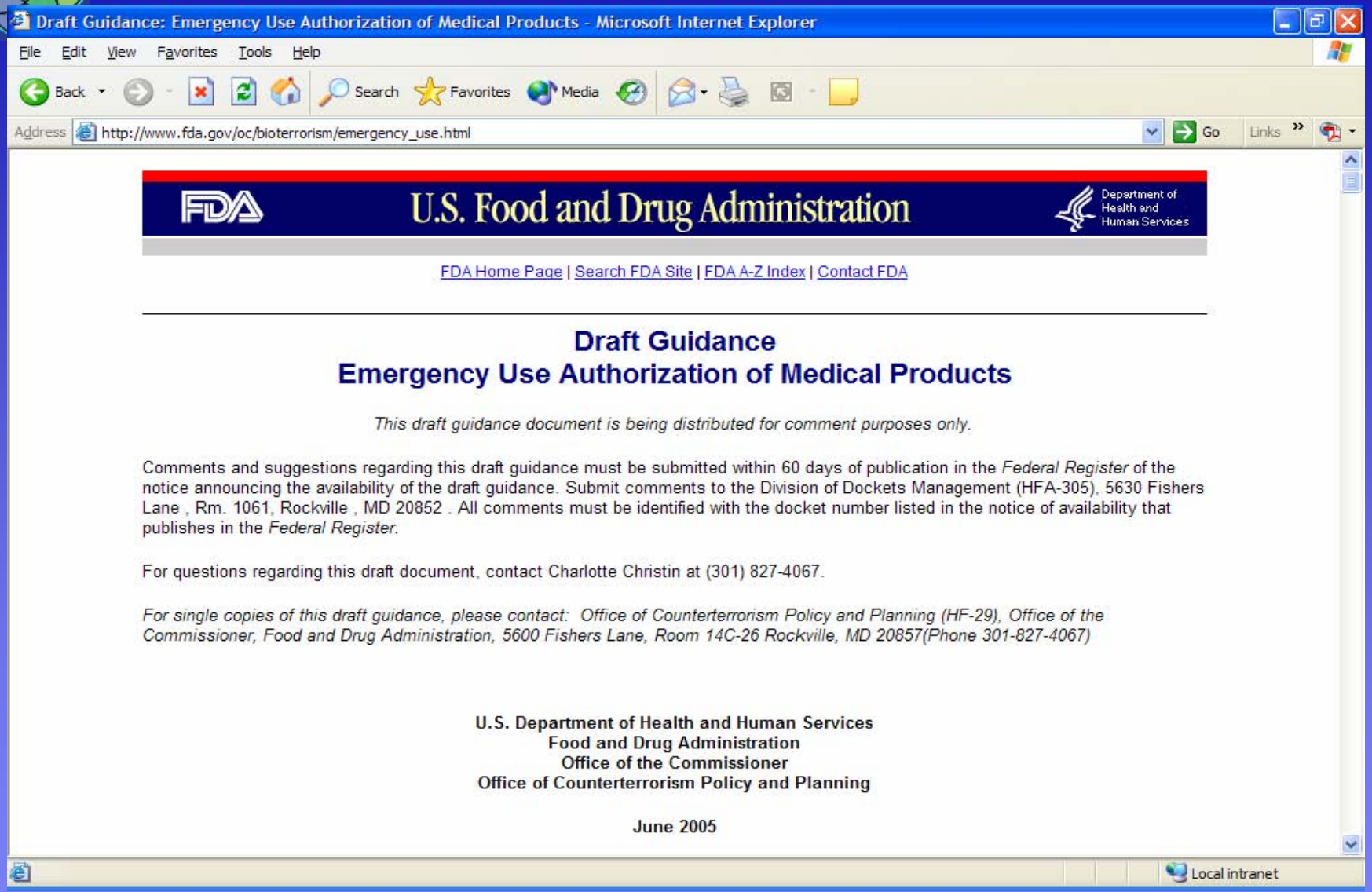
*to the extent feasible and appropriate

Conditions for Unapproved Products*

- MUST monitor and report adverse events
- MAY require collection and analysis of safety and efficacy data during emergency use
- MAY restrict distribution

*to the extent feasible and appropriate

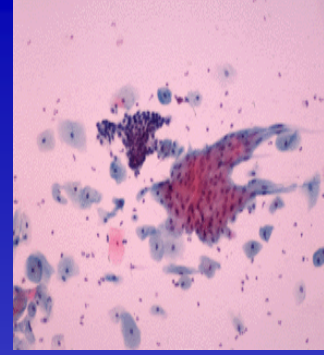
www.fda.gov/oc/bioterrorism/emergency_use.html



Impact on Patient Care

- Ensure device is safe and effective or as safe an effective as the predicate
- Ensure truth in labeling
- Ensure accountability for consistent manufacturing in conformance with labeling claims
- Ensure adverse events are reported, tracked and corrective action taken

OIVD Commitment



- Early collaboration with developers/future applicants
- Encourage coordination across disciplines
- Provide input on evaluation protocols & study design
- Encourage guidance and standard development
- Encourage partnerships with CDC, NIH, AACC, etc., and with device sponsors