Drug Good Manufacturing Practices Inspections

New England District Investigations Branch

Parenteral Drug Association
New England Chapter
May 17, 2006

DRUG MANUFACTURING INSPECTIONS

Inspections Include:

Domestic / Foreign Manufacturers

Repackers and Relabelers

Radiopharmaceuticals

Compressed Medical Gases

Active Pharmaceutical Ingredients/Chemicals

Rx and OTC Products

Sterile/Non-Sterile Products

DRUG MANUFACTURING INSPECTIONS

- F/Y-03 Risk Based Inspectional Assignments
  - High Risk Firms
    - Rx Drug Manufacturers/Repackers
    - Sterile Drugs
      - Rx and/or non-Rx
  - Low Risk Firms
    - Non-Rx
    - Medical Gas
    - Distributors/Warehouse Operations

Applying Risk Management to Drug Quality Regulation

- Identify parameters and processes that are critical for drug quality
  - What factors will adversely affect critical parameters/processes, increasing probability or severity or impact?
  - What factors will positively affect critical parameters/processes, decreasing probability or severity of impact?
    - E.g., greater process knowledge and capability

Applying Risk Management to Drug Quality Regulation (cont'd)

- Identifying critical processes and parameters
  - Sharing development report information?
  - Failure Modes and Effects Analysis (FMEA)?
  - Hazard Analysis and Critical Control Points (HACCP)?
  - Process Analytic Technologies (PAT)?
  - Statistical Process Control (SPC)?

Applying Risk Management to Drug Quality Regulation (cont'd)

- Focus regulatory scrutiny and resources on greatest perceived risks to quality
  - redirect scrutiny/resources from the areas with the lowest risk to quality to higher risk areas
- Adjust the intensity of regulatory oversight commensurate with the actual risk to drug quality
  - Provide additional incentives to mitigate risk and obtain decreased regulatory scrutiny

Applying Risk Management to Drug Quality Regulation (cont'd)

UNCERTAINTY

- To justify decreased regulatory scrutiny we need greater understanding of the sources of risk to product quality and the factors predictive of that risk
  - Enhanced hazard identification and risk assessment capacity
- Greater uncertainly requires greater regulatory scrutiny

Applying Risk Management to Drug Quality Regulation (cont'd)

- Burden must rest with regulated industry to demonstrate to FDA that reduced regulatory scrutiny is justified by the science/data
- Cannot individually examine GMP requirements in isolation from the system of which they are a part

Risk Management and Resource Allocation

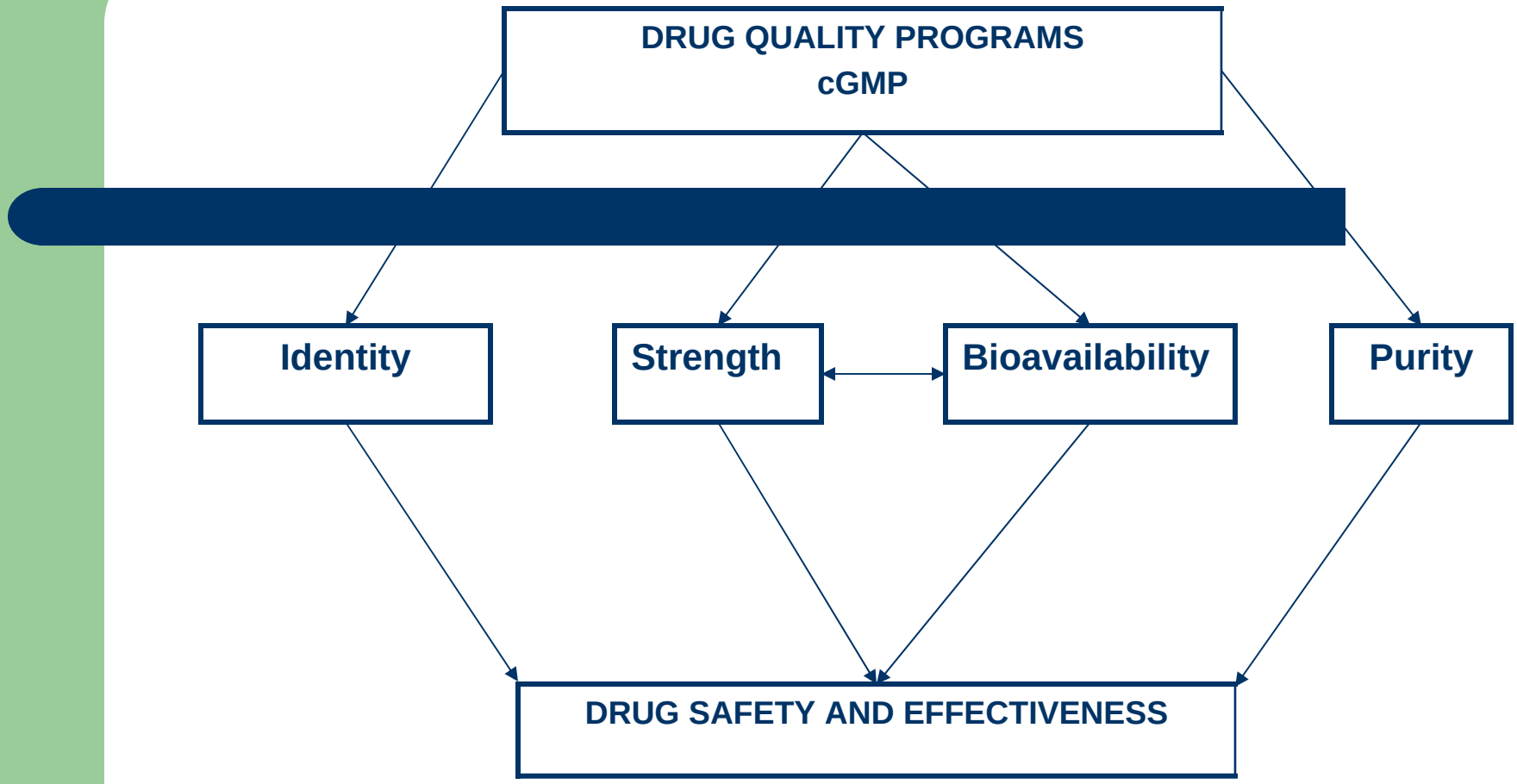
- Work-planning and risk management group
  - Risk-based approaches to targeting Field inspectional resources based upon the risk of manufacturing deficiencies that would reduce drug quality
  - Prioritize sites for inspections, focusing first on:
    - Post-approval inspections
    - Not including biologics (covered by Team Bio)

Risk Management and Resource Allocation (cont'd)

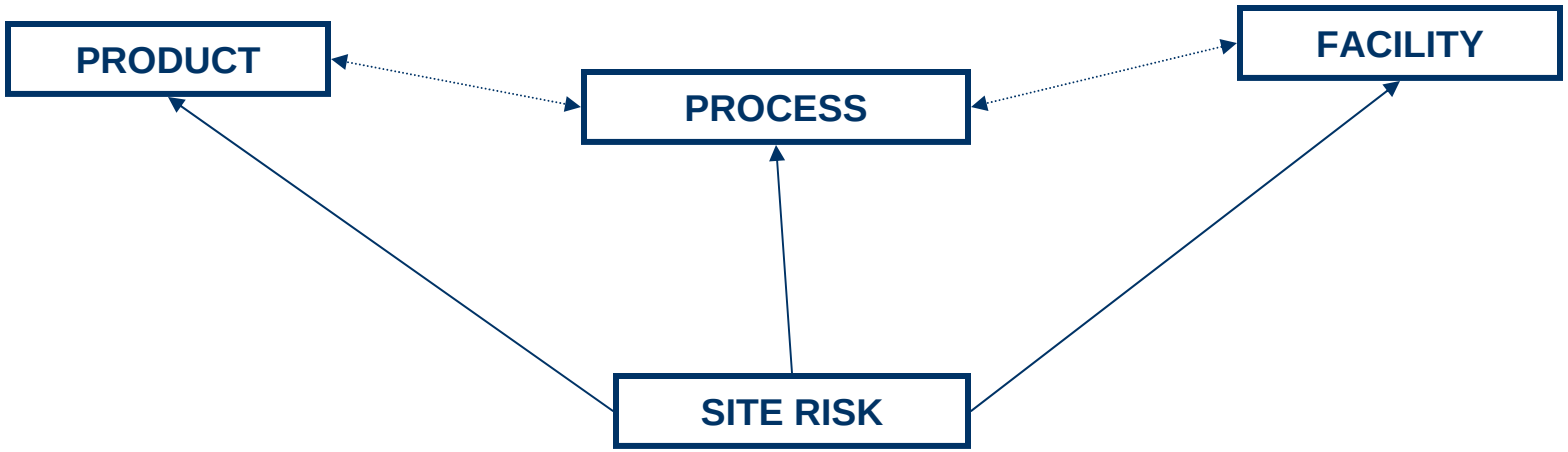
- Phase 1: Starting in FY '03, shifted emphasis to facilities making drugs perceived to be of higher risk if subject to manufacturing deficiencies
  - Sterile drugs
  - Rx drugs (non-medical gas)
  - New registrants
  - Far exceeded performance target to inspect at least 55% of facilities in these categories

Risk Management and Resource Allocation (cont'd)

- Developing more advanced risk-based models for prioritizing manufacturing sites for inspection: Work in progress
- Multi-factorial risk ranking and filtering provide a means of:
  - systematically incorporating our current knowledge about risks to drug quality
  - as a basis for allocating resources including prioritizing sites for cGMP inspections


DRUG QUALITY PROGRAMS
cGMP
Identity
Strength
Bioavailability
Purity
DRUG SAFETY AND EFFECTIVENESS

A RISK-BASED FRAMEWORK FOR PRIORITIZING SITES FOR CGMP INSPECTION



3 Decision Modules:

1) Product, 2) Process, 3) Facility

Risk Management and Resource Allocation (cont'd)

- Product-type factors
  - What are the intrinsic properties of products such that their deficiencies in quality would have more adverse public health impact than others?
    - Narrow therapeutic range
    - sterility
    - Rx vs. OTC
    - Route of administration
- Recall data (e.g., product or dosage form associated with prevalence of serious recalls?)

Risk Management and Resource Allocation (cont'd)

- Facility-type factors
  - Are some manufacturers or particular manufacturing facilities more likely to produce a product with quality problems?
    - Effectiveness of quality systems and process capability
    - Inspectional record and compliance history
    - Consumer exposure: volume produced at facility
      - Product sales volume
      - Special/sensitive populations
    - Other characteristics?
      - New Registrants?
      - New Products?

Risk Management and Resource Allocation (cont'd)

- Process-type factors
  - Are some manufacturing processes more likely to go wrong than others?
  - Are some process problems of greater public health significance? What are the consequences of process problems?
    - Risk of contamination or mix-ups
    - Maintaining state of control of the process
    - Identify additional risk factors and weightings
      - At the unit operation level
      - By product classes

Risk Management and Resource Allocation (cont'd)

- The product can only be as good as the scientific/technical input/assumptions that are used to develop the risk scores
- Implementing systematic risk-based approaches to focus regulatory oversight of drug quality regulation is a long term endeavor

DRUG MANUFACTURING INSPECTIONS

INSPECTIONAL STRATEGY

Biennial Inspection of Manufacturing Sites (includes repackaging, contract labs, etc.) Drugs and drug products are manufactured using many physical operations to bring together components and containers and closures into a product that is released for distribution. Activities found in drug firms can be organized into systems that are sets of operations and related activities.

DRUG MANUFACTURING INSPECTIONS

STRATEGY

Control of all systems helps to ensure the firm will produce drugs that are safe, have the identity and strength, and meet the quality and purity characteristics as intended.

DRUG MANUFACTURING SYSTEMS APPROACH

- Inspections of drug manufacturers are conducted and reported using a “system” definitions and organization. Focusing on systems, rather than profile classes (e.g., drug classes) will increase efficiency in conducting inspections.

- Coverage of a system will be sufficiently detailed so that the system inspection outcome reflects the state of control in that system.

- Any given inspection need not cover every system.

DRUG MANUFACTURING SYSTEMS APPROACH

- Complete inspection of one system may necessitate further follow up of some items within the activities of another system to fully document the findings.

- This coverage does not require complete coverage of these other systems.

DRUG MANUFACTURING SYSTEMS APPROACH

SYSTEMS:

- Quality
- Facilities and Equipment
- Materials
- Production
- Packaging/Labeling
- Laboratory Controls

DRUG MANUFACTURING SYSTEMS APPROACH

The Full Inspection Option

- The Full Inspection Option is a surveillance or compliance inspection which is meant to provide a broad and deep evaluation of the firm's CGMP.

- The Full Inspection Option will normally include an inspection audit of at least **four of the systems**, one of which must be the **Quality System** (includes annual product reviews).

DRUG MANUFACTURING SYSTEMS APPROACH

The Abbreviated Inspection Option

- The Abbreviated Inspection Option is a surveillance or compliance inspection which is meant to provide an efficient update evaluation of a firm's CGMP.

- The Abbreviated Inspection Option normally will include an inspection audit of at least **two of the systems**, one of which must be the **Quality System** (includes annual product reviews).

DRUG MANUFACTURING SYSTEMS APPROACH

Abbreviated Inspection Option - Continued

- Abbreviated inspection, verification of quality system activities, may require limited coverage in other systems. Some firms participate in a limited part of the production of a drug or drug product (e.g., contract laboratory with Quality and Laboratory)

- In these cases the inspection of these two systems will comprise inspection of the entire firm and will be considered the Full Inspection Option.

DRUG MANUFACTURING SYSTEMS APPROACH

State of Control

- A drug firm is considered to be operating **in a state of control** when it employs conditions and practices that assure compliance with the intent of Sections 501(a)(2)(B) of the Act and portions of the CGMP regulations that pertain to their systems.

DRUG MANUFACTURING SYSTEMS APPROACH

State of Control

A firm is **out of control** if any one system is out of control. A system is out of control if the quality, identity, strength and purity of the products resulting from that/those system(s) cannot be adequately assured. Documented CGMP deficiencies provide the evidence for concluding that a system is not operating in a state of control.

DRUG MANUFACTURING SIGNIFICANT DRUG PROCESSES

- Significant drug processes are those which utilize all the systems and/or which contain steps with unique or difficult manipulation including new drug products.
- Products posing special manufacturing features
  - low dose products
  - narrow therapeutic range drugs
  - combination drugs
  - modified release products, etc.,
  - new products made under an approved drug application are considered first in selecting products for coverage

DRUG MANUFACTURING SYSTEMS APPROACH

SYSTEMS:

- Quality
- Facilities and Equipment
- Materials
- Production
- Packaging/Labeling
- Laboratory Controls

QUALITY SYSTEMS

- Quality Control Unit has the responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use.

- Inspection will assess the data collected to identify quality problems and may link to other systems for inspectional coverage.

QUALITY SYSTEMS

- Product reviews: at least annually; should include batches reviewed, for each product, are representative of all batches manufactured; trends are identified; refer to 21 CFR 211.180(e).
- Complaint reviews (quality and medical): documented; evaluated; investigated in a timely manner; includes corrective action where appropriate.
- Discrepancy and failure investigations related to manufacturing and testing: documented; evaluated; investigated in a timely manner; includes corrective action where appropriate.
- Change Control: documented; evaluated; approved; need for revalidation assessed.
- Product Improvement Projects: for marketed products
- Review Out of Specification (OOS) procedures including trending of OOS results (e.g., equipment problem…)

QUALITY SYSTEMS

- Reprocess/Rework: evaluation, review and approval; impact on validation/stability.
- Returns/Salvages: assessment; investigation expanded where warranted; disposition.
- Rejects: investigation expanded where warranted; corrective action where needed.
- Stability Failures: investigation expanded where warranted; need for field alerts evaluated; disposition.
- Quarantine products.
- Validation: status of required validation/revalidation (e.g., computer, manufacturing process, laboratory methods).
- Training/qualification of employees in quality control unit functions.

FACILITIES AND EQUIPMENT SYSTEM

- Firm should have written and approved procedures and documentation. The firm's adherence to written procedures should be verified through observation. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage.

FACILITIES AND EQUIPMENT SYSTEM

- Facilities
  - Cleaning and maintenance
  - Facility layout and air handling systems for prevention of cross-contamination
  - Control system for implementing changes in the building
  - Lighting, potable water, washing and toilet facilities, sewage and refuse disposal
  - Sanitation of the building, use of rodenticides, fungicides, insecticides, cleaning and sanitizing agents

FACILITIES AND EQUIPMENT SYSTEM

- Equipment
  - Equipment installation, operational, and performance qualification where appropriate
    - Adequacy of equipment design, size, and location
    - Equipment surfaces should not be reactive, additive, or absorptive
    - Appropriate use of equipment operations substances, (lubricants, coolants, refrigerants, etc.) contacting products/containers/etc.
  - Cleaning procedures and cleaning validation
  - Controls to prevent contamination, particularly with any pesticides or any other toxic materials, or other drug or non-drug chemicals

FACILITIES AND EQUIPMENT SYSTEM

- Equipment
  - Qualification, calibration and maintenance of storage equipment, such as refrigerators and freezers for ensuring that products/components are stored at the proper temperatures
  - Equipment qualification, calibration and maintenance, including computer qualification/validation and security
  - Control system for implementing changes in the equipment identification practices (where appropriate)
  - Documentation of any unexpected discrepancy or non-conformance

MATERIALS SYSTEM

- Firm should have written and approved procedures and documentation. The firm's adherence to written procedures should be verified through observation.

- These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage.

MATERIALS SYSTEM

- Training/qualification of personnel
- Identification of components, containers, closures
  - Inventory of components, containers, closures
  - Storage conditions, quarantine until tested/examined
  - Representative samples collected, tested/examined using appropriate means
  - At least one specific identity test conducted on each component
  - Visual identification on each lot of containers and closures
  - Testing or validation of supplier's Certificate of Analysis results for components, containers/closures
  - Rejection of any component not meeting acceptance requirements including review of historical results

MATERIALS SYSTEM

  - Retesting of components, containers, closures
  - Use of components, containers, closures
  - Quarantine of rejected materials
- Water systems, design, maintenance, validation and operation
- Containers and closures should not be **additive, reactive, or absorptive** to the drug product
- Control system for implementing changes in the materials handling operations
- Qualification/validation and security of computerized or automated processes
- Finished product distribution records by lot (e.g., reconciliation of components)
- Documentation of any unexpected discrepancy

PRODUCTION SYSTEM

Firm should have written and approved procedures and documentation. The firm's adherence to written procedures should be verified through observation.

These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage

PRODUCTION SYSTEM

- Training/qualification of personnel
- Control system for implementing changes
- Adequate procedure/practice for charge-in of components
- Formulation/manufacturing at not less than 100%
- Identification of equipment with contents, and where appropriate phase of manufacturing and/or status
- Validation and verification of cleaning/sterilization/ depyrogenation of containers and closures

PRODUCTION SYSTEM

- Calculation and documentation of actual yields, percentage of theoretical yields, and reconciliation
- Contemporaneous and complete batch production documentation
- Established time limits for completion of phases of production
- Implementation and documentation of in-process controls, tests, and examinations
- Justification and consistency of in-process specifications and/or final specifications

PRODUCTION SYSTEM

- Prevention of objectionable microorganisms in non-sterile products
- Adherence to preprocessing procedures (e.g., line clearance)
- Equipment cleaning and use logs
- Master production and control records
- Batch production and control records
- Process validation, including validation and security of computerized or automated processes
- Change control; the need for revalidation evaluated
- Documented investigation into any unexpected discrepancy or non-conformance

PACKAGING AND LABELING SYSTEM

Firm should have written and approved procedures and documentation. The firm's adherence to written procedures should be verified through observation.

These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage

PACKAGING AND LABELING SYSTEM

- Training/qualification of personnel
- Acceptance operations for packaging/labeling materials
- Control system for implementing changes in operations
- Adequate storage for labels and labeling
- Control of labels with similar in size, shape, and color
- Finished product cut labels for immediate containers which are similar in appearance without 100 percent electronic verification system or use of dedicated lines
- Gang printing of labels is not done, unless differentiated by size, shape, or color

PACKAGING AND LABELING SYSTEM

- Control of filled unlabeled containers that are later labeled under multiple private labels
- Packaging records that will include specimens of all labels used
- Control of issuance of labeling, examination of issued labels and **reconciliation** of used labels
- Examination of the labeled finished product
- Inspection (proofing) of incoming labeling
- Use of lot numbers, destruction of excess labeling bearing lot/control numbers

PACKAGING AND LABELING SYSTEM

- Physical/spatial separation between different lines
- Monitoring of printing devices associated with labeling lines
- Line clearance, inspection and documentation
- Expiration dates on the label (as required)
- Conformance to tamper-evident (TEP) packaging requirements (see 21CFR 211.132)
- Validation of packaging/labeling operations including validation and security of computerized processes
- Limited access to packaging/labeling materials
- Documented investigation of any discrepancy

LABORATORY CONTROL SYSTEM

Firm should have written and approved procedures and documentation. The firm's adherence to written procedures should be verified through observation.

These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage

LABORATORY CONTROL SYSTEM

- Training/qualification of personnel
- Adequacy of staffing for laboratory operations
- Adequacy of equipment and facility for intended use
- Calibration and maintenance programs for analytical instruments and equipment
- Validation and security of computerized or automated processes
- Reference standards; source, purity and assay, and tests to establish equivalency to current official reference standards as appropriate

LABORATORY CONTROL SYSTEM

- System suitability checks on chromatographic systems (e.g., GC or HPLC)
- Specifications, standards, and representative sampling plans
- Adherence to the written methods of analysis
- Validation/verification of analytical methods
- Control system for implementing changes in laboratory operations
- Required testing is performed on the correct samples
- Documented investigation into any unexpected discrepancy

LABORATORY CONTROL SYSTEM

- Complete analytical records from all tests results
- Quality and retention of raw data (e.g., chromatograms)
- Correlation of result summaries to raw data; presence of unused data
- Adherence to an adequate Out of Specification (OOS) procedure which includes timely investigations
- Adequate reserve samples; documentation of reserve sample examination/storage
- Stability testing program, including demonstration of stability indicating test methods, and timely completion of testing

CDER September 3, 2003

FDA Announces New Progress Toward "21st Century" Regulation of Pharmaceutical Manufacturing

- Final guidance on electronic records and signatures
- Draft guidance on dispute resolution
- Draft guidance on aseptic processes
- Draft guidance on comparability protocols
- Draft guidance for Process Analytical Technology

Part 11 Guidance

- **Guidance for Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application**
- Published September 5, 2003
- Clarifies:
  - Scope of Part 11
  - Approach to Specific Part 11 Requirements

Key Concepts

- Narrow Interpretation of Scope
- Enforcement discretion applied as described
- Enforcement of all predicate rule requirements, including predicate rule record recordkeeping requirements.

Application of Part 11

- Part 11 applies:
  - when persons choose to use records in electronic format in place of paper format
- Part 11 does not apply:
  - When persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities

Part 11 Records (1)

- Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format in place of paper format.
- Records that are required to be maintained under predicate rules, that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities

Part 11 Records (2)

- Records submitted to FDA, in electronic format, under predicate rules (even if such records are not specifically identified in Agency regulations)
- (Assuming the records have been identified as the types of submissions the Agency accepts in electronic format).

Part 11 Signatures

- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules.
- Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g. approved, reviewed, and verified).

Part 11 Guidance Document

Guidance for Industry

Part 11, Electronic Records;
Electronic Signatures — Scope
and Application

August 2003

CDER Human Drugs

- **About CDER** (CDER Contacts)
  - http://www.fda.gov/cder/about/default.htm
- **Regulatory Information** (Guidance)
  - **http://www.fda.gov/cder/regulatory/default.htm**
- **What's Happening at CDER**
  - http://www.fda.gov/cder/calendar/default.htm
- **CDER Drug Information**
  - http://www.fda.gov/cder/drug/default.htm

CDRH Center for Devices and Radiological Health

- **Search Guidance Database**
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfggp/search.cfm
- **Search Premarket Approval Database**
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm
- Comments and Feedback
  - http://www.fda.gov/cdrh/comment4.html