

Nonclinical (Bench) and Animal Studies on Medical Devices

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Review of Product Development Process for Medical Devices

- Product specifications: components
- Classification of medical devices; controls
- Testing: nonclinical/bench and animal
- Clinical Testing: IRBs, IDEs
- Pilot plant - scale up - manufacturing
- Quality Assurance: clinical, manufacturing
- PMA Application

IDE Sections relating to bench and animal testing [21 CFR 812.20]

- Cover sheet
- Table of contents
- Report of prior investigations
- Environmental assessment
 - or request for categorical exclusion
- Labeling
 - labels
 - instructions for use; operator's manual
 - training materials
- Other relevant information, as requested by FDA

PMA Sections relating to bench and animal studies

- Applicant's name and address; signature of US representative
- Table of Contents
- Summary of Safety and Effectiveness data
- Reference to Performance Standards that are recognized
- Technical Sections of non-clinical and clinical data

PMA Sections, cont'd.

- Copies of Proposed Labeling
- Environmental Impact Statement or Assessment or claim of categorical exclusion
- Any other Information Requested by FDA



Bench Studies

Bench Studies

Sterilization and Shelf Life

www.fda.gov/cdrh/ode/guidance/361.html

Biocompatibility www.fda.gov/cdrh/g951.html

Software

www.fda.gov/cdrh/ode/guidance/337.html

Electromagnetic Compatibility and Electrical
Safety (IEC 60601-1-2; IEC 60601 1)

Other General Bench Testing, 1

Components: materials, biocompatibility
stability

Electromagnetic interference

Electrical leakage/shielding

Phantoms, simulators

Hazard analysis

Other General Bench Testing, 2

- Temperature range for optimal operation
- Humidity range for optimal operation
- Pressure (i.e., altitude) for optimal operation
- Radiation-emitting device (e.g., protect user, operator)
- Sterility requirements (e.g., use in operating suite)
- Particulate matter in atmosphere



Tox Studies

What Types of Nonclinical Studies Should Sponsors Conduct?

- ICH (International Conference on Harmonization) Guidelines
- Device specific guidance document (e.g., **POINTS TO CONSIDER FOR CERVICAL CYTOLOGY DEVICES** <http://www.fda.gov/cdrh/ode/968.pdf>)
- FDA Consultations

Types of Toxicology Studies

- General Toxicology
 - acute and repeat dose toxicology studies
- Special Toxicology Studies
 - local irritation studies, e.g., site specific, ocular
 - hypersensitivity studies for areas of exposure, e.g., inhalation and dermal products
- Reproductive and Developmental Toxicology Studies
 - male and female fertility
 - embryonic and fetal development
 - post-natal reproductive and developmental effects

Preclinical Testing

- Animal models: may not be possible to find that are analogous to disease/condition, or may provide meaningful insight
- Two species
 - Use relevant over non-relevant species
 - Demonstrate appropriateness of species chosen
- Mechanism of safety/effectiveness
- Chronic toxicity testing
 - Depends on length of time ens user will be “exposed” to the device
- Immunogenicity testing
 - Its implications (related to materials chosen)
- Carcinogenicity testing
 - Generally unnecessary unless material is immunosuppressive

Biocompatibility

www.fda.gov/cdrh/g951.html

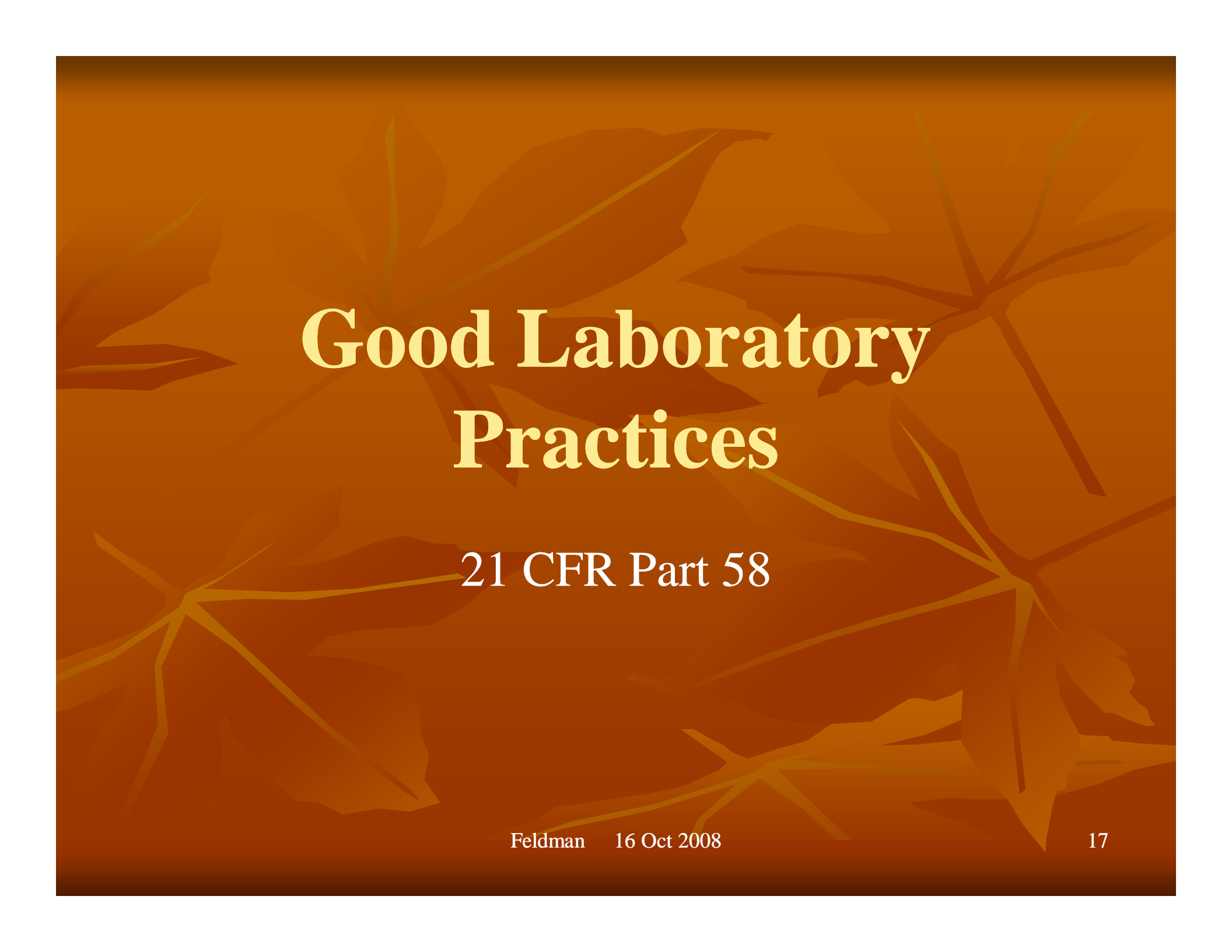
- Species selection
- Dose selection, power output
- Materials used for different parts of device; contact with end user
- How/where used (IV, on skin or mucous membrane surface, intra-organ, etc.)
- Expected duration of exposure to the medical device
- Endpoints/parameters to evaluate

Impact of Nonclinical Studies

- Setting initial doses (energy output), contact time, etc. in humans
- Identification of possible adverse effects
- Identification of reversible vs irreversible effects
- Identification of useful biomarkers for monitoring toxicity during clinical trials
- Labeling (warnings, precautions, contraindications for use of the device)

What Should You Expect to Get from a Nonclinical Study

- Did the test system (animal model) exhibit any effects?
- Were the effects treatment-related?
- Do you know the mechanism of the toxicology effect?
- Are the effects biologically significant?
- Are the effects reversible?
- Are the effects clinically relevant?
- Can the effects be monitored clinically?
- What is the estimated benefit: risk relationship that can be extrapolated to humans?



Good Laboratory Practices

21 CFR Part 58

Definition of GLPs

- *Basis: 21 CFR Part 58: GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES*
- *Nonclinical laboratory study* means *in vivo* or *in vitro* experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety.
 - The term does not include studies utilizing human subjects or clinical studies or field trials in animals.
 - The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

The term “GLP” is often misused!

- GLP does not mean:
 - Requirements for recording QC data
 - Requirements for any laboratory work (e.g., R&D or QC)
 - Definition of a material grade (“GLP-grade”)
- GLP does not pertain to **ANYTHING** other than a nonclinical laboratory study.

Concepts

- GLPs have more specific requirements, compared with other regulations.
- GLPs apply only to nonclinical safety studies.
- GLP studies can be *in vitro* or *in vivo*.
- Nonclinical studies are critical to any clinical study leading through market application (drug, devices, biologics).

GLP Studies are Enabling Studies

- These studies enable the company to obtain an IDE because they
 - Give an indication of toxicity, toxicology
 - Help to obtain a range of doses, time of exposure, et al for the test device
 - Help define safety parameters
 - Provide an early look at possible adverse effects

Major Sections

- Animal Care
- Standard Operating Procedures
- Records
- Equipment
- Analytical methods (from a guidance document)
- Disqualification

Pitfalls, 1

- Not ensuring the test article is representative of the process, materials, etc., of the clinical product
- You may have to repeat the study
- Your clinical study could be delayed
- Not using the data obtained from the study to establish monitoring in the human study.
- Not reporting safety issues from a GLP study while the clinical study is occurring.

Pitfalls, 2

- Assuming the contract lab knows what they're doing
- (trust but verify)
- Not seeking FDA concurrence of the study design before starting (risky)
- Not carefully reviewing the draft report before sending it to FDA.
- Not reporting ALL data obtained from a nonclinical study - you can discount it but you must report it.

GLP Summary

- GLPs are specific in their requirements
- GLPs may not be helpful if you cannot find an appropriate animal model
- GLPs are critical to clinical trial subject safety
- GLP studies are critical elements for an IDE, leading to market approval.

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