A Regulatory Perspective on the Introduction and Application of GLP Regulations:

What They Are, Why They Matter, and How They Apply to Toxicology Studies

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May 29, 2019

Disclaimer

The opinions expressed in this presentation are those of the presenter and do not necessarily reflect official support or endorsement by the Food and Drug Administration

I have no conflict of interest to report

Outline

- GLPs History is at the core of the FDA regulatory activity
- Timeline of GLPs Worldwide Development
- What is GLPs? Types of nonclinical studies requiring GLP compliance
- When do we need GLP?
- 21 CFR 58 Organization overview
- Value of GLP, compliance statement and importance of integrity and quality
- The Three Rs in GLP for CDER-OND Nonclinical Reviewers
- OECD Mutual Acceptance of Data (MAD) System
- A note on the FDA GLP Proposed Rule

Brief History on GLPs – Colonial Times to 1970

- 1906. The original Food and Drug Act passed by Congress and signed by President Theodore Roosevelt. The Act banned interstate traffic of mislabeled and adulterated products. The act required that active ingredients be placed on the label.
- 1938. The Federal Food, Drug, and Cosmetic (FDC) Act required that new drugs show safety before selling.
- 1960s. Environmental awareness raised by Rachel Carson “Silent Spring” book culminated with the formation of the EPA in 1970.
- 1962. Thalidomide, the sleeping pill, found to cause birth defects in thousands of babies in western Europe was not allowed marketing in the US by Dr. Frances Kelsey.
- The Kefauver-Harris Drug Amendments required that new drugs show efficacy and greater drug safety before selling.
- 1966. FDA contracts with the National Academy of Sciences/National Research Council to evaluate the effectiveness of 4,000 drugs approved on the basis of safety alone between 1938 and 1962.

Brief History on GLP - Faking It – Scientific Misconduct

- Adrian Gross, the associate director of nonclinical studies in the FDA's Bureau of Drugs, referred to the Searle and IBT events as they "occurred purely by chance.“
- 1972. G.D. Searle & Company of Shokie, Illinois produced Flagyl, Aldactone and aspartame.
- 80-w rat study to support long term use different from an independent investigator study that showed Flagyl caused cancer in test animals.
- 1974. Searle submitted a new version of the same study to the FDA. "Instead of changing the summary to more accurately reflect the data, the data was changed to more accurately reflect the summary“
- 1975. Aldactone studies suggested it also caused cancer in animals. Conclusions from FDA independent analysis different from Searle’s data submitted.
- Six teams of FDA investigators went through 25 toxicology studies from October 6 until December 19 included studies conducted
- Inspection findings were too numerous to list in the form FDA-483 (Inspectional Observations) issued

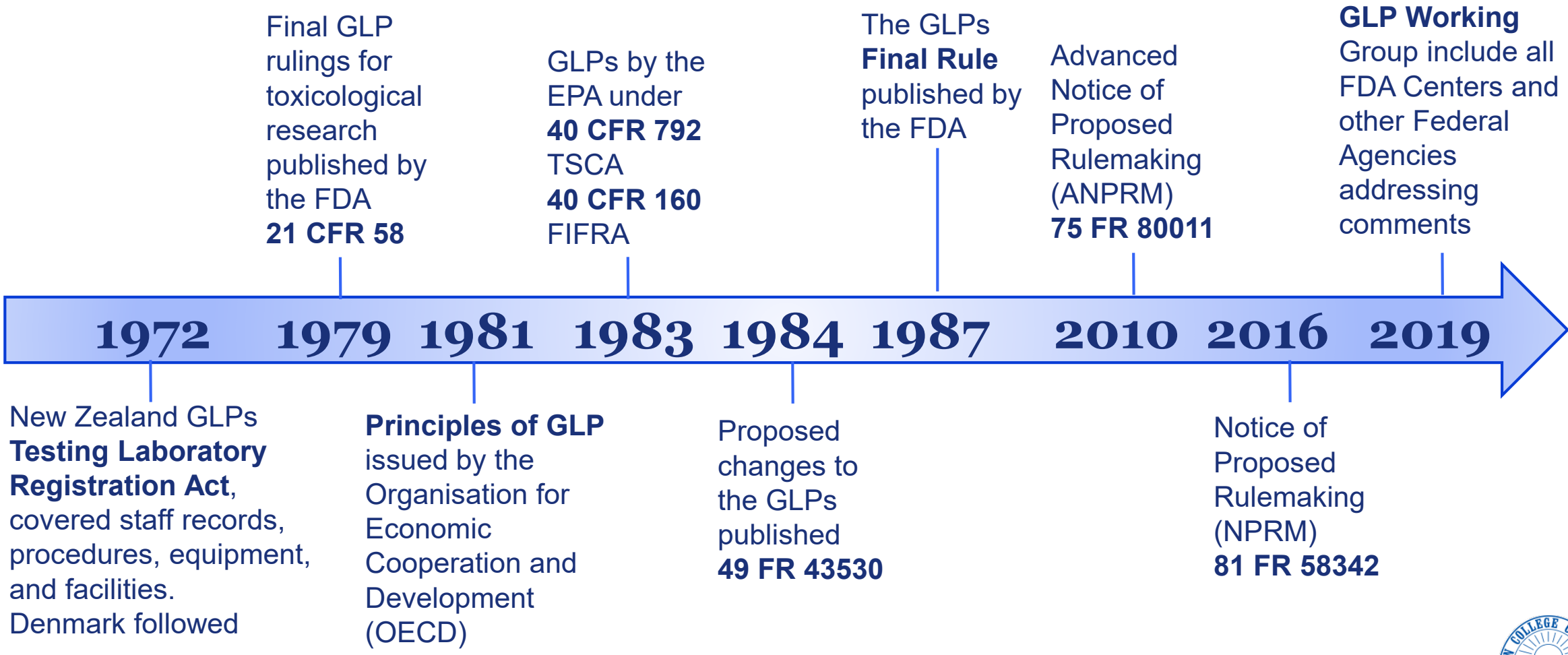
Brief History on GLP - Faking It – Scientific Misconduct

- Industrial Bio-Test Laboratories (IBT) a CRO from Illinois conducted in its last 10 years of operation approximately 35–40% of all of the toxicology studies in the United States: drugs, insecticides, herbicides, food additives, pesticides, cosmetics and cleaning products.
- 1975. FDA received a tip from Syntex but the FDA official pulled a file on IBT and found enough deficiencies to warrant an inspection.
- FDA inspection went from April 11 to July 12, 1976. Abundant and shocking evidence of scientific misconduct found. A rodent study room called the 'Swamp' was described by Keith Schneider in his article 'Faking It: The Case Against IBT."
- All kind of fabrication of data, records with acronyms TBD (too badly decomposed) and TDA (technician destroyed animal) were used.
- 1205 pesticide studies revised, 214 found acceptable. Sponsors spent millions of dollars repeating thousands of studies for pesticides and industrial chemicals. Careers ruined.
- 1981. Three company officers found guilty of mail fraud and making false statements to the government

Brief History on GLP – FDA Regulations Law enacted

- January 1976. Searle staff submitted a draft of GLP regulations to the FDA
  - Personnel, control of test substances, animal care, facilities and equipment, study design, study conduct, reporting of results, storage and retrieval of data, and compliance
- November 11, 1976. The FDA published in the Federal Register proposed GLP regulations based on the Searle document (two year comment period)
  - established the QAU to oversee compliance, write SOPs and assure studies were conducted according to the protocol
- A bioresearch monitoring program with 606 FDA positions began a pilot program of inspections of laboratories to determine compliance with the proposed regulations
- December 22, 1978. Final GLP regulations based on findings of these inspections were published in the Federal Register
- June 20, 1979. Law enacted. Regulations collected in Title 21: "Food and Drugs" of the Code of Federal Regulations (CFR) as Part 58: "Good Laboratory Practice for Nonclinical Laboratory Studies“

Worldwide Development of GLPs



Slide contents from Del Valle, PL CDER-OND Learning & Career Development Foundational Courses for New Pharmacology & Toxicology Reviewers 2012-2019.

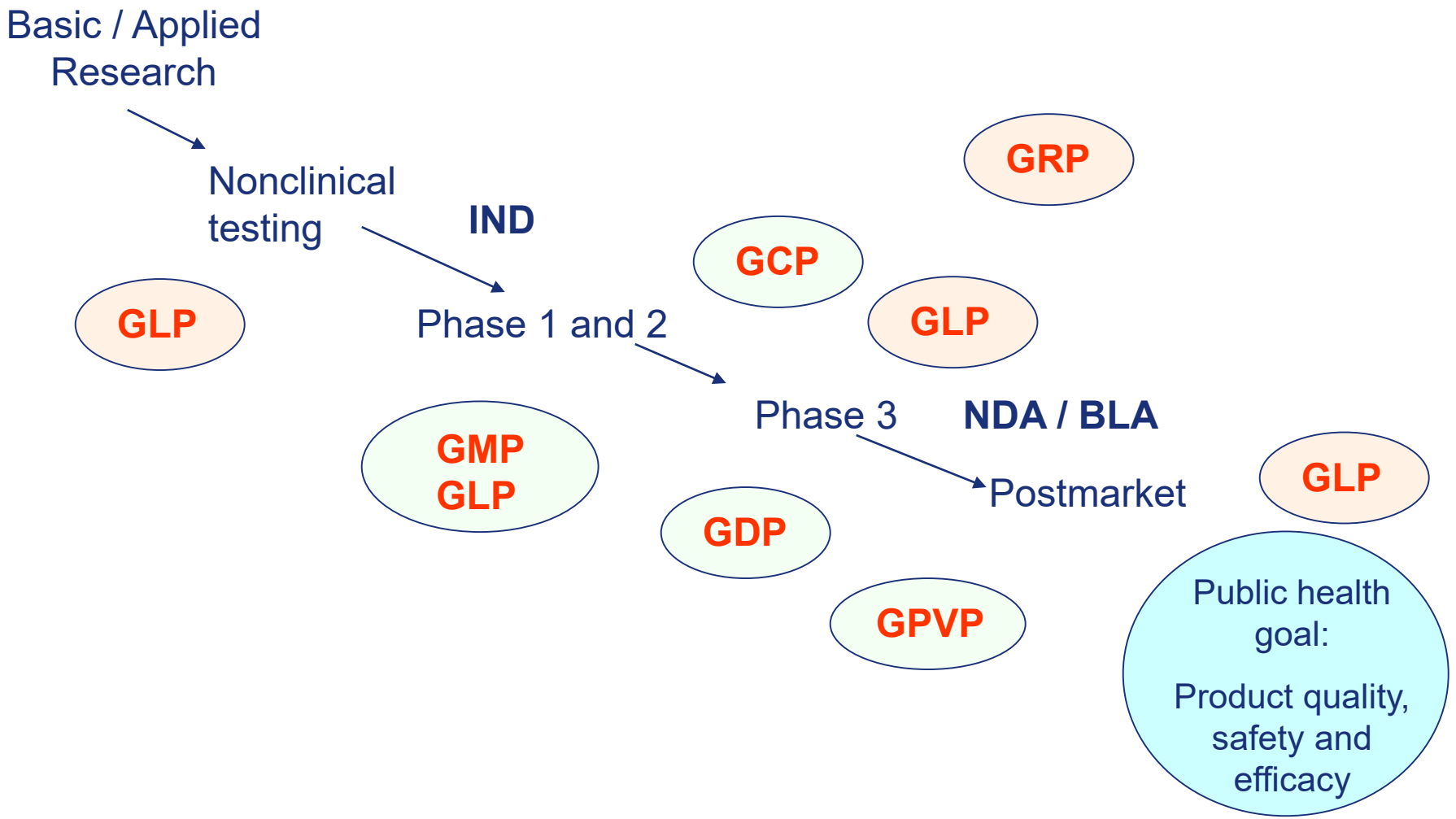
What is Good Laboratory Practices

- A quality system of management controls for research laboratories and organizations
- Ensure the uniformity, consistency, reliability, reproducibility, quality, and integrity of non-clinical safety tests (how studies are planned, performed, monitored, recorded, archived and reported)
- Tests include from test articles physio-chemical properties evaluations through acute and chronic toxicity assays conducted for chemicals and pharmaceuticals.

Common Nonclinical Studies and Tests used to support Regulatory Submissions

- Safety pharmacology (CNS, CVS, RS)
- Single and repeated dose toxicology studies in rodents (mice, rats) and nonrodents (dogs, monkeys) or other animal models
- Toxicokinetics, usually incorporated in tox studies
- Genetic toxicology studies
- ADME
- Reproductive toxicity (mice, rats, rabbits)
- Carcinogenicity
- Test Article characterization

When do we need GLP?



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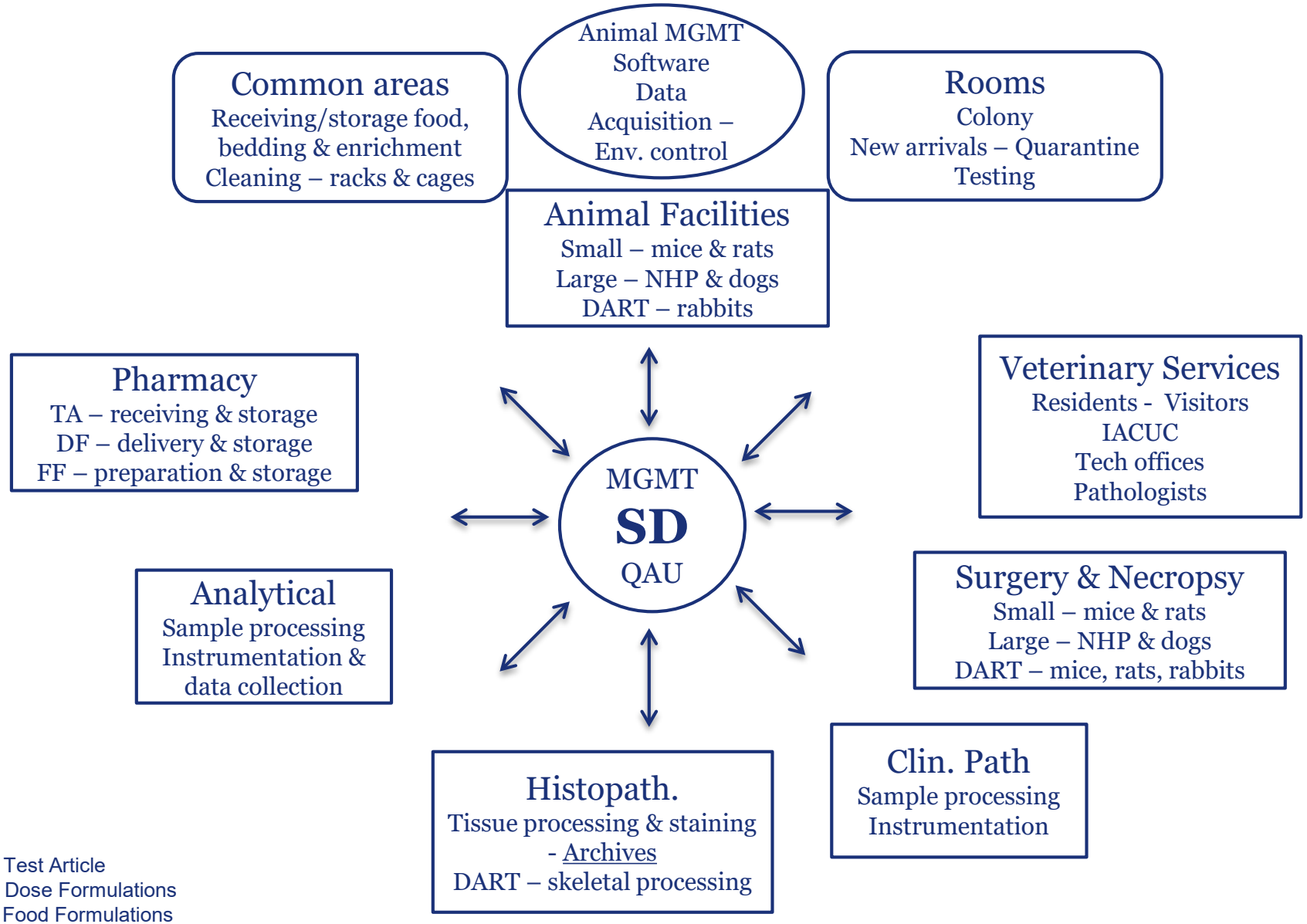

TA: Test Article
DF: Dose Formulations
FF: Food Formulations

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Organization of GLP 21 CFR 58

- ***GLP Subpart A —***
  GENERAL PROVISIONS
- ***GLP Subpart B —***
  ORGANIZATION AND PERSONNEL
- ***GLP Subpart C —***
  FACILITIES
- ***GLP Subpart D —***
  EQUIPMENT
- ***GLP Subpart E —***
  TESTING FACILITIES OPERATION
- ***GLP Subpart F —***
  TEST AND CONTROL ARTICLES
- ***GLP Subpart G —***
  PROTOCOL FOR AND CONDUCT OF NCL STUDY
- ***GLP Subparts H-I —***
  [RESERVED]
- ***GLP Subpart J —***
  RECORDS AND REPORTS
- ***GLP Subpart K —***
  DISQUALIFICATION OF TESTING FACILITIES

Value of GLP, the Compliance Statement and Importance of Integrity of Nonclinical Studies

Value of GLPs

- Assures data integrity
- Ensures that a study can be completely reconstructed from archived records
- Protects the well-being of subjects in clinical trials many of whom are healthy volunteers
- Provides job security for Study Directors, Technicians and an army of QA auditors and consultants

Compliance Statement

- Ultimate value of GLP compliance is assurance of **data integrity** and **quality** to FDA reviewers.

Importance of Integrity

- When recommending a safe human starting dose for a clinical study based on animal toxicology studies, the value of **data integrity** and **quality** is obvious.

Slide contents from Del Valle, PL CDER-OND Learning & Career Development Foundational Courses for New Pharmacology & Toxicology Reviewers 2012-2019.

The Three Rs in GLP for OND Nonclinical Reviewers

- Ratify. Need to inspect and verify that study reports comply
  - GLP principles, 21 CFR 58 and/or OECD regulations
  - Systematic approach conducted before reviewing study reports data that takes 10-30 min
  - After applying the first R, reviewers are certain of the value of the data in the study report

Sections of Study Reports to Ratify [§ 58.185]

- Study Director Compliance Statement, GLP exceptions and impact on study, date & signature, Contributor reports, dates & signature
- QAU statement, phases inspected, dates & signature [§ 58.35(b)(7)]
- Dates for Study Time Table – Signed Protocol [§ 58.120(a)]
- Personnel qualifications & location

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The Three Rs in GLP for OND Nonclinical Reviewers

- Review. Job function
  - Characterize pharmacology and toxicology of a drug product from information provided by Sponsors.
  - Present this information in a way that the entire review team can use in risk/benefit decisions and product labeling
  - While reviewing the experimental design, data collection, data integrity, reviewers continue Ratifying compliance with GLP

Additional Sections to Ratify

- Test System, Experimental Design – Individual data if necessary
- Dose formulations – CoA [§ 58.105], stability, errors. Does data looks real? Any Flags?
- Missing target tissues and impact on study
- Read protocol deviations, agreed/disagree with assessment by the Study Director

Slide contents from Del Valle, PL CDER-OND Learning & Career Development Foundational Courses for New Pharmacology & Toxicology Reviewers 2012-2019.

The Three Rs in GLP for OND Nonclinical Reviewers

- Report GLP non-compliance issues
  - Discuss issues with your Team Leader
  - Communicate any regulatory decision to the review team and to the Sponsor.
    - Any Review Team can send INDs to clinical hold
  - Report non-compliance issues to the Office of Study Integrity and Surveillance (OSIS)

- FDA OSIS can decide the type of inspection to conduct
  - Surveillance, that is a Periodic, routine inspection
    - Facility inspection, audit ongoing or recently completed studies
  - Directed, that is a follow up inspections “For cause”
    - Linked to an application, to verify study data
    - 3rd party or Sponsor audit result verification

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Summary of FDA GLPs

- Cases on faking data and scientific misconduct marked the law enactment for GLPs in the United States (1979)
- GLP Regulations and Guidelines are published in many countries
- The FDA GLP Regulations is a quality system of management controls (21 CFR 58, Final Rule) that ensure the uniformity, consistency, reliability, reproducibility, quality, and integrity of non-clinical safety tests
- The Proposed Rule to modify GLPs is in the final stage with public comments being addressed
- GLP compliance is assurance of data integrity and quality to FDA reviewers
- The three Rs in GLPs is a systematic approach used by CDER Reviewers to Ratify, Review and Report compliance issues
- FDA OSIS conducts surveillance or directed inspections
- The FDA review submissions and enforce GLPs regulations. Due your diligence making sure study reports comply.

OECD Mutual Acceptance of Data (MAD) System

- The Organisation for Economic Co-operation and Development (OECD) promotes policies to improve the economic and social well-being of people around the world and provides a forum in which governments can work together to share experiences and seek solutions to common problems.
- OECD also published the Guidelines for the Testing of Chemicals. GLP compliance is required by agencies conducting risk assessments of chemicals
- Decision C(97),186 of the OECD Council (1977;1981)
  - Data generated in one OECD Member Country, compliant of OECD Testing of Chemicals Guidelines and the Principles of GLP, are accepted in all other OECD Member Countries
  - Pharmaceuticals, pesticides, cosmetics, veterinary drugs, food additives, and industrial chemicals

MAD Criteria for non-clinical health and safety test study

- The study must have been conducted according to OECD Test Guidelines and OECD Principles of GLP;
- The study must have been conducted in a test facility which has been inspected by a national GLP compliance monitoring programme and;
- The national GLP compliance monitoring programme must have undergone a successful evaluation by OECD.

If all three criteria are met, all OECD member countries as well as adherents to MAD must accept the study data.

https://www.oecd.org/env/ehs/mutualacceptanceofdatamad.htm

OECD Member Countries

AUSTRALIA	AUSTRIA
BELGIUM	CANADA
CHILE	CZECH REPUBLIC
DENMARK	ESTONIA
FINLAND	FRANCE
GERMANY	GREECE
HUNGARY	ICELAND
IRELAND	ISRAEL
ITALY	JAPAN
KOREA	LUXEMBOURG
MEXICO	NETHERLANDS
NEW ZEALAND	NORWAY
POLAND	PORTUGAL
SLOVAK REPUBLIC	SLOVENIA
SPAIN	SWEDEN
SWITZERLAND	TURKEY
UNITED KINGDOM	UNITED STATES

OECD Non-Member Country Adherents:

ARGENTINA	BRAZIL
INDIA	MALAYSIA
SOUTH AFRICA	SINGAPORE

The MAD applies to all these countries

GLP Proposed Rule

Highlights of Proposed Changes

- Enhance (require) the existing quality system approach.
- Reflect current practices such as multisite studies.
- Incorporate wording consistent with domestic and international (OECD) guidelines or regulations.

Specifically,

- Expand scope
- Add definitions
- Clarify GLP roles and responsibilities
- Add animal welfare provisions
- Request comment on Animal Rule studies

Slide information presented by Mark Seaton, Ph.D., DABT, FDA/CDER/OTS/OSIS
SOT: Regulatory and Safety Evaluation Specialty Section Webinar. September 29, 2017

Topics Covered

- GLPs History is at the core of the FDA regulatory activity
- Timeline of GLPs Worldwide Development
- What is GLP? Types of nonclinical studies requiring GLP compliance
- When do we need GLP?
- 21 CFR 58 Organization overview
- Value of GLP, compliance statement and importance of integrity and quality
- The Three Rs in GLP for CDER-OND Nonclinical Reviewers
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- Code of Federal Regulations https://gov.ecfr.io/cgi-bin/text-idx?SID=4618315a02cfab6f467f69d087e04920&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl
- OECD Principles of Good Laboratory Practices http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en

Definitions of “Good Practices”

- Good Laboratory Practices (GLP)
- Good Manufacturing Process (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.
- Good Clinical Practices (GCP) is an international quality standard that is provided by ICH, an international body that defines a set of standards, which governments can then transpose into regulations for clinical trials involving human subjects.
- Good Distribution Practices (GDP) is a quality system for warehouse and distribution centers dedicated for medicines.
- Good Pharmacovigilance Practices (GPVP) a system to assess the risk of adverse events for patients taking drugs—bearing in mind that no medicine is completely safe—at the time of approval for sale and throughout the product’s lifecycle
- Good Review Practices (GRP) is a “documented best practice” within CDER that discusses any aspect related to the process, format, content and/or management of a product review.

An Industry Perspective on the Introduction and Application of GLP Regulations:

What They Are, Why They Matter, and How They Apply to Toxicology Studies

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BASi/Seventh Wave

Disclaimer

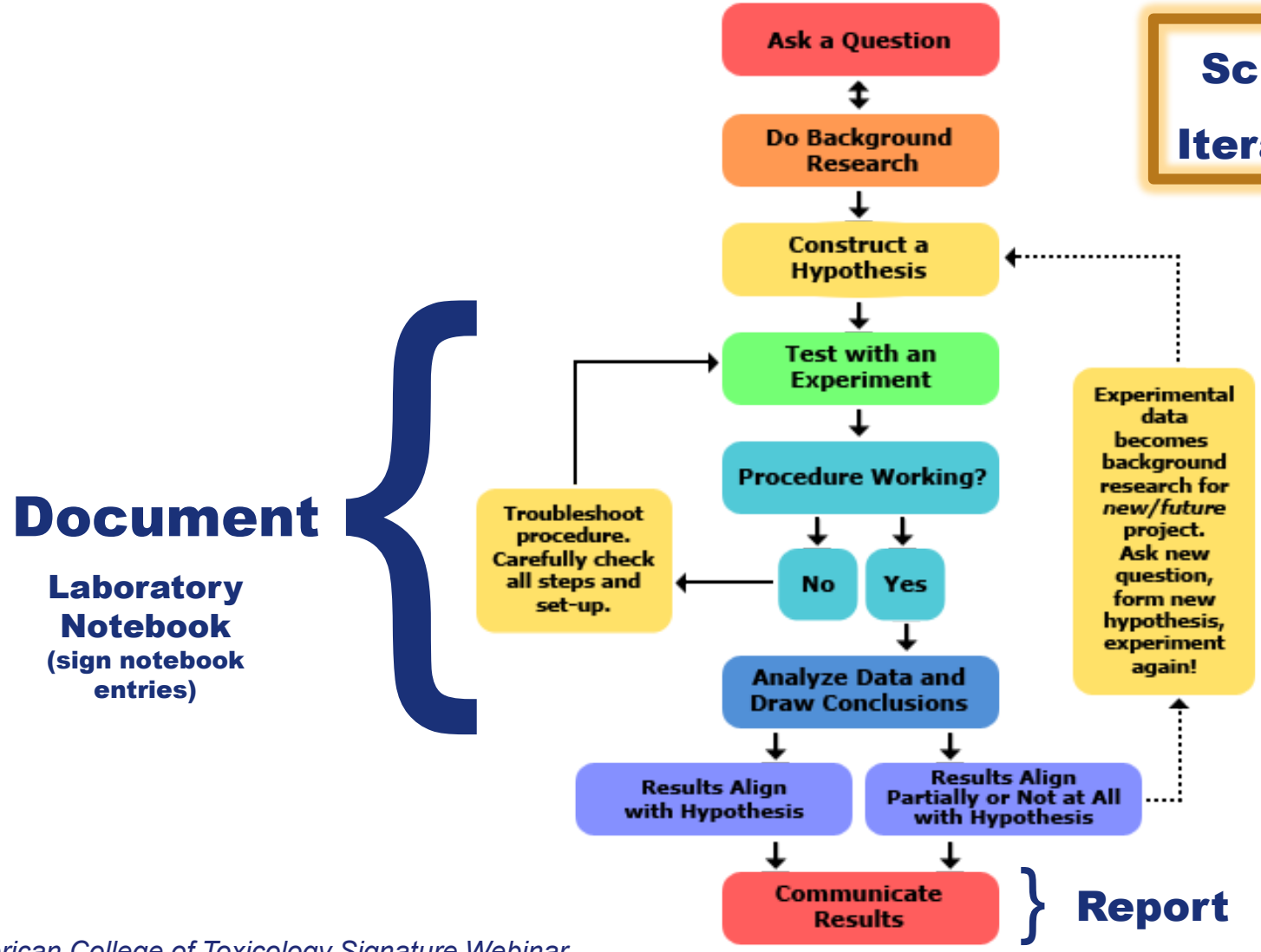
- The views expressed are those of the presenter
- The presenter is/has been executive management in pharmaceutical/agro and CRO industries
- No conflicts of interest
- **This is an introductory discussion of the impact and current state of GLPs**

GLPs: A Very Broad Topic

GLPs: Relationship to the "Scientific Method"

Science is an iterative process.

Iteration requires documentation.



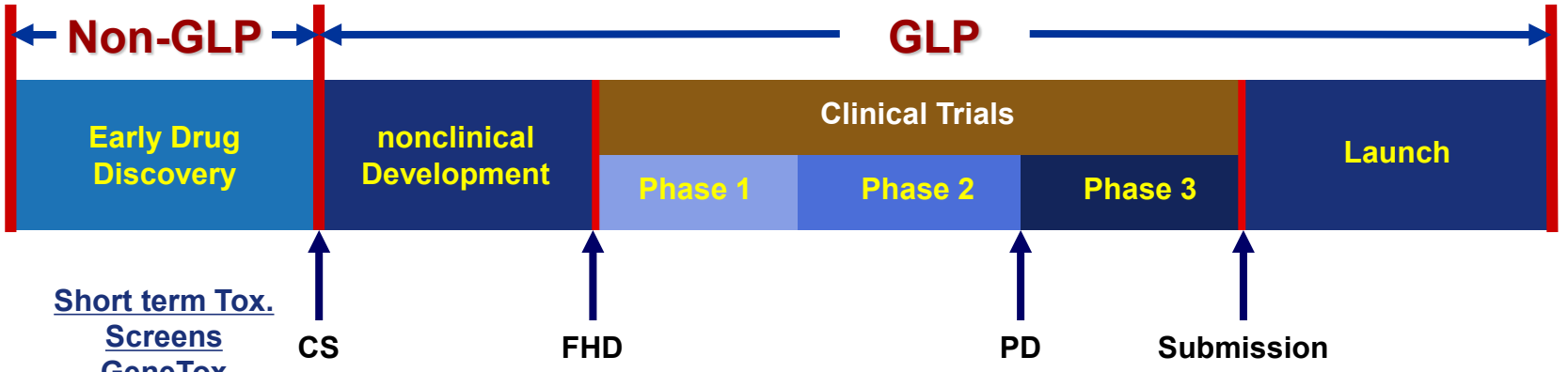
GLP Regulations, Why They Matter to Industry (Pharmaceuticals)

- The GLP principle is to assure quality, reproducibility, accountability and integrity in nonclinical evaluations supporting products regulated by governmental agencies, e.g., FDA
- GLPs address quality standards, not scientific standards
  - GLP compliance assures conduct according to established procedures, e.g., SOPs
  - GLPs were not implemented as a review of the scientific merits of a study
    - GLP compliance does not assure addressing the scientific question
- GLPs were proposed in the United States in 1976, 19 Nov, to address
  - Scientific misconduct, study quality and integrity issues in the conduct of animal safety testing at what was then the largest contract toxicology testing facility of its kind, in the 1970s

GLP Regulations, What Are They

- The Code of Federal **Regulations** (CFR) Title 21, Part 58 outlines the Good Laboratory Practices (GLP) for conducting nonclinical laboratory studies that are intended to support applications for research or marketing permits for products regulated by the FDA.
  - 1978: published Final with an effective date of 1979
  - 1984 proposed revision published as Final Rule in 1987
  - 2016: The Food and Drug Administration (FDA) proposed amending the regulations for good laboratory practice (GLP) for nonclinical laboratory studies
- Standard of Practice to ensure that nonclinical studies submitted to FDA are valid, reconstructable and accurately reflect the conduct of the study
- Laboratory conduct may be colored to FDA expectations, which evolve in the context of the existing regulations
- **Do not apply to basic exploratory studies conducted to assess test article utility**

Non-GLP or GLP



Short term Tox.
Screens
GeneTox
Recep binding
≤ 7 to 14-day tox

Definitive Tox
GeneTox
≤ 30-day Tox
Toxicokinetics

≤ 6-month Tox.
Metabolism
Toxicokinetics
Dev. Tox

≥ 6-month Tox.
Oncogenicity
Env. Asses.
CTD

Support for alternate
Deliveries, Formulations,
Combinations
Activities could begin post PD

CE = Candidate Evaluation
CS = Candidate Selection
FHD = First Human Dose
LO = Lead Optimization
PD = Product Decision

GLPs: The Pillars

- Study Director (SD)
- Quality Assurance Unit (QAU)
- Facility Management
- Sponsor
- The FDA Office of Regulatory Affairs (ORA) is an important part of GLPs too.

GLPs: Why they exist in the United States

- Dr. Mark Seaton (FDA/CDER) presented an update on FDA GLPs at the SOT Regulatory and Safety Evaluation Specialty Section Webinar 29 Sept 2017 and included the following:
  - **"Magic Pencil Study"** (FDA visit to IBT April 1976)
    - Terminal blood and urine samples were not collected.
      - Draft data tables for the blood and urine assessments were blank, as expected.
      - However, the final report had these values reported; appears to have been fabricated.
    - FDA and EPA reviewed compounds that relied on IBT for data in support of safety.
      - **Called into question the reviews of more than 200 pesticides, many were retested at manufacturer's expense.**
      - **618 of 867 (71%) of studies audited by the FDA were invalidated for having "numerous discrepancies between the study conduct and data".**
      - **"*What we found there is enough to make your hair stand up*"**

GLPs: Industry Reaction to GLP Introduction (1978)

- **Disclosure**: Strictly related to my recollection
- The findings in the FDA audit of the IBT facilities were shocking to the pharmaceutical and the agrochemical industries
  - Industry had to accept that systemic problems were uncovered
  - Industry had to prepare for routine inspections and re-inspections for
    - Compliance to established company procedures, *e.g.*, SOPs
    - Compliance to FDA Regulations covering conduct of scientific investigations
      - **Had to prepare SOPs and QAUs for nonclinical study areas**
        - Extent of detail was an issue
  - Practices considered **RESEARCH** were not *in sync* with FDA expectations developed from IBT investigations
- GLPS established strict standards missing in the non-GLP studies
  - Accountability: Study Director
  - Responsibility: Management
  - Compliance: QAU

The QAU is the best friend of the scientist in a GLP environment

GLPs: Common Reason for FDA Inspection

Source: internet, https://study4rac.files

GLPs: FDA Inspections of Pharmaceutical Industry and CROs

- Office of Regulatory Affairs (ORA)
  - Compliance Branch
    - Inspections of firms and plants producing FDA-regulated products
      - Compliance with FDA regulations
      - Not a review of the science
  - Review Divisions
    - CBER, CDER
      - Sponsor submissions
        - Pre-IND questions
        - INDA, and NDA submissions
        - Scientific review
  - Pharmaceutical companies with internal laboratories deal with both branches, Toxicology CROs deal primarily with Compliance branch

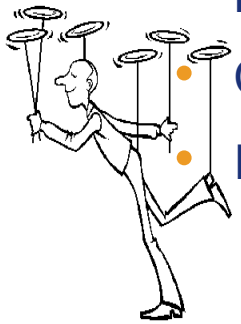
GLPs: FDA Inspections of Pharmaceutical Industry and CROs

- **Comment**: In the context of GLPs, Discovery and Development became a very important distinction
- FDA visit
  - Form 482: Official notice of FDA inspection, gives FDA the authority to enter and inspect
  - Form 483: Listing of observations in violation of FDA Regulations
    - Issued at end of observation
      - **Failure to follow protocol**
      - **Failure to comply with internal procedures/process**
      - **Reply in 15 days**
  - Warning Letter
    - Indicates serious compliance issue, repeat compliance issue or failure to take corrective action
    - Can be issued after Establishment Inspection Report (EIR) is reviewed by Senior FDA officials
      - **Allows for corrective action**
      - **Respond in 15 days**

GLPs: Study Director Responsibility

- **The Study Director is the Single Point of Control**
  - Design protocol
    - **Work with clients**, SD signs, client approves
  - Assure protocol is initiated as written
  - Assures all relevant SOPs are followed
    - deviations are recorded for necessary changes
  - Assure all information documented appropriately
  - Must be appropriately trained and experienced
  - Overall responsibility for technical conduct of the study, interpretation and reporting of results
  - Communicate with client prior to, during and in report phase of study
  - Resolve Study issues
  - Coordinate activities of **all** outside laboratories
  - Interpret data, manage client expectations and client interpretations
    - **FDA expectations do evolve**
    - **FDA evaluates management and client influence on study director interpretations**

"When you two have finished arguing your opinions, I actually have data!"



GLPs: Quality Assurance Unit Responsibilities

- Separate and independent from study conduct
- Maintains copy of Master Schedule
- Monitors studies, Inspects at intervals adequate to assure integrity of the study
- Inspections to ensure compliance with Federal Regulations, protocol, and company policies and procedures (e.g., SOPs)
  - Study based inspections (compliance)
  - Facility based inspections
  - Process based inspections
- Maintains written records of inspection
- Review final study report
  - Reflective of data
- Determines if deviations from , e.g., Protocol, SOPs, are documented and addressed
- Prepare and sign QA statement

GLPs: Facility Management Responsibilities

- Assign and/or replace Study Director as required
- QAU is in place and functional, establish a quality objective for the facility
- Appropriate Resources are available to accomplish the work
- Assure all equipment and processes employed meet the various /GLP requirement
- Personnel understand their function, have job descriptions
- Deviations are appropriately addressed
- Appropriate article is being tested
- Corrective actions are identified and taken
- Documented approval of the study plan by the Study Director

GLPs: 2016 Proposed Rules (Selected Topics)

- See Seaton, 2017
- Increased **Sponsor responsibility**
  - Meet section 58.120 requirements (PROTOCOL)
    - Includes providing humane care of animals
    - Increased responsibility for qualified personnel
    - Increased responsibility for Statement of Compliance
    - Inform SD of any known risks
  - Clarifies FDA inspection authority
    - Includes any person conducting a phase of nonclinical study
  - **Test Facility Management with Executive Responsibilities (TFMWER)**
    - Ultimate responsibility for GLP Quality System, commitment to Quality
    - Protocol review
    - Master schedule: compilation of information for assessment of workload

GLPs: 2016 Proposed Rules (Selected Topics cont'd)

- Study Director
  - Implement procedures for adequate communication
  - Document all communications
  - Consult with Attending Veterinarian on proposed protocol
  - Document multisite qualifications
  - Document need for PI
  - Archive specified materials NLT 2 weeks after study completion
- QAU
  - For multisite studies, Lead QAU designated by TFMWER
- Defines responsibilities for Principal Investigator (58.37) and Contributing Scientist (58.37)
- Section 58.185 Study Reports
  - Signed and dated report from each person analysing or evaluating data AFTER data generation completed
  - SD provide short summary report for all canceled studies

GLPs: 2016 Proposed Rules (Selected Topics cont'd)

- Section 58.190 Storage and Retrieval of records
  - SOPs addressing archiving must include specific procedures for removal of study materials
  - Must include specific time material can remain outside of archives
- **FDA may disqualify any person conducting a phase of a nonclinical laboratory study upon finding that person repeatedly or deliberately failed to comply with one or more of the regulations . . . Or repeatedly or deliberately submitted false information in any required report.**

GLPs: Concluding Comments

- Perform responsibly, follow protocol and communicate, communicate, communicate
- Do what you say you are going to do, in the way you specify doing it
- Be transparent relative to study deviations
- Always remember that the **internal QAU** is your **best friend** when it comes to **ALWAYS** being prepared for FDA Regulatory inspections.

GLPs: Selected References

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