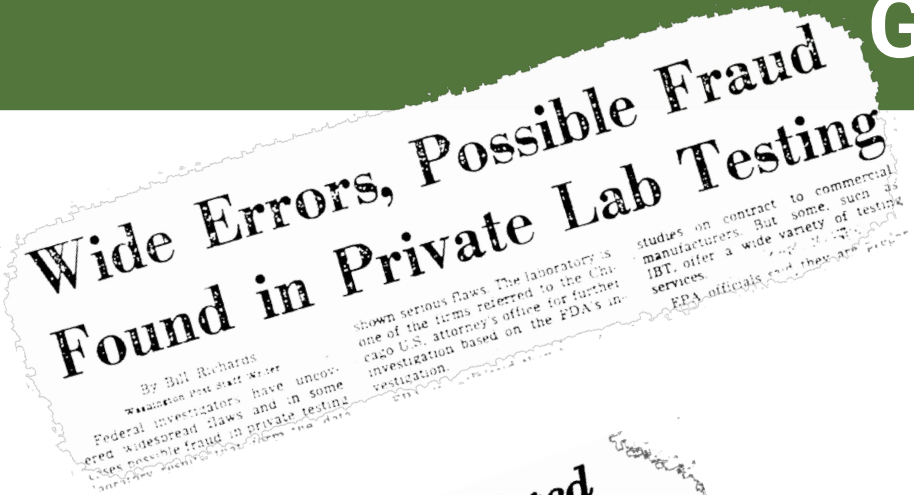
EPA GLP Refresher Webinar

March 11, 2025

IR-4 Project

Why Do We Have GLPS?

Landmark Cases in the Development of GLPs



Wide Errors, Possible Fraud Found in Private Lab Testing

By Bill Richards
Washington Post Staff Writer

Federal investigators have uncovered widespread flaws and in some cases possible fraud in private testing

shown serious flaws. The laboratory's one of the firms referred to the Chicago U.S. attorney's office for further investigation based on the FDA's in-

studies on contract to commercial manufacturers. But some, such as IBT, offer a wide variety of testing services.

FDA officials said they are

2 Plead Guilty in Falsification Of Animal Test Data on Drugs

By Bill Richards
Washington Post Staff Writer

Two former executives of a New Jersey research laboratory pleaded guilty in federal court yesterday to a charge that they conspired in the falsification of animal tests on drugs being investigated to see if they caused cancer.

Federal investigators said the guilty pleas were the f[illegible] their kind in an-

tencing next month. They face a maximum sentence of five years in jail and a $10,000 fine.

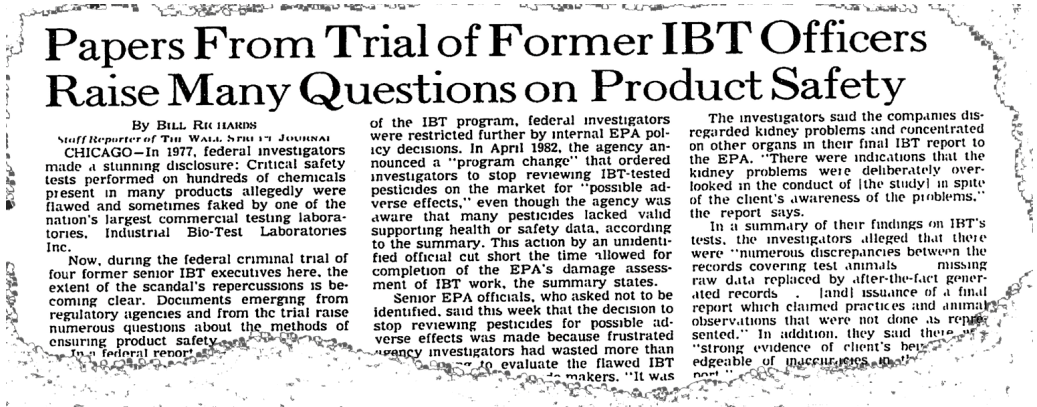
Posner and Carlson were named in an indictment returned this year by a federal grand jury in Newark. The indictment stemmed from irregularities disclosed during hearings in 1976 by Sen. Edward M. Kennedy's health subcommittee on the adequacy and safety [illegible] laboratories testi-

Three Convicted Of Falsifying Data At Nalco's IBT Unit

By a Wall Street Journal Staff Reporter

CHICAGO—A federal jury found three former officials of Industrial Bio-Test Laboratories Inc. guilty of falsifying product-safety tests.

After a 6½-month trial in federal cou[rt], the jury convicted Dr. Moreno L. [illegible] Paul L. Wrig[illegible]
[illegible]re, 53 year[illegible]



Papers From Trial of Former IBT Officers Raise Many Questions on Product Safety

By Bill Richards
Staff Reporter of The Wall Street Journal

CHICAGO—In 1977, federal investigators made a stunning disclosure: Critical safety tests performed on hundreds of chemicals present in many products allegedly were flawed and sometimes faked by one of the nation's largest commercial testing laboratories, Industrial Bio-Test Laboratories Inc.

Now, during the federal criminal trial of four former senior IBT executives here, the extent of the scandal's repercussions is becoming clear. Documents emerging from regulatory agencies and from the trial raise numerous questions about the methods of ensuring product safety.

In a federal report [illegible]

of the IBT program, federal investigators were restricted further by internal EPA policy decisions. In April 1982, the agency announced a "program change" that ordered investigators to stop reviewing IBT-tested pesticides on the market for "possible adverse effects," even though the agency was aware that many pesticides lacked valid supporting health or safety data, according to the summary. This action by an unidentified official cut short the time allowed for completion of the EPA's damage assessment of IBT work, the summary states.

Senior EPA officials, who asked not to be identified, said this week that the decision to stop reviewing pesticides for possible adverse effects was made because frustrated agency investigators had wasted more than [illegible] to evaluate the flawed IBT [illegible] makers. "It was

The investigators said the companies disregarded kidney problems and concentrated on other organs in their final IBT report to the EPA. "There were indications that the kidney problems were deliberately overlooked in the conduct of [the study] in spite of the client's awareness of the problems," the report says.

In a summary of their findings on IBT's tests, the investigators alleged that there were "numerous discrepancies between the records covering test animals . . . missing raw data replaced by after-the-fact generated records . . . [and] issuance of a final report which claimed practices and animal observations that were not done as represented." In addition, they said there [illegible] "strong evidence of client's [illegible] edgeable of inaccuracies in [illegible] port."

Takeaways

- Appreciate the relationship between scientific review and compliance monitoring
- Appreciate the consequences of non-compliance on public health
- Understand the origin of GLPs; every provision of the EPA GLPs in traceable to observations in these cases

IR-4 Project

1938 Food, Drug and Cosmetic Act

- Proposed in 1933; stalled in Congress
- 1937 Elixir of Sulfanilamide calamity
- Tested for appearance, flavor, and smell
- **Low solubility**
- Chemists decided to **use diethylene glycol** to get sulfanilamide into solution
- Resulted in the **deaths** of 107 consumers

IR-4 Project

1938 Food, Drug and Cosmetic Act

- Act passed in the wake of the sulfanilamide calamity
- Limited regulation of investigational use
  - Properly labeled
  - Used solely for investigational use
  - **No requirement for animal testing** prior to clinical trials in human subjects

IR-4 Project

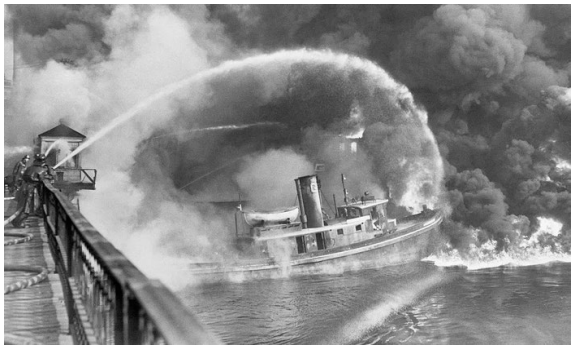
Before FDA/EPA GLPS -1960s

- Over time organizations learn they can get away with more and more without having consequences

- Ex. Speed limits

EPA

- Official birthday is December 1970
- Created by President Nixon
- “environment must be perceived as a single, interrelated system”



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1973 GAO report “Supervision over Investigational Use of Selected Drugs”

- FDA should **determine benefit > risks** before clinical use
- FDA should institute a program **to ensure sponsor’s timely performance and reporting of studies**
- Sponsor should provide a **schedule for completion and reporting of studies**

*GAO- Government Accountability Office

Searle Investigation - Flagyl®

- 1970 Supplemental NDA for prolonged administration of metronidazole (Flagyl®) for trichomoniasis
- FDA requested long-term tox studies
- Independent studies suggested positive carncinogenic effect
- Dr. Adian Gross
  - Noted discrepancies between summaries and individual animal data
  - Concluded there was a carcinogenic effect
- Initial attempts to inspect unsuccessful

IR-4 Project

Searle Investigation - Aldactone®

- 1975 Searle submits study on spironolactone (Aldactone®)
  - Study indicated positive carcinogenic effect
  - **Discrepancies observed among summaries, statistical analysis, and raw data**
  - Report **did not discuss** the existence of malignant mammary **tumors** despite evidence in histopathology raw data

IR-4 Project

Searle Investigation

- July 10, 1975 Congressional hearing
  - FDA presents Flagyl® and Aldactone® cases
  - FDA concludes an **in-depth study needed**
  - FDA agrees to investigate products marketed since 1968
- August 1975
  - On-site investigation begins
  - **Six investigation teams**

    4 teams at Searle / 2 teams to Searle CRO - Hazleton

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Searle Investigation - Findings

- Chemistry Operations
  - Use of "out of spec" test substances
    - TS assays in 1972, 73, & 74 > concentration than 1968 assays
    - No written specifications
    - Lots used that did not meet specifications
  - Failure to maintain adequate batch preparation records
  - Final report stated 12 lots were used; only 7 lots manufactured
  - Failure to maintain adequate assay records
  - 2 lots – no manufacture or assay records

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Searle Investigation - Findings

- Mixtures of substances

  - Searle

    No procedures for:

    - **Homogeneity**
    - **Concentration**
    - **Stability**

    Multiple labels on mixture containers

Searle Investigation - Findings

- Mixtures of substances

  - Hazleton

    Test material **purity "assumed" to be 100%**

    No inventory records

    No records for weighing or mixing

    Upon request - homogeneity, concentration or stability tests

    No testing for contaminants

    No reserve samples

    Mixers not cleaned or grounded

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Searle Investigation - Findings

- Protocols, Amendments, and Deviations
  - Lacked a consistent protocol approval process
  - **Verbal amendments**
  - Protocols written after study initiation
  - **Studies conducted without a protocol**

Searle Investigation - Findings

- Personnel and Supervision
  - 78 - week Aldactone® Study
  - **4 different Study Directors** and 2 different Advisors
  - **No study director for 11 months**
  - Lack of continuity in supervision
  - **Lack** of continuity and **training** among technicians

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Searle Investigation - Findings

- Study Conduct
  - Recorded on pocket notebooks/**scraps of paper**, then transcribed to notebooks
  - Technicians **did not always sign records**
  - When signed, **meaning of the signatures was not clear**
  - **Inconsistent observations**
  - Incidences reported for which there were **no records**

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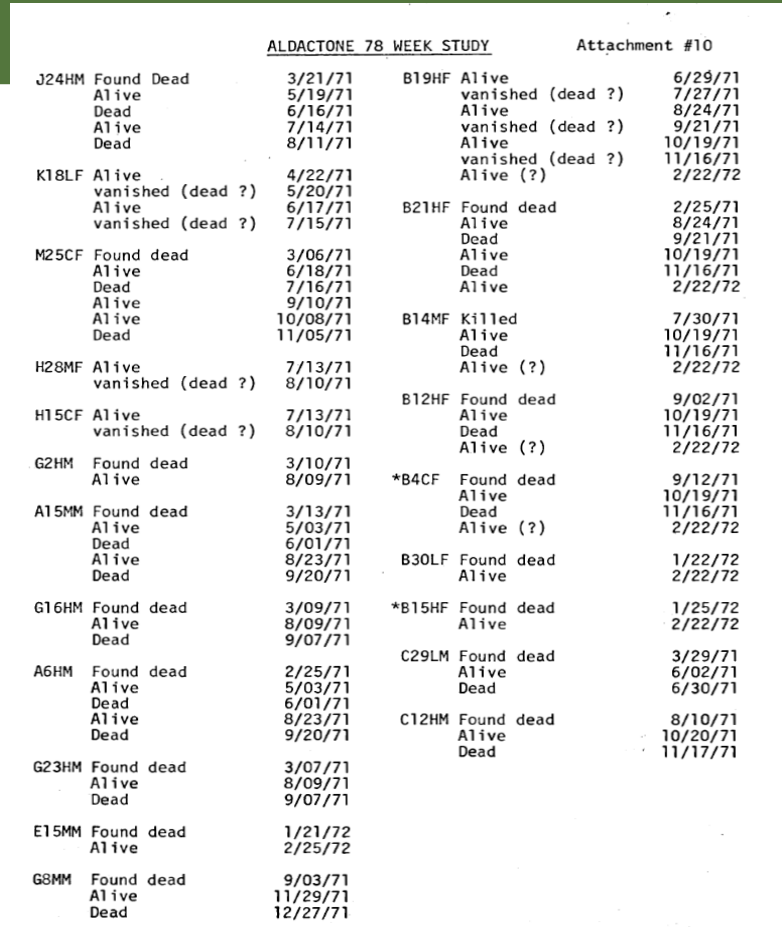
Searle Investigation - Findings

J24M	Found Dead	3/21/71
	Alive	5/19/71
	Dead	6/16/71
	Alive	7/14/71
	Dead	8/11/71



ALDACTONE 78 WEEK STUDY — Attachment #10

J24HM	Found Dead	3/21/71
	Alive	5/19/71
	Dead	6/16/71
	Alive	7/14/71
	Dead	8/11/71
K18LF	Alive	4/22/71
	vanished (dead ?)	5/20/71
	Alive	6/17/71
	vanished (dead ?)	7/15/71
M25CF	Found dead	3/06/71
	Alive	6/18/71
	Dead	7/16/71
	Alive	9/10/71
	Alive	10/08/71
	Dead	11/05/71
H28MF	Alive	7/13/71
	vanished (dead ?)	8/10/71
H15CF	Alive	7/13/71
	vanished (dead ?)	8/10/71
G2HM	Found dead	3/10/71
	Alive	8/09/71
A15MM	Found dead	3/13/71
	Alive	5/03/71
	Dead	6/01/71
	Alive	8/23/71
	Dead	9/20/71
G16HM	Found dead	3/09/71
	Alive	8/09/71
	Dead	9/07/71
A6HM	Found dead	2/25/71
	Alive	5/03/71
	Dead	6/01/71
	Alive	8/23/71
	Dead	9/20/71
G23HM	Found dead	3/07/71
	Alive	8/09/71
	Dead	9/07/71
E15MM	Found dead	1/21/72
	Alive	2/25/72
G8MM	Found dead	9/03/71
	Alive	11/29/71
	Dead	12/27/71
B19HF	Alive	6/29/71
	vanished (dead ?)	7/27/71
	Alive	8/24/71
	vanished (dead ?)	9/21/71
	Alive	10/19/71
	vanished (dead ?)	11/16/71
	Alive (?)	2/22/72
B21HF	Found dead	2/25/71
	Alive	8/24/71
	Dead	9/21/71
	Alive	10/19/71
	Dead	11/16/71
	Alive	2/22/72
B14MF	Killed	7/30/71
	Alive	10/19/71
	Dead	11/16/71
	Alive (?)	2/22/72
B12HF	Found dead	9/02/71
	Alive	10/19/71
	Dead	11/16/71
	Alive (?)	2/22/72
*B4CF	Found dead	9/12/71
	Alive	10/19/71
	Dead	11/16/71
	Alive (?)	2/22/72
B30LF	Found dead	1/22/72
	Alive	2/22/72
*B15HF	Found dead	1/25/72
	Alive	2/22/72
C29LM	Found dead	3/29/71
	Alive	6/02/71
	Dead	6/30/71
C12HM	Found dead	8/10/71
	Alive	10/20/71
	Dead	11/17/71

Searle Investigation - Findings

- Study Conduct

  - **Inconsistent observations** of masses

    Sept 20, 1971 - animals A2 and A3 have masses

    Oct 8, 1971 - A2 and A3 no masses

    Nov 5, 1971 - A2 and A3 masses regressed

  - Inconsistent clinical observations

    Animal A23 with cloudy left eye, then right eye, then to animal B4, then to animal C23, then E23, then D23 and back to right eye of A23 at necropsy

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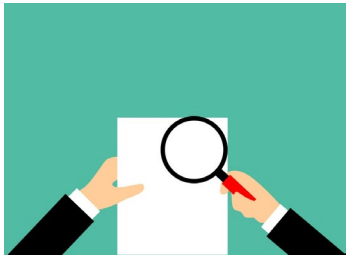
Searle Investigation - Findings

- Analysis and Reporting
  - In virtually **every report** there were numerous and **substantial discrepancies with original observations**
  - Analyses that **minimized differences**
  - Transcription errors during data entry
  - **Lack of critical review** prior to submission



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Searle Investigation - Findings

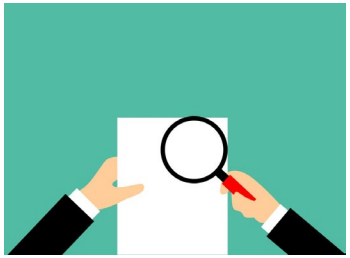
- Analysis and Reporting

  - Selective reporting

    Only favorable reports submitted to Agency

    Omission of data

      - Omitted malignant mammary tumors in transcribing data onto the computer entry sheet



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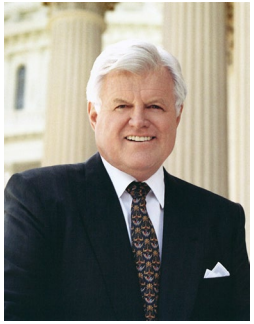
Searle Investigation - Findings

Dr. Stejskal (Study Pathologist) - "You should have seen things when this study was run--there were five studies being run at one time -- things were a mess."

Searle Investigation - Findings

- **Jan 20, 1976**



Senator Edward Kennedy - **"Inaccurate science, sloppy science, fraudulent science, -- these are the greatest threats to the health and safety of the American people**. Whether the science is wrong because of poor technique, or because of incompetence, or because of criminal negligence is less important than the fact that it is wrong."

"In the truest sense, **the errors identified by the FDA [deaths and masses] were completely irrelevant** to the scientific conclusions of the study…"
supplementary statement of Mr. Daniel C. Searle,
13-Feb-1976 to Senator Edward Kennedy.

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Congressional Hearings

- April 8, 1976

  - FDA Commissioner informs Congress about inspections:

    Biometric Testing

    Industrial Bio-Test Laboratories (IBT)

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IBT

- **Largest CRO Toxicology** lab in the **world**
- Over **22,000 studies**
- 40% of all US tox studies
- Work for US environmental chemical, pharma, foreign firms, federal agencies, etc.
- Studies support federal registrations of **insecticides, herbicides**, food additives, cosmetics, pharma, consumer products

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IBT

- FDA's Dr. Adrian Gross
  - IBT's data were "**unbelievably clean**"
  - Raw data contained description "**TBD**, TBD, I kept seeing it and I wondered, what the hell is this?"
- TBD stood for "**too badly decomposed**"

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IBT

- "The Swamp"
  - System for providing drinking water and flush waste from cages
  - Submerged floor with 4 inches cold water
  - Mice/rats regularly drowned in feeders or died of exposure
  - Techs had to wear boots and masks b/c water and stench
  - Mice/rats decomposed so rapidly they oozed through bottom of cages

IR-4 Project

IBT

- “The Swamp”
  - Example: During a 2 yr. study involving 200 animals, mortality reached 80%

160 animals died!!!

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IBT Findings

- Unwritten procedures were equivalent to written SOPs
- **Wrote data on lab coats and paper towels**, later transcribed into log books
- 7 animal techs responsible for 10K-15K rodents

  (1 tech = ~ 2,000 rodents)

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IBT Findings

- Harvade, herbicide, **5 test results submitted by IBT to Uniroyal were identical in all respects to results provided for 3 other pesticides**
- Nemacur (insecticide) and Sencor (herbicide) for Chemagro, 18 month studies only had 14 months of data. **Fabricated last 4 months of data**
- Some reports had **forged signatures**, taken from other reports

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IBT Investigation

- April 1977 – FDA/EPA investigators arrive for announced inspection
- Dr. Calandra (founder) greeted them " Gentlemen, I am very sorry. There has been an unfortunate misunderstanding; all our records were destroyed last night."
- **IBT shredded study data and communication between IBT officials showing knowledge of fraud**

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Conclusion of Investigations

- All referred to Grand Juries
- Searle – 1979

  - Referred to DOJ for criminal prosecution
- Biometric Testing Inc. – 1979

  - 2 officers plead guilty to submitting false docs

IR-4 Project

IBT Investigation

- 4 officers each indicted with 8 counts of conducting and distributing fake scientific research and then attempting to cover up their scheme
- Trial (Apr – Oct 1983) – 9 IBT criminal lawyers to 3 US Justice Department lawyers
- 3 people convicted of mail and wire fraud and submission of false documents
- Dr. Calandra - Mistrial

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Results

- March 22, 1978, EPA requested pesticide registrants with IBT's data to provide their raw data so that registration applications could be audited and validated

Results

- Summary of IBT Review Program in July 1983

TOTALS

38	COMPANIES
140	CHEMICALS
801	STUDIES

STUDY VALIDATION STATUS

131	16% VALID
44	6% SUPPLEMENTAL
32	4% PENDING
594	74% INVALID
801	

Results

- GLP regulations were written in direct response to the fraud that was committed
- QAU is intended to be the Agency's "left hand" hence shielded audit reports

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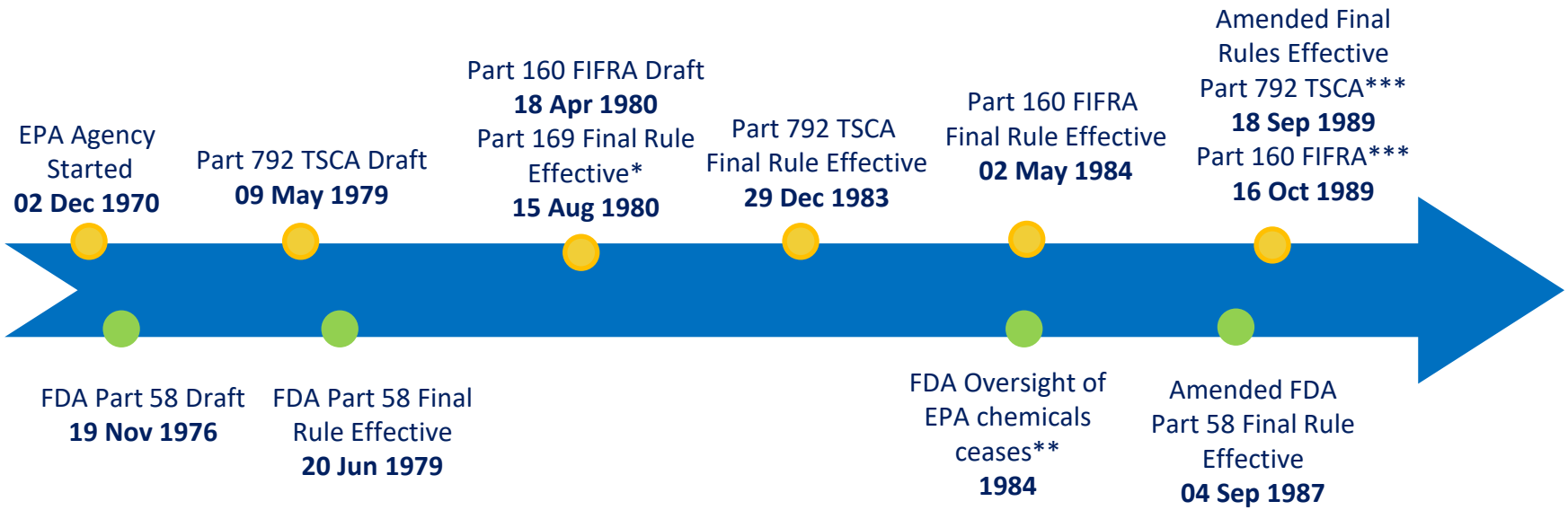

* Books and Records of Pesticide Production and Distribution regulations; amended 18 Feb 1993

** In 1984, FDA ceased oversight of those chemicals for which EPA is now responsible

*** FIFRA and TSCA revisions (1989) incorporate many changes made by FDA in 1987, and expand TSCA scope to apply to testing conducted in the field

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EPA GLPS

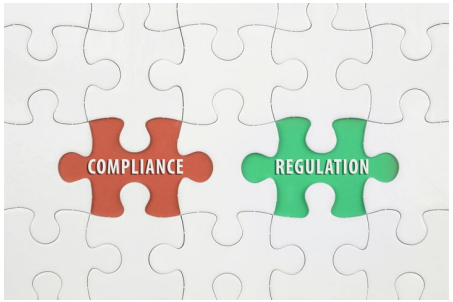
Compliance Statements

- EPA has 3 statements that can be used

  1) The study was done in accordance

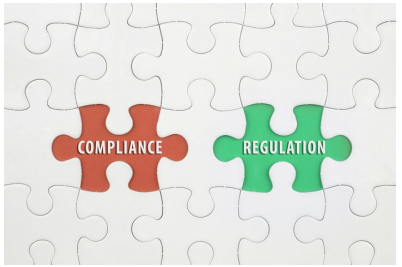
  2) The study was done in accordance with these exceptions

  3) Person was not the sponsor of the study, did not conduct the study, and does not know whether the study was conducted in accordance with the GLPS



Consequences of Non-Compliance

- False Compliance Statement
- Types of Penalties
  - Separate for Sponsor and Testing Facility Contractor
  - Notice of Warning
  - Cancellation, suspension, or modification of registration
  - Denial of application of registration
  - Civil Penalties
  - Criminal Penalties
  - Imprisonment



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Management (TFM) Responsbilities

- Poll: Testing Facility Management (TFM)
- Designate the study director before study initiation
- Replaces the study director as necessary
- Assure there is a QAU
- Assure testing of test, control, and references substances\mixtures

  - stability, identity, strength, purity, and uniformity
- Assure availability of personnel, resources, facilities, equipment, materials, and methods

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Management (TFM) Responsbilities

- Assure personnel clearly understand the functions they are to perform
- Assures deviations reported by the QAU are communicated to the study director and corrective actions are taken and recorded
- Assure SOPs in writing and adequate to ensure the quality and integrity of the data
- Authorizes in writing changes in established SOPs
- Approves protocols

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Study Director

- Represents the **single point of study control**
- Assumes overall responsibility for the conduct of the study
- Has appropriate education, training, and experience or combinations

SD in charge of the study and TFM in charge of the facility b/c too much for 1 person to do

From the FDA 1978 preamble

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Study Director Responsibilities

- Protocol is approved and followed
- All data are accurately recorded and verified
- Circumstances affecting the study are noted, action taken and documented
- Test system are as specified in the protocol
- GLPs are followed
- All raw data, documentation, protocols, specimens, and final reports are transferred to the archives at study completion

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Quality Assurance

- Functions of QA:
  - **Audit**
  - **Inspect**
  - Consult
  - Teach
  - **Understand current trends of the EPA**
  - Facilitate regulatory inspections
  - Facilitate CRO audits/ perform vendor audits

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Quality Assurance

The 1976 FDA proposed rule states "experience has shown that detailed protocols and written standard operating procedures alone will not ensure the quality and integrity of the results of a non-clinical laboratory study. A mechanism is needed to monitor ongoing studies to determine that the protocols and written standard operating procedures have been followed.

The experience of FDA with quality control units in manufacturing facilities has shown this mechanism to be effective. Thus, these proposed good laboratory practice regulations provide for a quality assurance unit in each testing facility. This unit would report to management and provide a focal point for FDA inspection of studies."

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Quality Assurance

- Monitor each study to assure management the facilities, equipment, personnel, methods, practices, records and controls are in conformance with the GLP regulations
- Maintain written records of the inspections
- Report problems which are likely to affect study integrity to the study director and management

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Quality Assurance

- **Inspect each study** at intervals adequate to ensure the integrity of the study
  - **In-life inspections**
  - **Facility inspections**
  - Protocol audits
  - Data audits
  - Final Report audits
  - Facilitate CRO audits/ perform vendor audits

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Picture Recall

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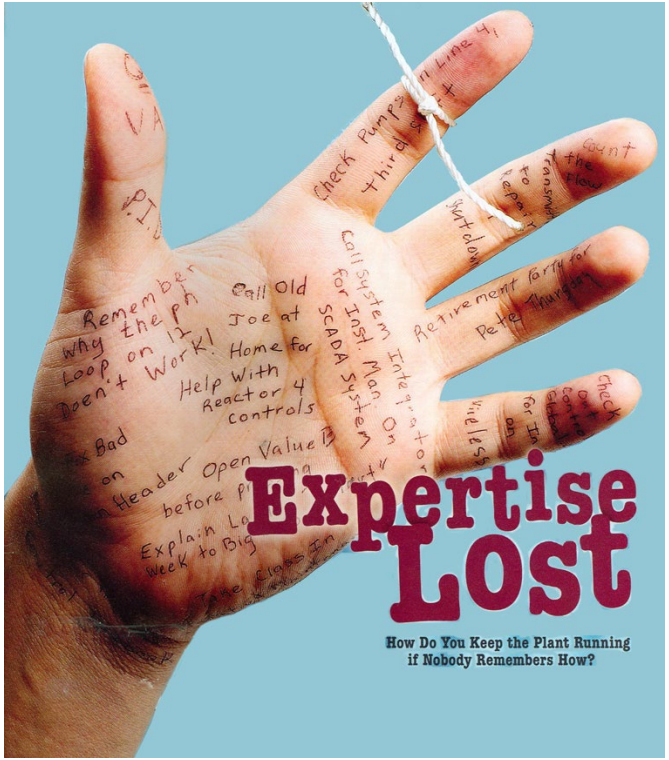
If you didn't write it down,

it never happened!



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Data Recording

- Directly, promptly, legibly, in ink
- Initial and date entries
- Proper corrections

~~7.89 mL~~ 7.98 mL JM 3/9/25 transposed numbers

- Sometimes error codes work and sometimes you need to write a note for clarification

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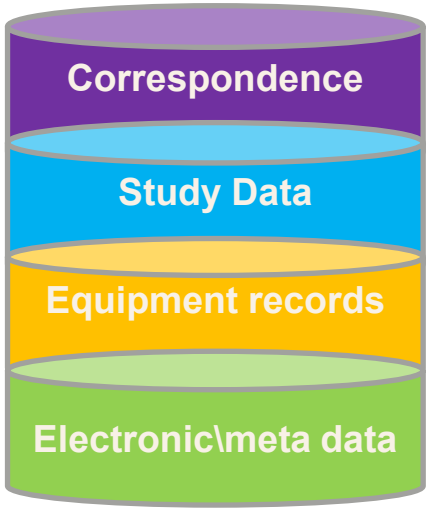
Raw Data

- Any lab worksheets, records, memoranda, notes or exact/true copies, thereof, that are the result of ORIGINAL observations and activities of a study, and are necessary for the reconstruction and evaluation of the report of the study



Think Jenga

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SOPs

- **Poll: When writing SOPs, ….**

SOPs

- Are Standard Operating Procedures

  Not Sometimes Operating Procedures
- Direct actions to be performed, provide step by step instructions to trained users
- Approved by management to ensure data quality and integrity
- Ensure consistent ways of working
- Required by the GLPS
- SOPs should be readily available
- Deviations should be documented in the study records

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SOPs – The Dirty Dozen

1. Test system area preparation
2. Test system care
3. Receipt, identification, storage, handling, mixing, and method of sampling of test, control, and reference stds
4. Test system observations
5. Laboratory or other test
6. Handling of test systems found moribund or dead during study
7. Necropsy of test systems or post mortem examination
8. Collection and identification of test systems
9. Data handling, storage, & retrieval
10. Transfer, proper placement, & identification of test systems
11. Maintenance & calibration of equipment
12. Histopathy

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SOPs

- Maintenance and calibration of equipment
  - Sufficient detail
  - Methods, materials
  - Schedule to be used in routine inspection, cleaning, maintenance, testing, calibration and/or standardization
- Remedial action to be taken in the event of failure or malfunction
- Designate the “person” responsible

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Relationship between Protocol, SOPs, and Data

- A **protocol** directs **what to do**: protocol supersedes SOPs
- A **SOP** directs **how to do** that task
- **Raw data** tells **what was done**

*Just because the protocol told you what to do, and the SOP told you how to do it, you still must document what you did

IR-4 Project

EPA GLP Inspectional Update

EPA Inspectional Findings from 54 Sites

- Lack of QA Inspections
- Protocol deviations not signed by Study Director
- Miscalculations and misreporting
- Final report does not reflect raw data
- Thermometer not calibrated against a NIST thermometer
- SOP not complete
- Missing SOP deviations

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EPA Inspectional Findings from 54 Sites

- Incorrect equation was used
- Raw data was not initialed at the time of entry
- Missing raw data of study temperature
- Lack of names of other scientists/supervisory personnel in the final report
- Poll: Non-routine maintenance

EPA Inspectional Findings from 54 Sites

40 CFR 169.2 (k) – Books & Records of Pesticide Production & Distribution

Records containing research data relating to **registered pesticides** including all test reports submitted to the Agency in support of registration or in support of a tolerance petition, ***all*** **underlying raw data, and interpretations and evaluations** thereof, whether in the possession of the producer or in the possession of the independent testing facility or laboratory (if any) which performed such tests on behalf of the producer. **These records shall be retained as long as the registration is valid and the producer is in business.**

- **Lack /missing raw data**

IR-4 Project

63 studies rejected in 2024

No. of studies rejected	Reasons for rejection
2	Numerous violations found in studies and product not registered
2	Multiple errors in final report. Calculation errors, lab notebook missing due to fire, lack of limited access archives, lack of calibration records for incubator, missing raw data for control results
1	Error in report and corrected by sponsor
6 52	Numerous GLP deficiencies. Fabrication of data.

IR-4 Project

3 Alerts to all EPA GLP Organizations

- Lack of QA that is independent
- Final Report does not reflect raw data
- Final report should include a description of the transformations, calculations or operations performed on the data

IR-4 Project

2024/2025 IR-4 EPA Inspections

Year of Inspection	Location
2024	University of California – Davis Lab University of California – Davis Field Dragon Run Ag (VA) Turner Ag Research (CA) NC State University - Field Pest Management Enterprises, Inc (LA) SD State University Field Michigan State University –Trevor Nichols Field University of Florida – Citra Field
2025	Oregon State University – Field Adpen Laboratories Texas A&M, Weslaco, TX – Field (desktop audit)

IR-4 Project

IR-4 EPA Inspections

- 4 of the inspections had 2 inspectors

- IR-4 was part of the in-person training that led to credentials for:
  - Henry Armstead III
  - Christine Phebus

EPA Inspectors' Comments

- Be careful on how you write dates
  - ex 6/2025 instead of 6/25
- They have had difficulty following some calculations
- Temperature logs need to be archived sooner than every 3 yrs.

EPA inspectors Comments

- An equipment SOP referring to an equipment manual results in the manual being part of the SOP and the expectation is that the manual will be with the SOP

- Manuals need to be archived

- IR-4 Advisories need to be SOPs and required procedures need to have TFM signatures.

EPA Inspectors' Comments

- Excel alone or saved as a PDF does not automatically comply with 40 CFR Part 160.130(e)
  - Is an automated data entry
  - Doesn't have an audit trail
  - Changes in entries cannot obscure original entry, shall indicate reason for the change, and have an associated signature /date

IR-4 Project

IR-4 Project

Thank you