Landmark Cases in the Development of GLPs
Why are these cases important?

- 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 FDA GLPs is traceable to observations in these cases
FDA Before GLPs

• 1906 Food and Drugs Act
  ▪ Dr. Harvey Wiley
    ◦ Purdue University
    ◦ Chief Chemist in Dept. of AG
    ◦ Leader of the “Poison squad” – testing food preservatives

• Manufacturers not required to submit evidence of safety or effectiveness

• Government permitted to take action if drug proved dangerous or misbranded
FDA Before GLPs

- 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
FDA Before GLPs

- **1938 Food, Drug, and Cosmetic Act**
  - Act passed in the wake of the elixir of 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
FDA Before GLPs

• 1960s – Increasing concern for toxicology studies
  ▪ Triparanol (MER-29)
    ✷ Approved as a cholesterol lowering agent
    ✷ Caused balding, impotence, cataracts, and liver damage
    ✷ Investigation revealed animal studies that showed adverse effects were withheld from FDA
    ✷ Merrell Company VP and 3 managers pled no contest
FDA Before GLPs

• 1960s – Increasing concern for toxicology studies
  ▪ Thalidomide tragedy
    ◆ Anti-nausea and sedative introduced in Europe
    ◆ Marketed from 1957 to 1962, more than 10,000 children in 46 countries born with deformities, such as phocomelia (Teratogen)
    ◆ Not approved in US, some distribution to physicians during a clinical testing program
FDA Before GLPs

- 1965 FDA plans surveys of toxicology labs
  - Impeded by Bureau of Drugs reorganization
  - Resumed in 1969, a few visits by pharmacologists from the Bureau of Drugs toxicology review divisions
  - Program expanded in 1971 to include a pharmacologist from the Bureau of Drugs, Scientific Investigations Staff (Dr. Adrian Gross) and field investigators
  - Focused on determining time required to complete long-term studies because some INDs were found to be carcinogenic after clinical trials were underway
FDA Before GLPs

- 1973 GAO* Report, “Supervision over Investigational Use of Selected Drugs”
  - FDA should determine benefits > risks before clinical use
  - FDA should institute a program to ensure sponsors timely performance and reporting of animal safety studies
  - Sponsors should provide a schedule for completion and reporting of studies

*GAO - Government Accountability Office
Searle Investigation

- 1970 Supplemental NDA for prolonged administration of metronidazole (Flagyl®) for trichomoniasis
- FDA requested long-term tox studies
- Searle submitted an 80-week rat study
- Independent studies suggested positive carcinogenic effect
Searle Investigation

- NDA Review - Dr. Adrian Gross
  - Noted discrepancies between summaries and individual animal data
  - Concluded there was a carcinogenic effect
  - Searle advised in May 1972
  - Additional studies and corrected 80-week rat study submitted in 1974
Searle Investigation

- New studies did indicate a carcinogenic effect
- “Corrected” rat study
  - Rat CM-21
    - 1970 report - discrepancies between raw histopathology data and summary
    - 1974 report - raw data corrected
    - “Considered to be highly unusual”
- Initial attempts to inspect unsuccessful
Searle Investigation

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

- July 1, 1975 audit of discrepancies
  - Searle “discrepancies are clerical errors”
- 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
Searle Investigation

- August 1975
  - On-site investigation begins
  - Articles selected based person-years at risk with higher priority given to long-term studies
  - Six investigation teams
    - 2 field investigators and pharmacologist
    - 4 teams at Searle and 2 teams at Searle contract laboratory - Hazleton
Searle Investigation

- Articles Investigated
  - Aldactone® - human drug
  - Aspartame® - food additive
  - Flagyl® - human drug
  - Norpace® - human drug
  - Cu-7 - device
  - Ovulen® - human drug
  - Syncro-mate® - veterinary drug
Searle Investigation - Findings

• Chemistry Operations
  ▪ Use of “out-of-spec” test articles
    • Test article assays in 1972, 73, and 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 were manufactured
  ▪ Failure to maintain adequate assay records
    • 2 lots - no manufacture or assay records
Searle Investigation - Findings

• Mixtures of articles
  ▪ Searle
    ♦ No procedures for homogeneity, concentration, or stability
    ♦ Multiple labels on mixture containers
  ▪ Hazleton
    ♦ Test material purity “assumed” to be 100%
    ♦ No inventory records
    ♦ No records for weighing or mixing
Searle Investigation - Findings

- Mixtures of articles
  - Hazleton
    - Tests for homogeneity, concentration, or stability only upon request
    - No testing for contaminants
    - No reserve samples
    - Mixers not cleaned or grounded
Searle Investigation - Findings

- Monitoring of Contractors
  - Three of 25 studies reviewed were performed solely by contractors and portions of many other studies were conducted by contractors
  - Pathology performed for 14 studies prior to any oversight
  - Critical primate study of Aspartame initiated at the University of WI without a protocol
  - Hazelton could only perform re-cuts on poor quality slides if the client agreed; path report indicated this fact
Searle Investigation - Findings

- Protocols, Amendments, and Deviations
  - Lacked a consistent protocol approval process
  - Verbal amendments
  - Excision of tissue masses from live animals during studies without authorization
  - Protocols written after study initiation
  - Studies conducted without a protocol
Searle Investigation - Findings

- Personnel and Supervision
  - 78-week Aldactone® Study
    - Four different Monitors (study director) and three different Advisors
    - No “study director” for 11 months
    - Lack of continuity in supervision
    - Lack of continuity and training among technicians
Searle Investigation - Findings

• Facilities
  ▪ Pest control
    ◦ Animal rooms were fogged twice per month
    ◦ Wheels and legs of racks painted with insecticide
    ◦ Animals remained in rooms treatment
Searle Investigation - Findings

- Study Conduct
  - Selection of animals violated protocol specifications
  - Quarantine practices
    - No procedures for quarantine or acclimatization
  - Identification
    - Animals, cages, and feeders not identified
Searle Investigation - Findings

- Study Conduct
  - Recorded on pocket notebooks or scraps of paper, then transcribed to notebooks
  - Technicians did not always sign records
  - When signed, meaning of the signature was not clear
  - Inconsistent observations*
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Searle Investigation - Findings

- Study Conduct
  - Inconsistent observation of masses
    - 20-Sep-1971 animals A2 and A3 have masses
    - 08-Oct-1971 A2 and A3 no masses
    - 05-Nov-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, and then to D23, and back to the right eye of A23 at necropsy
  - Excision of masses from live animals without evaluation
Searle Investigation - Findings

- **Study Conduct**
  - Procedures for animals found dead
    - Animals fixed *in-toto*; up to 50%
    - Held for up to 1 year before necropsy
    - Loss of tissues due to autolysis; up to 14%
  - Dr. Rao memo to Dr. McConnell July 13, 1973
    - “I realize animals which die during the study are the most critical ones to evaluate the compound effects. Hence our people are now ready to perform a complete autopsy of the dead animals.” Week 78 of a 115-week Aspartame study
Searle Investigation - Findings

- “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.
Searle Investigation - Findings

• Conduct of the study
  ▪ Necropsy Procedures
    ♦ No training for prosectors
    ♦ Pathologists edited prosectors observations
    ♦ Records unsigned
    ♦ When signed, significance questionable
    ♦ Obliterated and undated observations
Searle Investigation - Findings

• Study Conduct
  ▪ Histopathology Procedures
    • Poor quality slides
    • Different cuts than specified in protocol
    • Tissues specified in protocol not sectioned
    • Masses detected at necropsy not sectioned for histological examination
Searle Investigation - Findings

- Study Conduct
  - Histology Procedures
    - Consulting pathologists reported that in studies
      - 13 of 16 slides had artifacts that precluded evaluation
      - 14 of 15 slides of eyes had artifacts
      - 29 of 64 slides were unreadable and 7 missing
    - Records not or improperly identified
    - Incidence tables replete with errors
    - Incidences reported for which there were no records of slides being made
Searle Investigation - Findings

- **Study Conduct**
  - **Histology Procedures**
    - Rat K23CF
      - Gross necropsy - 10x8x3 cm tumor
      - Note on necropsy sheet - “no mass found in bottle”
      - Pathologist’s findings - “necrotizing cystadenocarcinoma well differentiated”
    - 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

- Study Conduct
  - Reproduction and Teratology
    - Study director not qualified
    - No protocols
    - Test article administered in a carrier in which it is insoluble
    - High dose 50% of reported
    - Variables cited in protocol not measured
    - Use of sexually immature animals
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
Searle Investigation - Findings

- Analysis and Reporting
  - Selective reporting
    - Multiple pathology reports - only favorable reports submitted to FDA
    - Omission of data
      - Clerical error in omitting malignant mammary tumors in transcribing data into computer entry sheet
      - Clerk failed to transcribe four malignant tumors on three separate data sheets
      - Of 10 tumor types in the path report only mammary tumors were omitted
Searle Investigation - Findings

- Reporting of Studies
  - Segment II Repro Study
    - 5 month study; not completed for 6 yrs
  - 78-week Aldactone® Study
    - Animals necropsied March 1972
    - Slides sent to Dr. Jacqueline Mauro in Dec 1972 (9 months after necropsy)
    - Mauro’s report received in March 1973
    - Searle response “the report looks just fine” in June 1973
    - 2nd pathologist review requested August 1974 (17 months after Mauro’s report)
Searle Investigation - Findings

- Reporting of Studies
  - 78-week Aldactone® Study
    - 2nd pathologist’s report received Dec 1974
    - Reported to FDA January 1975 (1 month)
    - Mauro’s findings not reported until FDA investigation began in August 1975
    - Mauro’s report showed a dose-dependent increase in liver and testes tumors
Searle Investigation - Findings

• Reporting of Studies
  ▪ 104-week Aldactone® Study - Hazleton
    • Two-year study initiated September 1970
    • Hazleton submitted draft report May 1973
    • Searle returned draft August 1974 (16 months)
    • Hazleton submitted final report Nov 1974
    • FDA received report January 1975
Congressional Hearings

- January 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.”
Congressional Hearings

- January 20, 1976
  - 1976 budget supplement
  - 1977 budget amendment
    - $16,000,000
    - 606 positions
    - Agency-wide program
    - All bureaus and product areas
Congressional Hearings

- April 8, 1976
  - FDA Commissioner informs Congress about inspections of Biometric Testing and Industrial Bio-Test Laboratories
Industrial Bio-Test Laboratory

- At the time IBT was the largest contract toxicology laboratory in the world
- Over 22K studies (40% of all US tox studies) for nearly every US environmental chemical and pharmaceutical company, foreign firms, and federal agencies
- Studies used to support federal registrations of insecticides, herbicides, food additives, cosmetics, pharmaceuticals, and consumer products
- Founded in 1953 by Dr. Joseph Colandra (NW University Pathologist)
  - Dr. Moreno L. Keplinger – Manager of Toxicology
  - Mr. James B. Plank – Senior Group Leader, Rodent Toxicology
  - Dr. Paul L. Wright – Head of Rodent Toxicology
Industrial Bio-Test Laboratory

- 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”
Industrial Bio-Test Laboratory

• “The Swamp” or “Plank’s Folly”
  ▪ In 1970, IBT’s management installed an automatic watering system in an animal room in Building 3
  ▪ Designed to provide drinking water and flush waste from rodent cages, but rarely worked properly
    ◆ Misted room, showering animals with cold water
    ◆ Submerged floor in 4 inches of water
    ◆ Mice regularly drowned in feeders
    ◆ Rats dies of exposure
    ◆ Technicians had to wear boots and masks to protect themselves from the water and stench
• “The Swamp”
  ▪ During a 2-year study involving 200 animals, mortality reached 80%
  ▪ Rats and mice decomposed so rapidly they oozed through the bottom of wire cages
Industrial Bio-Test Laboratory

• A Hunting We Will Go!
  ▪ Each week, dozens of rats and mice squeezed through wire cages and bred with feral rodents living behind piles of bedding kept in the animal rooms
  ▪ During the night the free-range rodents would climb the cages and eat feed and cannibalize the toes of animals in the cages. “In the morning we would see where the toes had been chewed off. So, you know, we were at a loss as to what to do ... It was a never-ending battle.”
  ▪ Squads of animal technicians armed with chloroform in squeeze bottles to hunt escaped rats and mice
Industrial Bio-Test Laboratory

- Chemagro’s Sencor Study
  - Two, 18-month mouse studies
  - Mortality was “enormous,” ≈1000 replacements
  - Dr. Wright ordered technicians not to document the replacements
  - Mice sacrificed at 14 months
  - Dr. Wright provides a technician completed mortality tables detailing the number and dates of deaths, none prematurely
  - Positive controls did not exhibit tumors, Keplinger and Wright order technician to report control data from another study
Industrial Bio-Test Laboratory

- Syntex’s Naprosyn Study
  - 24-month rat study
  - Blood and urine data only available for 15 months
  - Technician assigned to prepare the study report left blood and urine tables blank and provided the unsigned draft to Dr. Wright
  - Data tables were fabricated by Dr. Wright and Mr. Plank, technician’s signature forged on signature page
  - Pathologist convinced by clinical chemistry tables that stomach lesions were not drug related
Industrial Bio-Test Laboratory

The Monsanto Connection

- Dr. Paul Wright came to IBT in 1971 from Monsanto to manage test the safety of triclocarban (TCC, Monsanto anti-bacterial agent suspected by FDA of causing testicular atrophy)
- Monsanto needed a “clean” IBT study to convince FDA that TCC was safe
- Wright was employed at IBT for 18 months and supervised most of the TCC studies, then returned to Monsanto
- After returning to Monsanto, Wright wrote critical sections of the TCC final summary report and pressured an IBT scientist into changing his finding that TCC caused testicular atrophy
Monsanto’s TCC Studies

- 24-month rat study conducted in the Swamp, a large control group caged in another room
- Mortality began immediately and continued throughout the study
- Dead rats replaced with animals from across the hall, technicians ordered by Wright not to document replacements
- Six-month interim report mortality tables showed no deaths
- Interim sacrificed animals indicated testicular lesions in high and medium doses
- Dr. Wright leaves IBT (Month 15) and returns to Monsanto
- Pathologist pressured by Monsanto scientists for “a good presentation” to FDA panel on TCC
Industrial Bio-Test Laboratory

• Monsanto’s TCC Studies
  ▪ Wright’s replacement assigned to write the report and after reviewing the raw data concluded, “the study would be impossible to report without disclosing all of its inadequacies”
  ▪ Keplinger orders the emphasis of pathology findings and the downplaying of mortality
  ▪ Study pathologist concludes TCC caused lesions in all treatment groups
Monsanto’s TCC Studies

- Wright (at Monsanto) meets with IBT staff multiple times regarding pathology findings
- Calandra orders pathology report removed and the report state that decomposition, “precluded meaningful evaluation of testicular tissues.”
- Calandra orders the study pathologist to sign new version of the final report with the findings revised
Biometric Testing Investigation

- Technicians were poorly trained and supervised
- Records for all operations inadequate
- Test systems in poor health
- Animal identity not maintained
- No monitoring of contracted work
- Reported laboratory tests were not conducted
- Falsification of pathology reports
Conclusions 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 documents
- Industrial Bio-test Laboratories - 1981
  - 4 indicted*, 3 convicted of mail and wire fraud, and submission of false documents