A Brief History of Nonclinical Statistics in the Pharmaceutical Industry

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Abstract

- The earliest statisticians in the pharmaceutical industry date back to the early 1950s.
- Separate administratively organized statistics departments began to be formally established in the mid to late 1970s. These were mainly clinical statistics departments, supporting human drug trials, that formed because of the passage in 1962 of the Kefauver–Harris Amendment to the 1938 Food, Drug and Cosmetic Act.
- Hiring of nonclinical statisticians within the industry can be traced back to the 1978 government regulation 21 CFR Part 58 - Good laboratory practice for nonclinical laboratory studies. This prompted companies to hire statisticians to support drug safety and toxicology studies and marked the impetus for the creation of nonclinical statistics groups with a distinct administrative identity. These groups went on to expand the scope of their statistical services to early development and Chemical Manufacturing and Control (CMC) studies.

Working definition of Nonclinical Statistics

- "Nonclinical Statistics" is a term that is unique to the pharmaceutical industry. It acquired a natural identity as descendants of earlier "industrial" statistics groups following on the formation of clinical statistics groups starting in the early 1980s.
- The field of Nonclinical Statistics is comprised of those statistical applications in pharmaceutical scientific or engineering experimentation concerned with data on primary statistical units from non-human target populations. Examples include genomics/proteomics/transcriptomics experimentation for the purpose of target identification or target validation, animal efficacy or safety studies, experiments to determine the physical and chemical characteristics of a drug product, the determination of the potency of a manufactured biologic, and repeated measurements of a batch of drug product to study its stability properties.

The early years, the dawn of Nonclinical Statistics(<1963)

- The first statistician in the pharmaceutical industry was Joe Ciminera. He was hired by Sharp and Dohme as a Research Pharmacist in 1938. In 1952, he was given the title Biometrician and led the first biostatistics group in the industry (named Biometrics Research).
- Lilly hired Chester Bliss in 1939 to work on a short-term project. In 1953 Lilly hired a mathematician, Edward King, establishing sustained statistical support at Lilly.
- Lederle had formed a statistics group under Frank Wilcoxon in 1953. Charles Dunnett was hired into the group the same year and later became head of the group (he left in 1974).
- Smith Kline and French (later becoming GSK) hired Mike Free in 1955, a student of Gertrude Cox at NC State.
- The British company ICI, which later became AstraZeneca, employed industrial statisticians through the 50s and 60s. Some of them were prominent names we recognize today: George Box, Owen Davies, Jeff Harrison, and I.J. Good.
- In 1962, amendments to the 1938 Food Drug and Cosmetic Act gave the Food and Drug Administration authority to require that sponsors of new drugs prove that the drugs were effective for the medical indications. Before this, they had only to demonstrate that the new drug was "safe". This act prompted many pharmaceutical companies to form clinical statistics groups, primarily focused on the design and analysis of human clinical trials.

1963 – 2003, regulatory impetus and the years of growth and expansion

- Companies had research groups performing studies on animals in connection with preclinical safety studies of perpsective therapeutic compounds. These groups also expressed a need for statistical support, and consequently, some companies began to see the need for such nonclinical statistical support, as the clinical statistics groups expanded.
  - David Salsburg was hired by Pfizer in 1968 to support preclinical studies.
  - Lilly hired Bruce Rodda in 1969 to manage a preclinical support group.
- The 1978 regulation 21 CFR Part 58 - GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES established rules for the proper conduct and compliance requirements of laboratory studies, including the need for a protocol. It prompted many companies to recognize the need for statistical resources supporting drug safety/toxicology studies. Starting in the late 1970s, it prompted companies to form nonclinical statistics departments as a formal administrative identity.
- Earl Nordbrok headed nonclinical statistics at Ayerst in 1978.
- Ciba-Geigy formed a nonclinical statistics unit by 1980. Ciba-Geigy later merged with Sandoz to form Novartis.
- J&J formed a preclinical statistics group in 1980, led by Ran Sharma, supporting primarily drug safety. By 1984, the group extended their support to the discovery and CMC organizations.
- Wyeth formed a discovery sciences support group in 1981 led by Tom Copenhaver.
- ICI appointed Bob Ferguson leader of Nonclinical Statistics in 1982.
- Abbott formed a nonclinical group in 1982, led by Joseph Chmiel.
- Squibb, which later became BMS, formed a nonclinical group under Tom Graves in 1986.
- In some cases these groups merged with the earlier existing statisticians supporting laboratory and manufacturing studies.
- The expansion of these nonclinical groups was a consequence of having proved their worth by efficient information gathering methods, modeling, decision making and effective collaborations with scientific colleagues to advance the sciences.

▪ List of early notable nonclinical statisticians

Table 1 Prominent Statisticians

Subject	Name	Application
Discovery /Screening	Mike Free	QSAR modeling
	John R. Murphy	Screening designs
Manufacturing /Quality	Joseph Ciminera	Control charting
	Charles B. Sampson	Quality control
	Wayne A. Taylor	Sampling plans
	Lynn Torbeck	Process validation
	Charles B. Pheatt	Dissolution
	Shein-Chung Chow	Stability
	Earl Nordbrock	Stability
	Stephen Ruberg	Stability
	Jun Shao	Stability
	John R. Murphy	Content Uniformity
Analytical Methods	David Salsburg	Methods Comparison

▪ A nonclinical biostat group at Genentech was started in January 1991 with the appointment of David Giltinan.

▪ Throughout this period, companies grew their nonclinical statistics resources, although not at the same pace as their clinical statistics groups.

2004-Present The formation of the Nonclinical Biostatistics Leaders' Forum

- During this period, the rise of biotech companies added to the expansion, Biogen formed their nonclinical group in 2006 under Don Bennett.
- In 2003, Ersen Arseven (Schering-Plough) proposed an informal venue for nonclinical statistical leaders to meet and communicate on common issues. It was referred to as the nonclinical statistics managers' group. The first meeting was held on October 10, 2003 and continued to meet annually.
- The spring 2008 meeting was held at Biogen in Cambridge, MA , formally adopted the name "Nonclinical Biostatistics Leaders' Forum" (NCBLF).
  - A steering committee was appointed to provide focus and direction to the group. The first chair was Jim Colaianne (J&J).
  - A mission statement and governance charter were written and approved.
  - It was decided to formally organize the Nonclinical Biostatistics Conference as a biennial conference to discuss emerging technical methods relevant to nonclinical statistics applications.
- The biennial Nonclinical Biostatistics (NCB) Conference has been held continuously since 2009. A historical overview of the conferences over that period is shown in Table 2.
- Each of the NCB conferences over the period 2009 - 2025 have resulted in a special nonclinical journal section.
- The best nonclinical statistics paper award was initiated in 2015.
- 2017 the NCBLF was formally Integrated into the ASA Biop. section as an official ASA working group and conference.
- The first working group was formed In 2019, to promote the use of Bayesian approaches in CMC and preclinical areas.
- Scholarship fund created in 2021 to attract graduate students to study problems in nonclinical biostatistics with both an academic and industry advisor.

Table 2 Overview of Conferences 2009 – 2025

Year	Venue	Chairs	Attendees	ASA President	Keynote Speakers
2009	Harvard	M. Thoma, D. Bennett	149		ShaAvhree Buckman (FDA), Steve Ruberg (Lilly
2011	Harvard	M. Thoma, D.Bennett	91	Bob Rodriguez	Bob O'Neill (FDA)
2013	Villanova	P. McCallister P. Lupinacci	115	Marie Davidian	Stan Young (NISS
2015	Villanova	P. McCllister P. Lupinacci	116	David Morganstein	Christian Airiau (GlaxoSmithKline)
2017	Rutgers	S. Novick J. Kolassa	123	Lisa Lavange	- Cancelled -
2019	Rutgers	S. Novick J. Kolassa	128	Karen Kafadar	Jose Pinheiro,
2021	Rutgers (Virtual)	X. Huang J. Kolassa	135	Wendy Martinez	Nassim Nicholas
2023	Rutgers	X. Huang J. Kolassa	123	Bonnie Ghosh	Ajaz Hussain
2025	Rutgers	P. Faya J. Kolassa	128	Ji-Hyun Lee	Daniel Lee

Summary and Looking Forward

- Nonclinical Statistics is a term specific to the pharmaceutical industry, describing statistical applications concerned with non-human studies.
- The beginnings of nonclinical statistics dates to 1938 with the hiring of Joe Ciminera at Merck, and 1939 at Lilly with the hiring of Chester Bliss.
- The growth of nonclinical statistics groups was accelerated through regulatory requirements 21 CFR Part 58 in 1978, that mandated more rigorous management of laboratory studies.
- Companies increased nonclinical statistics resources throughout the 80s and 90s. With the growth of the biotech industry, those companies also expanded their nonclinical statistics support in the 2000's.
- The NCBLF was established to promoted the value and importance of nonclinical statistics to drug development while representing the nonclinical statistics community to the larger statistical constituencies.

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