

The fundamental role of frequentist statistics in CMC decision making

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Statistics in Pharmaceutical Development and Manufacturing (JQT, 2009)

➤ Authors

➤ John J. Peterson, Ronald D. Snee, Paul R. McAllister, Timothy L. Schofield, Anthony J. Carella

➤ Discussants

➤ Roger W. Hoerl, Jeff Hofer, Lynn Torbeck,

➤ FDA: Yi Tsong, Roswitha Kelly, Meiyu Shen, Jinglin Zhong

Topics Covered in the Paper

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- History
- Phases of Development: API, Drug Product, Analytical Methods
- Emerging statistical methods
- Impact of statistical software and information technology
- Role of the statistician

History

Early contributors to the area of “industrial statistics” in the pharmaceutical industry

Shein-Chung Chow	Product stability
Joseph Ciminera	Control charting, process monitoring
Mike Free	Product stability
John R. Murphy	Screening designs, content uniformity
Earl Nordbrock	Product stability
Charles B. Pheatt	Product dissolution
Steven Ruberg	Product stability
David Salsburg	Methods comparison
Charles B. Sampson	Quality control
Jun Shao	Product stability
Wayne A. Taylor	Sampling plans
Lynn Torbeck	Process validation

Phases of Development: API, Drug Product, Analytical Methods

➤ API

- Involves experimentation, so DOE is the most important tool for both small- and large-molecule development.

➤ Drug product

- DOE, mixture designs, regression analysis, multivariate analysis, stability analysis (large molecules), expiry setting, and SPC once production commences

Phases of Development: API, Drug Product, Analytical Methods

- Analytical methods and quality assessment
 - Pharmaceutical quality system
 - DOE for robustness studies
 - Validation
 - Method transfer and equivalence testing
 - Product shelf-life calculations (ICH Q1E fixed effects)
 - Mixed effects modeling of “random batches”
 - Bracketing and matrixing stability designs
 - Treatment of OOS observations
 - Method bridging using concordance analysis

Emerging Methods

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- Process analytical technology (PAT) initiative (2003)
 - Tools are multivariate in nature including DOE, response surface methods, process simulation, and pattern recognition in conjunction with knowledge-management systems.
- Data mining statistical methods
- Quasi- or semi-continuous manufacturing
 - Produce many small batches similar in size to clinical trial supplies, obviating the need for scale ups.
- Development of continuous manufacturing as opposed to batch manufacturing.

Emerging Methods

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- ICH Q9 (2005) Risk assessment tools
 - Failure modes and effects (FMEA) and fault tree (FTA)
- Design space as detailed in ICH Q8 (2005)
 - Would provide manufacturers with the ability to make small-to moderate changes in manufacturing conditions without time-consuming process of regulatory approval.
 - Several Bayesian papers and approaches are cited.

Impact of statistical software and information technology

- Increased availability of easy-to-use statistical software allows non-statistician scientists to perform their own analyses.
- A new wave of sophisticated assay and measuring devices with proprietary statistical algorithms.
- Opportunities for high-dimensional visualization.
- Data base and knowledge management, relational data bases.
- Enterprise statistical and information systems
 - SAS, StatSoft, Inc., Minitab
- Software validation

Role of the Statistician

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TABLE 4. Expanded Role of Statisticians

Consultant (Old)	Leader (New Expanded)
Analyze data and design experiments	Determine the appropriate strategy and approach
Teach statistical tools	Design training systems, coach, mentor, and train
Work with technical people	Work with managers and technical personnel
Consult on other people's projects	Lead cross-functional projects
Narrow expertise and accountability	Broad expertise and accountability
Follow simple regulatory guidelines	Collaborate with regulatory agencies to influence new guidance
Reactive	Proactive

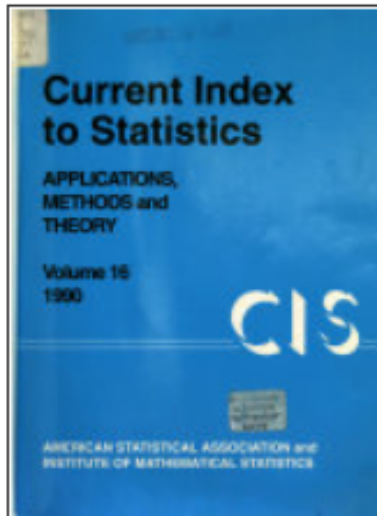
Where are we now?

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What Do We Find in the Literature?

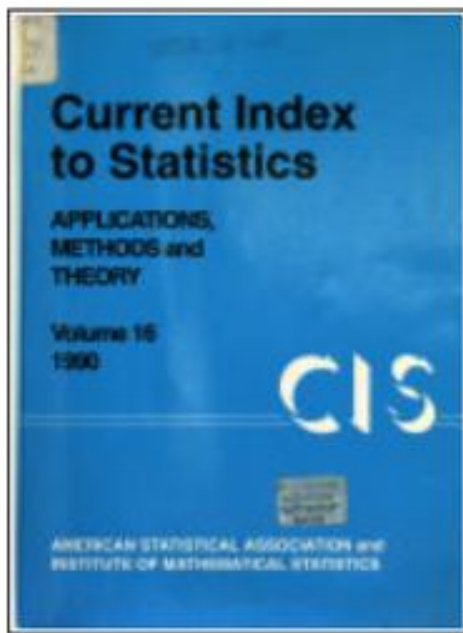
Current Index to Statistics, Applications, Methods and Theory, Volume 16



American Statistical Association., 1990 - [Mathematical statistics](#)

The Current Index to Statistics (CIS) is a bibliographic index of publications in statistics, probability, and related fields.

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Andrew

AI (New Trick)



Rick (Old dog)



Selection Process



- Seeded from Burdick et al. (2017), Rick's personal library of CMC articles
 - Analytical procedures
 - Comparability
 - Specifications
 - Stability
 - Process Qualification Stage 1: Characterization
 - Process Qualification Stage 2: PPQ
 - Process Qualification Stage 3: CPV

Selection Process

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- Claude Opus 4.8 expanded the search from 2009 to the present
 - Codex 5.6 Sol extended it back to 2000 and produced the visual summaries.
 - Authenticated OpenAlex API searches added keyword, author, venue, and citation-network routes.
 - Across the v11 routes, 21,221 candidates were identified

Selection Process

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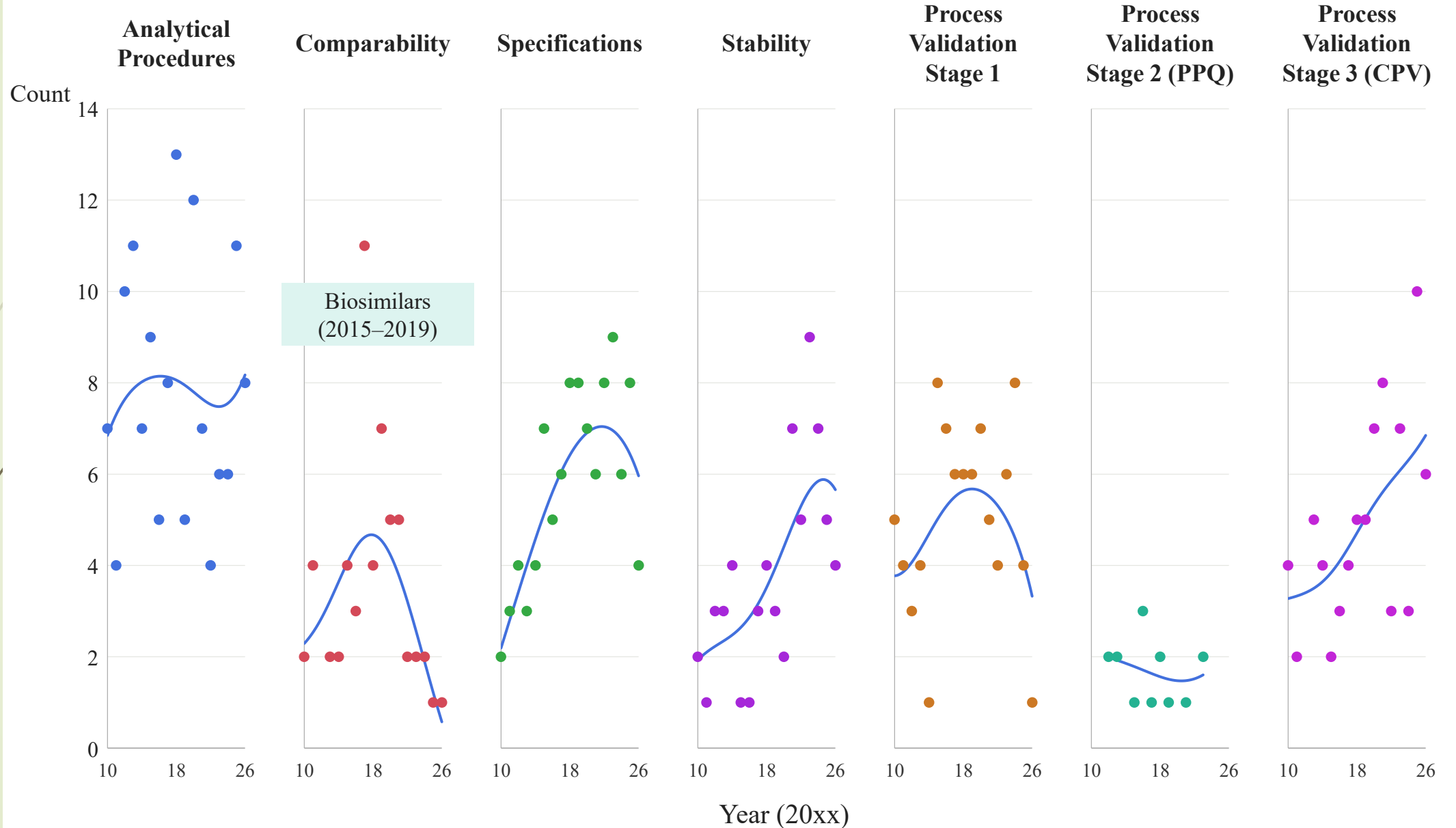
- Candidate identifiers were checked against bibliographic metadata.
- All 590 retained DOIs were re-resolved and corroborated against the record title and at least one additional field.
- This was an AI-assisted scoping search, not a systematic review.
- OpenAlex and public publisher archives substantially improved coverage, but they have indexing limits.
- The corpus should be interpreted as broad and reproducible, not exhaustive.

“Cleaning Up” Process

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- Articles prior to 2000 that were not cited in the JQT article were removed.
- References to general statistical methods if they did not have a particular CMC application (e.g., Montgomery on DOE).
- Book chapters (the edited book title in which each appeared was retained).
- Workshop and meeting presentations.
- Articles with “Bayesian” in the title.
- Guidance documents.
- Expanded author designations containing “et al.” to include all author names.
- Result: 21,221 unique candidate records → 692 retained articles

Article Count by Topic and Year



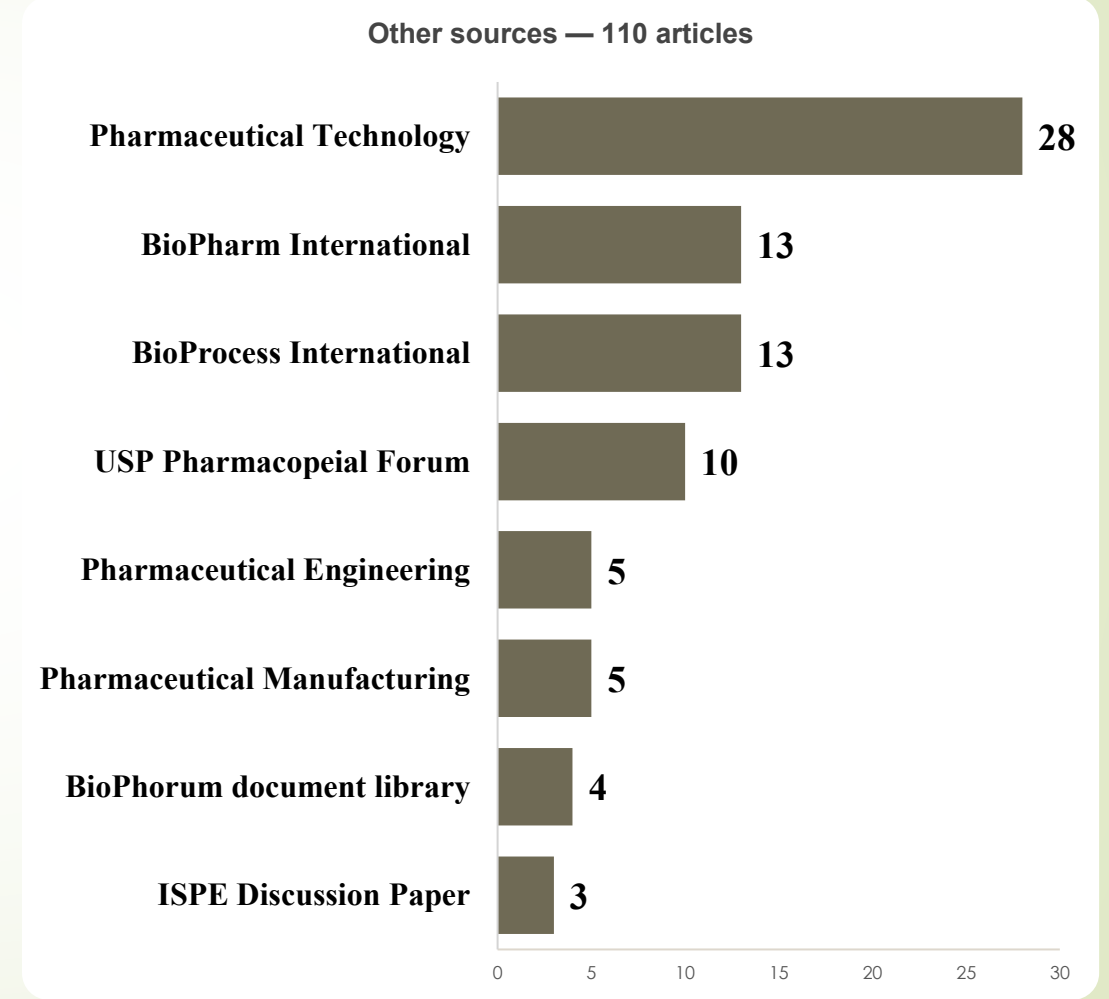
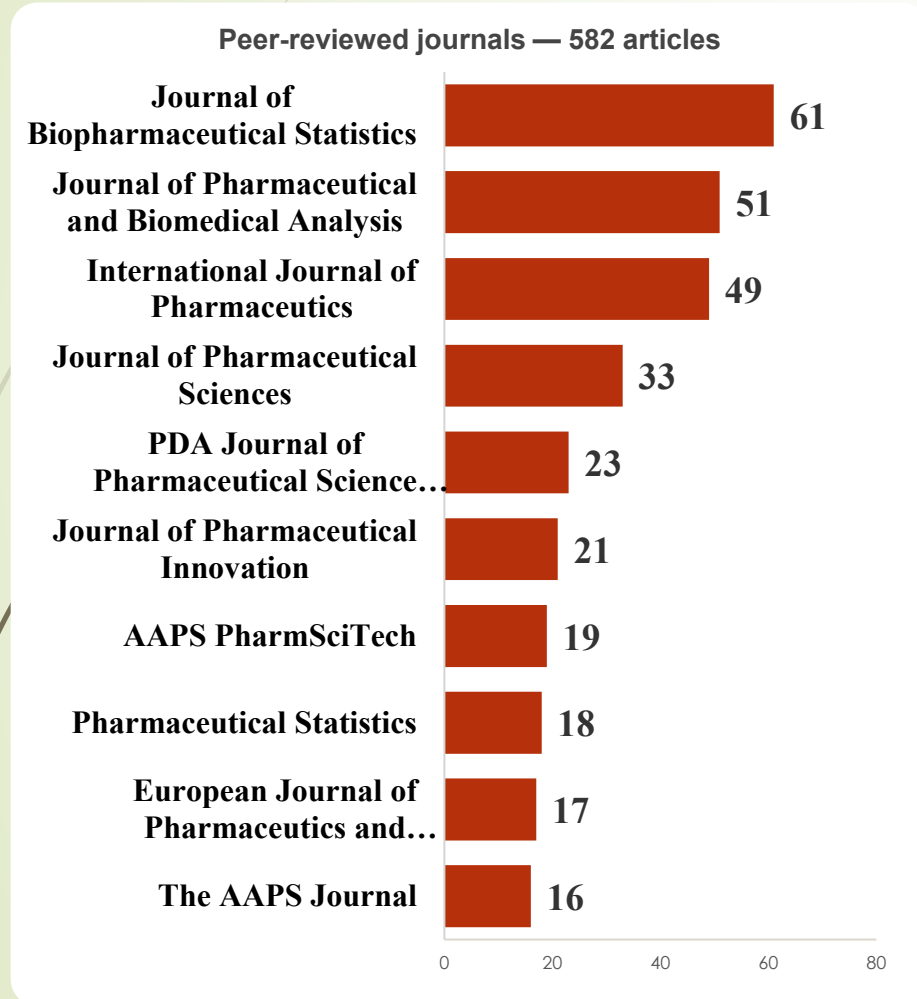
Dots: annual article counts (2026 partial year). Lines: smoothed trends.

Sub-topic vs. Topic(s)

Article count ranges

Sub-topic	1 Analytical Procedures	2 Comparability	3 Specifications	4 Stability	5 Process Validation Stage 1	6 Process Validation Stage 2 (PPQ)	7 Process Validation Stage 3 (CPV)
Validation	69						
Bioassay	25						
Transfers	22						
Biosimilarity		29					
Equivalence testing		24					
Acceptance criteria		9					
Content uniformity			27				
Patient-Centric			12				
Setting specifications			12				
Shelf-life				25			
Accelerated				10			
Kinetic modeling				8			
Process characterization					42		
Design Space					31		
Process capability					14		
PPQ batch size						10	
PPQ criteria						3	
Multivariate CPV							12
SPC							8
CPV criteria							7

History Top Journal/Source Counts



History: Top 20 Authors

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Author	Top Category	Top Subcategory
Altan S	3 Specifications	Dissolution
Bergum JS	3 Specifications	Content uniformity
Boulanger B	1 Analytical Procedures	Validation
Burdick RK	2 Comparability	Biosimilarity
Chow S-C	2 Comparability	Biosimilarity
De Beer T	5 Process Validation Stage 1	Process characterization
Dewé W	1 Analytical Procedures	Validation
Hauck WW	3 Specifications	Content uniformity
Hubert Ph	1 Analytical Procedures	Validation
LeBlond DJ	4 Stability	Shelf-life
Lourenço FR	1 Analytical Procedures	Validation
Pazhayattil AB	7 Process Validation Stage 3 (CPV)	CPV criteria
Rozet E	1 Analytical Procedures	Validation
Schofield TL	3 Specifications	Patient-Centric
Schwenke JR	4 Stability	Shelf-life
Shen M	2 Comparability	Biosimilarity
Tsong Y	2 Comparability	Biosimilarity
Vervaet C	5 Process Validation Stage 1	Process characterization
Vukovinsky KE	5 Process Validation Stage 1	Design Space
Yang H	1 Analytical Procedures	Bioassay

Topics Not Mentioned in 2009

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- Biosimilars (2015–2019)
- New USP bioassay chapters <1030-1034>
- FDA 2011 Process Validation Guidance
- Comparability
 - Equivalence testing
 - Quality ranges
- Gene and cell therapy
- Patient-centric specifications
- AI based strategies

Role of the Statistician: Still seems relevant

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Frequentist Statistical CMC Toolkit—General

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- Rounding rules
- Transformations
- Approximations
- Graphics

Frequentist Statistical CMC Toolkit— Estimation/Testing

- Confidence intervals
 - Equivalence testing
 - Noninferiority testing
- Tolerance intervals
- Prediction intervals
- Generalized Fiducial Inference (Generalized Confidence Intervals)
- Quality ranges

Frequentist CMC Toolkit—Modeling

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- Regression analysis
- Experimental design (DOE)
- Mixed models (variance components)
- Generalized (mixed) models
- Nonlinear modeling
- Simulation (JMP profiler)
- Statistical process control
- Acceptance sampling

Why Continued Frequentist Development Matters

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- Easier for non-statisticians to use.
- Easier to explain to higher-level management.
- Widely available in standard statistical software.
- Doesn't let perfection be the enemy of the good.

Key Takeaways

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- Frequentist methods remain a practical foundation for transparent CMC decisions.
- The literature map shows broad use across the CMC lifecycle.
- The 692-article corpus illustrates breadth; it is not exhaustive.
- Continued development is needed alongside Bayesian and computer-intensive approaches.

What Do You See as Emerging Topics?

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