



## A REVIEW ON BIOSTATISTICAL METHODS USED IN PHARMACOLOGY

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**ABSTRACT**

Biostatistics forms the quantitative foundation of pharmacology, enabling objective evaluation of experimental and clinical data across all stages of drug development. It ensures scientific validity, reproducibility, and precision in interpreting pharmacological findings through statistical tools such as hypothesis testing, regression analysis, ANOVA, and survival analysis. Recent advances, including Bayesian modeling, adaptive clinical trial designs, and machine learning-based analytics, have expanded its role from traditional efficacy and safety evaluation to real-world evidence assessment and precision pharmacotherapy. The integration of biostatistical approaches in pharmacokinetics, pharmacodynamics, and pharmacovigilance enhances decision-making and regulatory compliance, ultimately bridging the gap between laboratory research and clinical application.

**KEYWORDS:** Biostatistics, pharmacology, drug development, clinical trials, statistical modeling, bayesian analysis, pharmacovigilance.

**INTRODUCTION**

Robust statistical inference is the backbone of pharmacological research, shaping investigations from early-stage dose-response studies to pivotal Phase III trials.<sup>[1,2]</sup> While the classical paradigms - Fisher's significance testing and the Neyman-Pearson decision framework remain central to most analyses, emerging Bayesian methodologies and machine-learning approaches are increasingly influencing the field.<sup>[5,6]</sup>

Fisher's method treats the *P*-value as a continuous measure of evidence against a null hypothesis.<sup>[1]</sup> In a first-in-human antihypertensive trial, for example, a mean systolic reduction of 8 mmHg versus placebo might yield *P* = 0.04. Fisher would interpret this not as a binary verdict but as "moderate evidence" that the drug exerts a true effect, inviting replication rather than immediate clinical adoption.<sup>[3,4]</sup> Misinterpretation, however equating *P* with the probability that the null is true or chasing arbitrary thresholds remains widespread and fuels the broader reproducibility crisis.<sup>[5]</sup>

The N-P approach reframes inference as a formal decision. Investigators specify a Type I error rate ( $\alpha$ ) and statistical power ( $1 - \beta$ ) before the trial begins, then reject or retain the null based on whether results cross the pre-set boundary.<sup>[2]</sup> Regulatory Phase III studies typically adopt  $\alpha = 0.05$  and 80 % power, ensuring that clinically meaningful effects are unlikely to be missed. Yet the rigidity of this framework can create false dichotomies: a survival benefit with *P* = 0.051 may be dismissed despite potential clinical importance, while very large trials can yield "significant" results of trivial magnitude.<sup>[3,5]</sup>

Analysis of variance (ANOVA), long regarded as a cornerstone for multi-arm evaluations such as dose-finding studies, exemplifies both the strengths and inherent limitations of classical statistical methods.<sup>[1]</sup> By partitioning total variability into between- and within-group components, ANOVA efficiently tests whether mean responses differ across treatments. Nonetheless, surveys consistently reveal widespread misuse, including the omission of required post-hoc tests or the inappropriate application of one-way ANOVA to two-

group comparisons—errors that can compromise inference as severely as an underpowered trial.<sup>[3,4]</sup>

Contemporary pharmacology increasingly complements traditional frequentist approaches with Bayesian methods, which integrate prior knowledge with emerging data to refine estimates of parameters of interest.<sup>[6]</sup> For example, Bayesian population pharmacokinetic models enable real-time dose optimization as patient-specific laboratory data become available, thereby providing a robust foundation for model-informed precision dosing.<sup>[16,18]</sup>

Taken together, these statistical approaches enable discovery and regulation alike. When applied carefully they make drug development more efficient and reliable; when misapplied they propagate irreproducible findings and, ultimately, risk patient harm. Any serious effort to advance pharmacology must therefore pair scientific innovation with continued reform in statistical education and practice.<sup>[3,6]</sup>

## 2. CLASSICAL FRAMEWORKS OF STATISTICAL INFERENCE

### 2.1 Fisher's significance testing

Ronald A. Fisher introduced the  $P$ -value in the 1920s as “the probability, under the assumption of the null hypothesis, of obtaining a result equal to or more extreme than what was actually observed”.<sup>[1]</sup>

#### Example

Suppose an investigational antihypertensive yield a mean systolic reduction of 8 mmHg versus placebo (standard deviation 10 mmHg,  $n = 40$  per group). A two-sample  $t$ -test gives  $t = 2.1$ ,  $P = 0.04$ . Under Fisher's framework this is “moderate evidence against  $H_0$ ,” suggesting a real effect worthy of further study.<sup>[1,3]</sup>

#### Advantages

- Flexible; no need to pre-specify an alternative hypothesis.
- Provides a continuous measure of evidence rather than a binary decision.

#### Limitations

- Widely misread as the probability that  $H_0$  is true.<sup>[3,5]</sup>
- Encourages dichotomous thinking around the arbitrary 0.05 threshold.<sup>[5]</sup>
- Ignores Type II error (false negatives).

### 2.2 Neyman–Pearson hypothesis testing

Neyman and Pearson reframed inference as a decision problem.<sup>[2]</sup> One specifies

- Null hypothesis
- Alternative hypothesis
- Type I error rate (false positive)
- Type II error rate (false negative)

#### Advantages

- Explicit control of both false positives and false negatives.
- Essential for regulatory submissions.

#### Limitations

- Rigid binary decision:  $P = 0.049$  is “significant,”  $P = 0.051$  is “not,” despite negligible difference.<sup>[3,5]</sup>
- Large trials can make clinically trivial effects statistically significant.<sup>[3]</sup>

### 2.3 Analysis of Variance (ANOVA)

ANOVA, also pioneered by Fisher, partitions total variability into between-group and within-group components.<sup>[1]</sup>

#### Example

Three doses of a novel anti-inflammatory drug are compared with placebo in 80 subjects. ANOVA tests the null hypothesis that all group means are equal. If  $F(3,76) = 5.4$ ,  $P = 0.002$ , post-hoc Tukey tests identify which doses differ.<sup>[1]</sup>

#### Common Misuses

A survey of African biomedical journals found 21.4 % of ANOVA applications incorrect, including.<sup>[3,4]</sup>

- Applying one-way ANOVA to only two groups (where a  $t$ -test suffices).
- Omitting necessary post-hoc tests.
- Failing to report the ANOVA design (one-way vs. two-way).

### 2.4 Beyond the classical paradigms

Modern pharmacology increasingly employs.<sup>[6]</sup>

- Regression modelling – e.g., logistic regression for binary outcomes, nonlinear mixed-effects models for population PK/PD.
- Bayesian inference – integrates prior knowledge with new data.
- Multiple-testing corrections – Bonferroni, Holm, or false discovery rate procedures to control Type I error across many endpoints.

## 3. Applications of Biostatistics in Modern Pharmacology

Modern pharmacology rests on a diverse toolkit of quantitative and translational approaches that together accelerate the journey from molecule to medicine. Among these, rigorous statistical inference ensures that therapeutic claims are reliable, while drug repurposing transforms existing compounds into novel therapies with remarkable efficiency. Although conceptually distinct, these two areas share a common theme: both rely on extracting maximal insight from data already in hand—whether experimental or clinical—and both illustrate how careful methodology can shorten the distance between discovery and patient benefit.<sup>[3,4]</sup>

### 3.1 Statistical foundations and their practical reach

From the earliest dose–response experiments to the multinational Phase III trial, statistics provides the grammar through which pharmacological hypotheses are articulated and tested.<sup>[1,2]</sup> Two classical paradigms dominate: Fisher’s significance testing, which treats the *P*-value as a continuous measure of evidence against a null hypothesis, and the Neyman–Pearson decision framework, which formalizes hypothesis testing as a balance between false positives and false negatives.

*Fisher’s approach* is particularly influential in exploratory research. Suppose a first-in-human antihypertensive lowers mean systolic blood pressure by 8 mmHg compared with placebo (SD = 10 mmHg, *n* = 40 per arm). A two-sample *t*-test yields *P* = 0.04. Fisher would interpret this as “moderate evidence” against the null hypothesis of no difference—enough to merit replication but not, in itself, a license for clinical adoption.<sup>[1,3]</sup> The elegance of this framework lies in its flexibility; yet its very simplicity fosters misinterpretation. A *P*-value is not the probability that the null hypothesis is true, nor does *P* < 0.05 automatically imply clinical relevance.<sup>[5]</sup> Over-emphasis on a single threshold has contributed to the wider reproducibility crisis in biomedical research.<sup>[4,5]</sup>

The *Neyman–Pearson framework* reframes inference as a decision problem. Investigators specify a Type I error rate ( $\alpha$ ) and a desired power ( $1 - \beta$ ) before the trial begins.<sup>[2]</sup> Consider a Phase III oncology study designed to detect a 20 % improvement in one-year survival: with  $\alpha = 0.05$  and power of 80 %, the sample size is chosen so that if the alternative hypothesis is correct, there is only a 20 % chance of failing to reject the null. This structure is invaluable for regulatory decisions, but its rigidity can be misleading. A survival benefit with *P* = 0.051 may be dismissed despite clinical significance, while very large trials can yield “significant” differences of negligible magnitude.<sup>[3,5]</sup>

Beyond these paradigms, analysis of variance (ANOVA) remains a workhorse for multi-arm comparisons such as dose-finding studies.<sup>[1]</sup> By partitioning total variance into between- and within-group components, ANOVA efficiently tests whether mean responses differ across treatments.<sup>[3,4]</sup> Yet persistent misapplications—such as omitting post-hoc tests or applying one-way ANOVA to only two groups—can distort inference as surely as an under-powered trial.

Together, these statistical frameworks—when applied correctly—provide the quantitative backbone of pharmacology, ensuring that therapeutic claims are reproducible and clinically meaningful.

### 3.2 Drug repurposing: from serendipity to systems biology

If rigorous statistics safeguards credibility, drug repurposing accelerates innovation.<sup>[8]</sup> Repurposing, or

repositioning, identifies new therapeutic uses for molecules with established human safety profiles. By leveraging existing toxicology, manufacturing, and pharmacokinetic data, developers can often bypass early-phase trials, reducing cost and time to market.<sup>[7,9]</sup>

Historical precedents reveal both the promise and the diverse pathways to success,<sup>[8,9]</sup>

- *Sildenafil* was synthesized as an anti-anginal agent; serendipitous observations of improved erectile function redirected its development toward erectile dysfunction and later pulmonary arterial hypertension.
- *Amantadine*, once an antiviral for influenza, demonstrated benefits in Parkinson’s disease through modulation of dopaminergic pathways.
- *Aspirin*, long used for analgesia and platelet inhibition, continues to attract interest as a chemo preventive agent in colorectal and other cancers.

Where early successes depended on clinical chance, contemporary repurposing is increasingly data-driven. Large electronic health-record (EHR) systems enable retrospective epidemiological studies that detect unexpected associations between drug exposure and disease outcomes. Transcriptomic resources such as the Connectivity Map (CMap) match disease-specific gene-expression signatures with drug-induced profiles, suggesting compounds that may reverse pathogenic pathways. Network pharmacology maps complex drug–target interactions, while machine-learning algorithms integrate chemical, genomic, and clinical datasets to predict novel drug–disease relationships at scale.

Regulatory innovation has accompanied these scientific advances. The U.S. Food and Drug Administration’s 505(b)(2) pathway allows approval of repurposed drugs on the basis of existing safety data, dramatically lowering barriers relative to de novo applications.<sup>[7,8]</sup> The European Medicines Agency provides analogous hybrid routes. These mechanisms have enabled repurposed approvals in oncology, rare metabolic disorders, and central nervous system diseases where traditional pipelines lag.<sup>[8,9]</sup>

The COVID-19 pandemic offered a stress test of the approach. Agents such as remdesivir, dexamethasone, and monoclonal antibodies were deployed or trialed at unprecedented speed. Not all efforts succeeded—hydroxychloroquine, for instance, failed in large randomized trials despite early in-vitro promise—but the rapid mobilization underscored the strategic value of a well-curated pharmacopeia ready for redeployment.

Despite these achievements, repurposing remains scientifically demanding. Computational predictions must be validated in rigorous clinical trials, and intellectual-property uncertainties often deter investment in off-patent compounds. Nevertheless, the combination of extensive human exposure data and modern analytics

ensures that repurposing will remain a central driver of therapeutic innovation.

### 3.3 Post-market surveillance and pharmacovigilance

Even the most carefully designed pre-approval trials cannot capture every clinically important risk.<sup>[10,14]</sup> Trial populations are relatively small, carefully selected, and followed for limited periods, leaving rare, delayed, or population-specific adverse events undetected until a medicine reaches routine practice.<sup>[10,11]</sup> Post-marketing surveillance—the systematic collection, analysis, and interpretation of safety data once a product is licensed—therefore acts as the discipline’s long-term safety net.<sup>[12,13]</sup>

**Historical lessons.** The withdrawal of rofecoxib (Vioxx) remains the defining example. Initially hailed as a gastro-protective COX-2 inhibitor, it was removed from global markets in 2004 after meta-analyses revealed a roughly two-fold increase in myocardial infarction and stroke. Retrospective examination showed that cardiovascular signals were present in trial data years earlier, but fragmented reporting and inadequate early warning systems delayed action. Earlier tragedies—thalidomide-associated teratogenicity, fen-phen-induced valvopathy, and the cardiac risks of rosiglitazone—underscore the recurring pattern: post-marketing vigilance is not optional.<sup>[11]</sup>

**Analytic infrastructure.** Today’s pharmacovigilance relies on a combination of spontaneous-report systems (e.g., the FDA’s FAERS, WHO’s Vigibase, the EU’s EudraVigilance), electronic health-record mining, and increasingly sophisticated statistical algorithms. Signal detection employs disproportionality metrics such as the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR), which compare the observed frequency of a drug–event pair to its expected frequency across the database. Bayesian hierarchical models and Empirical Bayes Geometric Mean (EBGM) estimates add probabilistic refinement, while trial-sequential analysis helps determine when cumulative evidence is sufficient to trigger regulatory review.

**Public-health impact.** Active surveillance programs such as the U.S. Sentinel Initiative now link tens of millions of longitudinal patient records, enabling near real-time detection of safety signals. These systems have supported timely risk communication and label changes for anticoagulants, vaccines, and biologics. Their success illustrates how big-data analytics can transform spontaneous reporting into a proactive, learning health-care system.

### 3.4 Model-informed precision dosing (MIPD)

Where pharmacovigilance safeguards against harm, model-informed precision dosing (MIPD) aims to maximize benefit by tailoring therapy to individual patients. Conventional fixed dosing assumes that a standard regimen is suitable for most patients, yet

pharmacokinetic (PK) variability—from genetic polymorphisms to renal function—can span an order of magnitude.<sup>[16,18]</sup>

**Conceptual framework.** MIPD integrates population PK/PD models with patient-specific covariates and real-time drug-level measurements. A prior model provides estimates of clearance (CL), volume of distribution (Vd), and other parameters. As patient data accumulate, Bayesian updating refines the posterior distribution.

### Clinical examples

- Aminoglycosides and vancomycin—narrow therapeutic-index antibiotics—are now routinely managed with Bayesian software that integrates patient-specific levels to target optimal AUC/MIC ratios.
- In oncology, busulfan dosing guided by real-time PK sampling improves engraftment and reduces toxicity in hematopoietic stem-cell transplantation.
- Pediatric settings, where developmental changes in clearance are profound, particularly benefit from adaptive dosing informed by sparse sampling.<sup>[18,19]</sup>

**Implementation and infrastructure.** Successful MIPD requires validated population models, seamless integration with electronic health records, and clinical decision-support systems that can deliver dose recommendations at the bedside. Several commercial and academic platforms—BestDose, TDMx, InsightRx—are emerging, but widespread adoption is limited by cost, clinician training needs, and heterogeneous regulatory guidance.<sup>[18,19]</sup>

### 3.5 Integrative perspective on applications

Although presented separately, these application areas are mutually reinforcing. Robust statistics underpin the discovery and evaluation of repurposed indications, guide pharmacovigilance signal detection, and form the mathematical core of MIPD algorithms.<sup>[14,18]</sup> Repurposing efforts often rely on post-marketing safety and efficacy data, while insights from pharmacovigilance feedback to refine population models used in precision dosing. Collectively, these strategies exemplify a cycle of evidence: data from clinical practice refine statistical models, which in turn enable more targeted therapy and safer deployment of both novel and repurposed drugs.<sup>[15,18]</sup>

### 4. Challenges

Despite the striking advances taken place in the field of biostatistics as described above, it still faces persistent scientific, regulatory, and operational barriers. These challenges play a crucial role in shaping the credibility of evidence, determining the pace of translation, and ultimately influencing the therapy outcomes.<sup>[3,5]</sup>



#### 4.1 Statistical rigor and reproducibility

##### 4.1.1 Misinterpretation of the $P$ -value

The most frequently cited weakness is the continued over-reliance on  $P < 0.05$  as a binary decision rule.<sup>[1]</sup> This threshold, rooted in Fisher's early work, was never intended to demarcate truth from falsehood.<sup>[3,5]</sup> Yet it is routinely misread as the probability that the null hypothesis is correct. Such misconceptions foster "significance chasing," where investigators design experiments to achieve nominal significance rather than to estimate effect sizes with precision.<sup>[4,5]</sup> The result is a literature populated by fragile findings that fail replication.<sup>[1]</sup>

##### 4.1.2 Pitfalls in classical tests

The Neyman–Pearson framework, while elegant, can yield perverse incentives.<sup>[2]</sup> Consider a cardiovascular outcomes trial with a prespecified  $\alpha = 0.05$ . If the primary endpoint yields  $P = 0.051$ , the finding is declared "negative" despite a clinically meaningful hazard ratio of 0.80. Conversely, an extremely large trial may detect a hazard ratio of 0.98 with  $P < 0.001$ , a result statistically "positive" yet clinically trivial. Analysis of variance (ANOVA) carries its own hazards: violations of homoscedasticity, failure to perform post-hoc comparisons, and inappropriate use for two-group comparisons can inflate Type I error or mask true differences.<sup>[1,3,4]</sup>

##### 4.1.3 Multiple testing and data dredging

High-dimensional omics and real-world data create fertile ground for false positives. Without rigorous control of the false discovery rate or appropriate Bayesian priors, exploratory analyses can produce apparently convincing—but ultimately spurious—associations that misdirect resources and patient care.<sup>[6]</sup>

#### 4.2 Drug repurposing

##### 4.2.1 Intellectual-property constraints

Because many repurposing candidates are off-patent, commercial incentives for large, confirmatory trials are weak.<sup>[7,8]</sup> Sponsors may fear that competitors can market the same compound for the new indication with minimal additional investment, eroding exclusivity and profit.<sup>[8]</sup>

##### 4.2.2 Biological complexity and translational gaps.

Computational predictions often fail in prospective studies.<sup>[8,9]</sup> Transcriptomic signatures may not replicate across tissues; network models trained on cell-line data may overlook pharmacokinetic realities such as poor bioavailability or tissue penetration.<sup>[8]</sup> Negative trials of hydroxychloroquine and lopinavir–ritonavir for COVID-19 highlight how preclinical promise can evaporate under the scrutiny of randomized evaluation.<sup>[8,9]</sup>

#### 4.3 Post-market surveillance

##### 4.3.1 Under-reporting and data heterogeneity

Spontaneous-report systems such as FAERS and Vigibase capture only a fraction of true adverse events.<sup>[13,14]</sup> Reporting is influenced by media attention,

litigation risk, and regional practices, creating biased estimates of incidence. Integrating data across national databases introduces additional complexity, including variable coding standards and privacy regulations.<sup>[14,15]</sup>

##### 4.3.2 Industry influence and delayed action.

The rofecoxib episode illustrates how selective publication and sponsor control of trial data can delay recognition of harm. Even today, access to complete clinical-trial datasets remains inconsistent, hampering independent verification of safety signals.<sup>[12,13]</sup>

#### 4.4 Model-informed precision dosing

##### 4.4.1 Data and infrastructure requirements

MIPD depends on timely laboratory results, validated population models, and seamless electronic health-record integration. Many healthcare settings lack these capabilities.<sup>[16,18]</sup> Sparse or inaccurate sampling undermines Bayesian forecasting, leading to dosing recommendations that are no better than conventional weight-based methods.<sup>[17,18]</sup>

##### 4.4.2 Regulatory uncertainty and clinician training

Few regulatory agencies provide detailed guidance on the validation and real-time use of adaptive dosing algorithms. Clinicians may be reluctant to trust "black-box" software, and additional training is required to interpret model outputs and incorporate them into busy clinical workflows.<sup>[16,18,20]</sup>

#### 4.5 Interconnected nature of the challenges

These obstacles do not exist in isolation. Weak statistical practice undermines every domain—from the false discovery of repurposing candidates to the misidentification of pharmacovigilance signals and the mis-specification of population PK models. Conversely, gaps in post-market data limit the refinement of precision-dosing models, while intellectual-property barriers slow the clinical testing needed to confirm statistical predictions. Addressing any one challenge therefore requires coordinated reform across the entire pharmacological ecosystem.<sup>[4,5,7]</sup>

#### 5. Future Perspectives

The four application domains reviewed here—rigorous statistical methodology, systematic drug repurposing, post-market surveillance, and model-informed precision dosing—are not discrete silos but interconnected components of a single, data-driven pharmacological enterprise. Looking forward, their convergence, supported by emerging technologies and regulatory evolution, defines the next decade of therapeutic innovation.<sup>[18,20]</sup>

##### 5.1 Methodological renewal

The most urgent priority is a cultural and educational shift in the use of statistics. Journals and funding agencies are beginning to move beyond a binary " $P < 0.05$ " framework toward effect-size estimation, confidence intervals, and Bayesian inference.<sup>[5,6]</sup> Wider

adoption of pre-registration, open data, and reproducible workflows will help address the reproducibility crisis and strengthen the evidentiary base for all downstream applications. Training programs that integrate pharmacology, biostatistics, and data science will be essential for the next generation of investigators.<sup>[4,6]</sup>

### 5.2 Data integration and real-world evidence

The growing availability of electronic health records, genomic sequencing, wearable devices, and patient-reported outcomes creates unprecedented opportunities to close the loop between discovery and practice. Harmonized, privacy-protected global networks can enable near-real-time signal detection, refine population PK/PD models, and validate repurposing hypotheses on a scale previously impossible. The success of initiatives such as the U.S. Sentinel System and the European Health Data Space suggests that such integration is feasible when technical and legal standards are aligned.

### 5.3 Incentivizing repurposing and adaptive dosing

Economic and regulatory frameworks must evolve to match scientific capability. Extended market-exclusivity provisions, public-private partnerships, and non-profit development models can help overcome the intellectual-property disincentives that currently slow repurposing of off-patent compounds. For MIPD, regulatory agencies are beginning to recognize adaptive dosing algorithms as part of the drug label, but formal guidance on validation and quality assurance is still emerging.<sup>[18]</sup> Incentives for health-system adoption—reimbursement structures, integration with electronic health records, and clinician training—will be crucial.<sup>[15]</sup>

### 5.4 Ethical and societal considerations

As pharmacology becomes more data-intensive, protecting patient privacy and ensuring algorithmic fairness are paramount.<sup>[14,15,19]</sup> Biases in training data can propagate inequities in drug dosing recommendations or in the detection of adverse events. Transparent model development, independent auditing, and active engagement with diverse patient communities will be essential safeguards.<sup>[15,19]</sup>

## 6. CONCLUSION

Modern pharmacology stands at a pivotal moment. Statistical discipline provides the foundation, drug repurposing extends the therapeutic arsenal, pharmacovigilance protects patients after approval, and precision dosing personalizes treatment at the bedside. Each component strengthens the others: surveillance data feed Bayesian dosing models; repurposing opportunities arise from post-marketing observations; rigorous statistics keep the entire system credible.<sup>[14,18]</sup>

The lessons are clear. Serendipitous successes such as sildenafil remind us of the creative potential of repurposing; tragedies such as rofecoxib warn of the cost of inadequate surveillance; and the promise of model-informed dosing illustrates how mathematics and clinical

medicine can merge to benefit individual patients. Realizing this vision will require sustained commitment to statistical reform, open data, regulatory flexibility, and multidisciplinary education.<sup>[15,20]</sup>

If these challenges are met, the next generation of pharmacology will not merely discover new drugs but will also ensure that every drug—new or old—is used more wisely, more safely, and more personally than ever before.<sup>[15,18]</sup>

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