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Review Article

Bayesian Statistics and the FDA: Historical Foundations and Solutions for Drug Development

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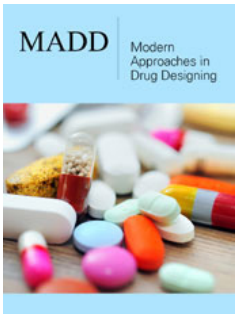

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Abstract

This paper reviews the development of Bayesian statistical methods and identifies the main barriers limiting their adoption by the U.S. Food and Drug Administration (FDA) in drug and biologics regulation. Advantages of the Bayesian framework are highlighted, contrasting their adoption with that of frequentist methods. A synthesis of key historical, regulatory, and industry trends describes advances in regulatory science. For stakeholders aiming to improve drug development efficiency without compromising scientific rigor, the careful use of Bayesian methods-anchored in systematic prior construction, scenario-based evaluation of operating characteristics (often via simulation), transparent documentation and reproducible computation with early regulatory engagement-offers an increasingly practical pathway for drug development and post-approval surveillance.

Keyword: Bayesian framework; Frequentist approach; Clinical trials; Regulatory challenges in drug development; Regulatory science

Introduction

Bayesian statistics offers a distinct framework for statistical inference from frequentist methods. Frequentist approaches use observed data to make inferences without incorporating formal prior knowledge. In contrast, the Bayesian framework formally integrates prior information, enables direct probability statements about parameters (such as the probability that a drug is effective given the data), and supports adaptive trial designs [1,2]. Despite these strengths and over 250 years of theoretical development, Bayesian methods remain uncommon in FDA drug approval decisions based on pivotal Phase 3 trials. Nevertheless, Bayesian methods appear more widely in earlier Phase 1/2 clinical work and internal decision-making. In addition, Bayesian methodology is widely used in other scientific fields and has become a well-established option in medical device regulation [3,4].

This paper is a narrative review and does not aim to be an exhaustive, protocol-driven retrieval and quantitative pooling that characterize systematic reviews. Methodologically, an interpretive synthesis of heterogeneous sources is employed, organized around a chronological and thematic framework. Source material was purposively selected rather than identified through an exhaustive, pre-registered search protocol, to characterize the historical, regulatory, and industry landscape, and comprised four principal categories: (1) peer-reviewed statistical and methodological literature; (2) primary regulatory documents, most notably the FDA's 2026 draft guidance Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products and the 2010 medical device guidance; (3) surveys and commentary on perceived and actual barriers to Bayesian adoption; and (4) publicly available data and reports on Bayesian trial usage [1-6]. These sources were integrated using a narrative synthesis approach: evidence was grouped thematically, findings were

compared and interpreted qualitatively, and a hypothetical case study was used to illustrate application rather than to generate new data. The authors also draw on domain expertise, where noted, as clinical trialists or in regulatory science. This design carries recognized limitations, principally the potential for selection and interpretation bias inherent to purposive sampling, and the absence of quantitative synthesis. These limitations are mitigated through transparent sourcing, explicit reasoning, and balanced presentation of countervailing evidence.

Consistent with this framework, the review is structured to summarize: (1) the historical evolution of Bayesian statistics from the 18th century to the present; (2) the current FDA regulatory framework and guidance for Bayesian methods; (4) systematic barriers to adoption in drug development; and (3) recent trends suggesting an increased likelihood of future adoption. This paper thereby provides an informative overview of selected, highly relevant Bayesian topics in regulatory science and biostatistical methodology.

Historical Development of Bayesian Statistics

Foundational period (1763-1850)

Bayesian statistics originated with Thomas Bayes' 1763 work on updating beliefs in the light of new data. Pierre-Simon Laplace extended these ideas in the late 18th and early 19th centuries, applying Bayesian reasoning to scientific problems and introducing practical methods for calculating priors and posteriors.

Laplace articulated the core Bayesian principle: probability represents the degree of rational belief, and Bayes' theorem provides the mechanism for coherent belief updating when new evidence arrives [7,8]. He formalized the use of prior distributions to represent initial knowledge states and derived posterior distributions analytically for various practical problems. Laplace's "principle of indifference" proposed uniform priors to represent ignorance, establishing an early framework for the specification of non-informative priors [7,8].

Bayes' theorem can be written as: Posterior $\propto$ Likelihood $\times$ Prior. In other words, the probability of the parameter of interest after observing the data (the posterior) is proportional to the likelihood of the observed data given the parameter, multiplied by the prior belief about the parameter before seeing the data. More formally, Bayes' theorem states: Posterior = (Likelihood $\times$ Prior) / Evidence, where 'Evidence' is a normalizing constant ensuring that the posterior probabilities integrate (or, for discrete parameters, sums) to one.

Bayesian decline and frequentist ascendance (1850-1950)

In the late 19th and early 20th centuries, frequentist methods dominated, owing to the contributions of Pearson, Fisher, Neyman, and others, who laid the foundations of hypothesis testing and long-run error control. In contrast, Bayesian methods faded due in large part to criticisms of subjectivity and computational difficulty. Several factors contributed to the perception of Bayesian decline during this period:

A. Philosophical objections: Frequentists criticized Bayesian methods as "subjective" due to reliance on prior distributions, arguing that scientific inference should be based solely on observed data and long-run frequencies [7,8].

B. Computational limitations: Bayesian inference typically involves integrating over the full parameter space to obtain posterior distributions or expectations. For many realistic models, these integrals lack closed form solutions and numerical methods were required. In contrast, many early frequentist procedures that became standard in practice (e.g., t tests, simple linear regression, and ANOVA) were deliberately developed to have closed form or table-based solutions that were feasible to compute by hand or with limited numerical tools, contributing to their dominance before modern computing.

C. Institutional momentum: The emerging fields of agriculture, industrial quality control, and clinical trials adopted frequentist frameworks, establishing teaching traditions and analytical standards [8].

During this period, the term "Bayesian" was used relatively infrequently, and these methods received attention primarily in philosophical debates rather than in mainstream applied statistics [8].

Theoretical resurgence (1950-1980)

Mid-20th-century statisticians, including Leonard J. Savage, Bruno de Finetti, Harold Jeffreys (an objective Bayesian), and Dennis Lindley, revived Bayesian thinking through axiomatic approaches to subjective probability and decision theory [7,9]. De Finetti's representation theorems and Savage's axioms of rational choice provided rigorous foundations for interpreting probabilities as coherent degrees of belief [7,9].

This theoretical work established that a coherent belief system satisfying basic consistency axioms follows Bayes' theorem when updating beliefs. In addition, statistical theory was developed to show that Bayesian decision theory provides optimal strategies under well-defined loss functions. An attractive feature of Bayesian methodology was that prior distributions could represent various levels of knowledge, from complete ignorance to strong prior information. However, computational barriers still limited practical application to complex, high-dimensional problems typical of modern clinical trials [7,9].

Computational revolution (1980-2000)

Late 20th-century computational innovations, such as MCMC algorithms, enabled routine practical Bayesian analysis of many complexes, high dimensional models that had previously been computationally prohibitive, fuelling a resurgence across disciplines. Combined with extraordinarily increasing computing power and accessible software packages, these advances helped spark what some described as a 'Bayesian renaissance' across scientific fields [7,9]. Researchers could now fit hierarchical models borrowing strength across related studies or subgroups and handle complex missing-data structures via data augmentation. It was now feasible to incorporate multiple sources of information coherently

and provide direct probability statements about parameters and predictions.

Modern era (2000-Present)

In the 21st century, Bayesian methods have become widely accepted in fields such as biostatistics, epidemiology, machine learning, and environmental science [7,9]. The historical debates between Bayesian and frequentist schools have, in much applied work, subsided into a pragmatic recognition of the value each framework offers, depending on the context [7,10].

Contemporary guidance on good Bayesian practice emphasizes a rigorous workflow of systematic model building, transparent prior specification, computational diagnostics, posterior predictive checking, and sensitivity analysis [7]. During this timeframe, regulatory science has begun to formally acknowledge that Bayesian methods are feasible, as evidenced by explicit regulatory documents and publications. Nevertheless, adoption of Bayesian methodology in drug development appears more limited compared to other fields [3,4,10].

Current FDA Regulatory Framework for Bayesian Methods

This section shifts the focus from history to a review of recent FDA positions on Bayesian methodology.

Medical device guidance (2010)

One of the FDA's earliest major guidance documents formally enabling/endorsing Bayesian methods appeared in 2010 entitled "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials." This document described how Bayesian methodology can streamline some medical device evaluations and encouraged consideration of Bayesian approaches in certain settings. These settings include borrowing historical or external control data to reduce sample size requirements and using hierarchical models to borrow strength across related studies, device generations, or indications.

The guidance emphasized that Bayesian designs require a protocol with full documentation explaining how priors (initial assumptions) are constructed to minimize bias. The design should also demonstrate acceptable operating characteristics through simulation studies. Specifically, the operating characteristics of type 1 error control (the probability of a false positive) and power (the probability of detecting an effect when one exists) are expected to meet usual regulatory standards for type 1 error control and power [4,11]. This regulatory framework allowed sponsors to leverage extensive experience with similar devices while maintaining regulatory rigor. Medical device trials proved particularly amenable to Bayesian methods due to typically smaller sample sizes, shorter-term outcomes, and substantial historical data availability [4,11].

Drug and Biologics Draft Guidance (2026)

In early 2026, the FDA published a draft guidance document entitled "Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products," representing an important step toward broader acceptance of Bayesian approaches in pharmaceutical development. The guidance describes how Bayesian methods can be used to support primary inference in drug and biologic trials, including the use of borrowing or leveraging external information. The draft guidance provides recommendations on success criteria, operating characteristics, prior distributions, handling of missing data, and software. Examples of applications included adaptive and flexible designs for interim decision-making, historical borrowing where data are combined from previous trials or external sources to augment control information or support extrapolation, use in settings with limited data such as paediatric or rare diseases where external data can be leveraged to reduce required sample sizes, and subgroup evaluations where hierarchical modeling is used to borrow strength across related subpopulations.

The Bayesian framework brings specific expectations for protocol development in the FDA's 2026 draft guidance. First, prior specification: sponsors should construct priors using a systematic, transparent, and well documented process, and pre specify and justify the proposed prior distribution in the protocol, including its influence on results and trial operating characteristics [3,12]. Sources may include historical data, mechanistic understanding, or structured expert elicitation, with a clear rationale. Second, operating characteristics: sponsors are expected to evaluate type 1 error, power, and other relevant performance metrics-typically via clinical trial simulations-across clinically relevant scenarios, including situations where external information may conflict with new data [3,12]. Third, sensitivity analysis: key conclusions should be examined under alternative reasonable priors to assess robustness [3,12]. Fourth, prospective specification: design elements, priors, decision rules, and statistical analysis plans are to be pre specified and submitted to FDA before trial initiation to support transparency and appropriate control of error. Finally, when these conditions are met and operating characteristics are acceptable, Bayesian methods can support primary efficacy and safety conclusions in pivotal trials [3,12].

The guidance acknowledges that Bayesian and frequentist methods can coexist, with Bayesian analyses serving as primary, supportive, or exploratory depending on context and sponsor preference [3,12].

Historical Use Cases in Drug Development

Prior to the 2026 draft guidance, Bayesian methods appeared in various drug development contexts, typically in supportive or secondary roles, sometimes referred to as 'low-hanging fruit.' Examples include: 1) adaptive phase II seamless designs using Bayesian predictive probabilities for sponsor go/no-go decisions, 2) paediatric extrapolation from adult data using hierarchical models (e.g., used in some oncology and rare disease programs), 3) dose-response modeling in early-phase trials, and 4) safety signal detection and monitoring using Bayesian sequential methods. However, most pivotal efficacy trials for drug approval have continued to rely on frequentist primary analyses with fixed or group-sequential designs [11,13].

Quantitative assessment of bayesian trial usage: Data limitations

A gap exists in systematic, publicly available data tracking FDA Bayesian trial usage by clinical phase and time period. Despite the importance of such metrics for assessing regulatory trends, comprehensive phase-specific data (Phase 1, 2, 3, and post-approval) across distinct time periods (e.g., 2017-2019 vs. 2023-2025) do not appear to have been widely disseminated in the peer-reviewed literature or in FDA reports [14,15].

Research primarily focused on oncology trials provides the most comprehensive published data on Bayesian clinical trial distributions by phase [14]. This description of Bayesian clinical trials by phase, 2004-2024 (an oncology-focused sample), demonstrates clear concentration in early-phase trials. Dose-finding, adaptive designs, and smaller sample sizes make Bayesian methods particularly attractive. This is readily apparent when categorized by study phase: approximately 41.1% were Phase 1, while only 2.2% were Phase 3, illustrating a strong phase gradient in usage. The low percentage in Bayesian usage for Phase 3 trials (2.2%) reflects barriers to using Bayesian methods, examined below.

At the institute level, the MD Anderson Cancer Center reported that approximately 28% of its cancer trials used Bayesian methods during 2009-2013 [15]. This average, when categorized by study phase, was as follows: 34% were Phase 1 or 2, and 6% were Phase 3 or 4. Even within a single institution with specialized expertise in Bayesian methods, their use was limited. We suspect that FDA-wide or industry-wide adoption rates are lower, although we found no published data to support this.

Why are published phase-specific temporal data difficult to find? There are several reasons. First, there is the issue of the sponsor's proprietary information. Sponsors may not publicly disclose statistical approaches for competitive reasons until regulatory submission. Second, there appears to be little systematic FDA tracking information available to the public or reported in the peer-reviewed literature. Prior to 2026 guidance, the FDA did not publicly provide to our knowledge systematic categorizations or reports of trials by statistical methodology (Bayesian vs. frequentist) [14,15]. Expanded consideration of Bayesian methods for pivotal trials appears to be emerging with the appearance of the 2026 draft guidance; historical rates were very low as noted previously [14,15]. Finally, ClinicalTrials.gov does not require or capture statistical methodology in searchable fields.

The FDA's Bayesian Statistical Analysis (BSA) Demonstration Project, part of FDA's Center for Drug Evaluation and Research (CDER) Center for Clinical Trial Innovation, provided a structured opportunity to use Bayesian approaches for the pre specified primary analysis, supplementary analysis, or monitoring of certain phase 3 efficacy or safety trials with simple designs [16]. This initiative indicated that future tracking and reporting of Bayesian trial applications may improve, facilitating more rigorous assessment of adoption trends as formal guidance is implemented. One intriguing question is whether Bayesian methodology should be incorporated within the regulatory framework of a Special Protocol Assessment (SPA). A SPA is a formal process in which sponsors can seek a binding agreement with the FDA that the design, endpoints, and analysis of a pivotal phase 3 (or other key) trial are adequate to support regulatory approval if the study is conducted as agreed. The aim is to reduce development risk by clarifying scientific requirements before major investments. In principle, a SPA could also reduce the risk of post hoc disagreement about Bayesian design elements such as choice of a prior. However, this strategy has trade-offs because SPA interactions may add time before trial initiation. Given the increasing regulatory visibility of Bayesian methods, it is a natural mechanism for sponsors to consider in internal discussions.

Available evidence indicates that Bayesian methods have been used in post approval contexts, including safety surveillance, benefit–risk monitoring, and post marketing requirement or commitment studies, where sequential updating of evidence is well aligned with Bayesian frameworks [14,15]. The next section exemplifies a hypothetical case study.

Case study: Bayesian approach in FDA post-approval safety monitoring

There are prominent exploratory and complementary examples of Bayesian methods in post-approval safety surveillance, notably within the Sentinel Initiative, whose routine methodology is dominated by frequentist approaches. The FDA's Sentinel Initiative, launched in 2008 for active drug safety surveillance, continuously monitors adverse event signals across large healthcare databases and has, on a more exploratory basis, incorporated Bayesian methods alongside its frequentist sequential analysis tools [17].

As an illustration of how Bayesian sequential methods could be applied in this context, consider a hypothetical post marketing safety program for new oral anticoagulants: Bayesian sequential analyses might (1) continuously update risk estimates as data accumulate from electronic health records and insurance claims databases, (2) calculate posterior probabilities that risk ratios exceed pre specified safety thresholds, (3) incorporate prior information from pre-approval clinical trials into post market surveillance using hierarchical models, and (4) implement stopping rules based on predictive probabilities of reaching definitive conclusions about emerging safety signals.

Several advantages would be possible if one or more features of this Bayesian approach to safety monitoring were implemented. First, continuous evidence synthesis is an important strength: Bayesian updating enables the integration of accumulating real-world evidence without requiring the same formal multiple-testing adjustments as traditional frequentist sequential tests, provided the design is appropriately calibrated. Second, the Bayesian framework would enable more informed post-approval safety monitoring by leveraging prior information from the completed Phase 3 program, thereby improving the precision of early safety estimates. Third, the approach would yield more interpretable probability statements: a posterior probability (e.g., "99% probability that the cardiovascular risk ratio is below 1.1") is more directly interpretable for regulatory

decision-making than a p-value. Finally, the framework would allow for efficient resource allocation and enhanced patient protection, since predictive probabilities could guide whether continued monitoring remains informative or whether conclusions could be reached early-optimizing surveillance costs while protecting patients if safety signals were confirmed.

There is regulatory precedent for active post-marketing safety surveillance that incorporates Bayesian and empirical-Bayes methods. First, empirical-Bayes disproportionality methods are already used routinely in FDA signal detection, and Bayesian sequential approaches have been evaluated in vaccine-safety surveillance. Second, observational data and large healthcare databases are well-suited to Bayesian hierarchical models, which can account for heterogeneity and, in some settings, help adjust for confounding when combined with appropriate design and adjustment strategies. The identification and control of confounding are critical in any safety analysis, especially in non-randomized studies: randomization tends to balance confounders, both known and unknown, whereas no such assurance exists in observational settings. Finally, adaptive monitoring aligns with the public health imperative for timely detection and evaluation of safety signals.

This hypothetical case illustrates how Bayesian methods can be applied in a setting in which its strengths align with regulatory needs, even as barriers persist to Phase 3 efficacy trials.

Barriers to Widespread FDA Adoption of Bayesian Methods

Despite theoretical advantages and recent regulatory encouragement, multiple interrelated barriers have limited the adoption of Bayesian methods in drug development. Understanding these obstacles is essential for stakeholders seeking to advance methodological innovation.

Training and expertise gaps

Empirical surveys of pharmaceutical statisticians and regulatory stakeholders consistently identify 'insufficient knowledge of Bayesian approaches' as the most important perceived barrier to implementation [5,11]. In one 2022-2023 survey of researchers involved in drug development, 48% of respondents ranked lack of Bayesian expertise as the primary obstacle, exceeding concerns about regulatory acceptance [5]. This can create a reinforcing cycle: limited expertise reduces the number of proposed Bayesian designs; fewer submitted protocols mean less hands-on review experience; the resulting lack of precedent increases perceived risk for sponsors, who continue to prefer frequentist approaches; and the expertise gap persists [11].

Perceived subjectivity and prior specification challenges

A central criticism of Bayesian methods is the requirement to specify prior distributions for the parameters of interest, which critics argue introduces subjectivity and possible bias into scientific inference [10,11]. In the frequentist framework, two independent individuals can analyze the same data, use the same statistical test, and obtain the same answer. This is a comfortable environment for clinicians and regulators to operate in. In the Bayesian framework, the same analytic setting may yield substantively different answers for data analysts who select different prior distributions. This outcome is problematic to the clinician and regulator alike, because the decision to accept/ use the therapy depends on prior data external to the clinical trial. Regulators must apply standards consistently across sponsors and therapeutic areas; disagreements over appropriate priors could introduce variability and complicate cross-sponsor comparisons.

The FDA's draft guidance addresses to some extent these concerns by mandating systematic prior derivation, transparent documentation, sensitivity analyses, and operating characteristic evaluation [3,12]. However, these requirements add complexity compared to standard frequentist designs, potentially deterring sponsors.

Regulatory standards and legal precedent

U.S. drug regulation has, in practice, evolved around frequentist concepts deeply embedded in standard operating procedures, regulatory precedents, and stakeholder expectations. Over decades, regulators, sponsors, courts, and advisory committees have relied on an extensive library of scientific, statistical, legal, and medical documents framed in terms of p values, confidence intervals, and hypothesis tests, which-despite frequent misinterpretation-have become familiar elements of the regulatory science landscape.

By contrast, Bayesian methods used to support primary inference typically require prospective evaluation of operating characteristics such as type I error and power, often via simulation, to demonstrate that Bayesian decision rules meet agreed upon performance standards [3,12]. Posterior probabilities and predictive probabilities can offer more directly interpretable measures of evidence, but they also demand more explicit explanation, raising concerns for some stakeholders about maintaining perceived objectivity and consistency relative to long standing frequentist norms [10,11]. While straightforward in principle, this calibration and communication layer adds analytical complexity and can be more challenging to convey to non-statistical audiences.

Computational and implementation complexity

Although modern computing has dramatically reduced barriers to Bayesian analysis, regulatory submissions using Bayesian methods can still be relatively resource-intensive [5,11]. For such submissions, regulators expect careful model specification and validation, including detailed documentation of how priors are constructed and justified, how likelihoods and data models are specified, and how computational algorithms are implemented. Sponsors are generally expected to conduct sensitivity analyses that assess how key conclusions change under alternative plausible priors and model assumptions. For complex or novel implementations, regulators may also ask sponsors to document software and computational validation-such as convergence diagnostics, reproducibility of code, and verification that algorithms produce correct results under test cases.

From the sponsor's perspective, this combination of analytical complexity, documentation expectations, and uncertainty about review timelines can create a higher perceived risk compared with "off the shelf" frequentist designs that benefit from extensive precedent and well understood review patterns. Planning and executing a Bayesian trial design that meets current regulatory expectations typically requires more upfront design work-particularly for prior development, simulations, and computational reproducibility-than a conventional design using standard frequentist methods. For senior pharma management, the relative scarcity of past Bayesian approvals and case examples in pivotal settings can further heighten concern about regulatory unpredictability and perceived risk of failure, reinforcing a preference for frequentist approaches even when Bayesian designs offer efficiency gains in time and costs.

Organizational heterogeneity and specific phase 3 challenges

The FDA comprises multiple centers (e.g., CDER, CBER, CDRH) and numerous review divisions within each center. Each division has its distinct culture, therapeutic expertise, and statistical traditions [10,11]. This heterogeneity increases perceived uncertainty. Several factors specifically constrain the use of Phase 3 Bayesian methods beyond the general barriers discussed above. Phase 3 trials represent the pivotal evidence for regulatory approval decisions, with hundreds of millions of dollars in development costs (or more) and future revenue at stake. This creates extreme risk aversion. Sponsors strongly prefer development programs with clear regulatory precedent. Novel Bayesian Phase 3 designs face uncertainty regarding review outcomes, even with FDA pre-approval [11]. Moreover, Phase 3 data undergo intense public review by FDA advisory committees, which historically expect frequentist metrics and may question Bayesian approaches [10]. The denial of marketing authorization due to concerns about statistical methodology (whether justified or not) represents an unacceptable business risk for pharmaceutical companies.

Phase 3 trials often involve multiple endpoints, subgroups, and interim analyses, creating complex multiplicity challenges in controlling the overall Type 1 error rate. While Bayesian methods avoid strict multiple-testing penalties through posterior-probability coherence, demonstrating adequate control of operating characteristics across multiple comparisons requires extensive simulation and justification. Moreover, reviewers have decades of experience evaluating frequentist multiplicity adjustments, but limited expertise in assessing Bayesian multiplicity strategies. Approved drug labels must clearly communicate evidence of efficacy to clinicians and patients. Converting Bayesian posterior probabilities into label language acceptable to regulators and interpretable to clinicians require careful consideration.

Independent Data Monitoring Committees (DMCs) overseeing Phase 3 trials for interim safety and efficacy analyses introduce additional considerations. Most DMC members are trained primarily in frequentist methods. Bayesian interim analyses may require specialized expertise that is not readily available. Bayesian predictive probability stopping rules must be prospectively defined and carefully calibrated. DMCs may prefer familiar alpha-spending approaches. DMC members may question whether priors appropriately balance informativeness vs. conservatism for interim decision-making.

In summary, these Phase 3-specific barriers compound the general obstacles that explain why Bayesian methods remain concentrated in early-phase trials (where flexibility, small samples and dose-finding suit Bayesian strengths) and post-approval monitoring (where continuous evidence synthesis is natural), while adoption of Bayesian methods in Phase 3 lags substantially. The 2026 FDA draft guidance may begin to address these barriers.

Emerging Trends Favoring Increased Adoption

Despite historical barriers, several converging trends suggest that Bayesian methods could play an increasingly prominent role in FDA drug evaluations in the coming years. The January 2026 draft guidance on Bayesian methodology for drug and biological products is likely to be a major step toward providing concrete, actionable standards for sponsors, with potential benefits including reduced regulatory uncertainty, a clearer framework for sponsor-agency dialogue, and the gradual establishment of regulatory precedents. This momentum, however, faces a source of uncertainty: the resignation of FDA Commissioner Marty Makary in May 2026, followed by broad senior-leadership turnover, has left several agency initiatives in transition and could slow programs such as the BSA demonstration project. Even so, the underlying rationale remains compelling: Bayesian methods are well suited to addressing high development costs and long timelines, particularly in rare diseases, paediatrics, and precision medicine, where traditional large-scale trials are often infeasible [3,12].

Evolution of FDA Bayesian acceptance during 2023-2026

The mid-2020s saw notable shifts in the FDA's posture toward Bayesian methods, driven by methodological advocacy and pressure to accelerate drug development. A central institutional vehicle is the CDER Center for Clinical Trial Innovation (C3TI), launched in April 2024, which manages a Demonstration Program to test and scale innovative trial approaches. One of its three demonstration project areas is the Bayesian Statistical Analysis (BSA) project, which invites sponsors of phase 3 trials with simple (non-adaptive or straightforward sequential) designs to apply Bayesian methods for a pre-specified primary analysis, a supplementary analysis, or trial monitoring, with dedicated CDER engagement and coordination support. Through workshops, this demonstration program, and collaborative research, C3TI aims to build regulatory experience and generate case studies across therapeutic areas. These efforts complement the FDA's January 2026 draft guidance on Bayesian methodology, and together they help build regulatory experience and internal Bayesian expertise across therapeutic areas [10].

While comprehensive quantitative data remain publicly unavailable, several qualitative indicators suggest growing openness to Bayesian methodology. The FDA's FY2025 commitment to publish Bayesian draft guidance, followed by its

January 2026 release, signalled institutional prioritization of the approach. FDA communications around clinical trial innovation have increasingly framed advanced statistical methods, including Bayesian approaches, as means to improve trial efficiency and make fuller use of existing data. This represents a notable shift from CDER's historically more cautious posture. Consistent with this, practitioners have reported greater FDA receptivity to Bayesian proposals in formal sponsor meetings, particularly for rare diseases and pediatric extrapolation, where prior-information borrowing is most readily accepted [18].

Despite these advances, several limitations persist. As of May 2026, FDA guidance remains in draft form pending resolution of public comments. Finalization will provide a more definitive regulatory standard [3]. Another limitation is the lack of a substantial precedent in Phase 3 studies. Increased acceptance appears to be concentrated in early-phase and post-approval contexts. Pivotal Phase 3 Bayesian trials leading to regulatory approval remain rare, limiting demonstration of feasibility [14]. Finally, many sponsors may have remained risk-averse during the 2023-2025 transition period, awaiting final guidance and accumulation of successful precedent before proposing Bayesian pivotal trials [18].

In conclusion, the 2023-2026 period represented an inflection point in FDA posture toward Bayesian methods, transitioning from theoretical acceptance to encouragement through formal guidance and demonstration projects. However, cultural and practical adoption varies across therapeutic areas and may lag institutional policy changes. Continued effort is needed by sponsors and the FDA to build expertise, establish precedents, and normalize Bayesian approaches across all phases of drug development.

Recommendations for Stakeholders

We enthusiastically support the expansion of Bayesian methodology in context-appropriate drug development. One of us (RWM) has been an active clinical trialist and frequentist for more than forty-five years, with a sporadic, universally brief excursion into the Bayesian world that always reached a dead end. Today, circumstances have changed and call for expanded usage of the Bayesian framework. The availability of diverse data sources for assessing safety risks and efficacy benefits (not just RCTs), computational advances, methodological publications, practical applications, and a range of regulatory information sources supports consideration of a Bayesian framework throughout the entire life cycle of clinical drug development.

Conclusion

Bayesian statistics originated as an 18th-century mathematical idea and, after remaining relatively dormant for practical inference, has over the past several decades evolved into a mature, computationally feasible framework that offers substantial advantages for modern drug development challenges. Despite this evolution and explicit regulatory encouragement through recent FDA draft guidance, Bayesian methods remain used relatively sparingly for primary inference in drug approval trials. This contrasts with their more established presence in medical device regulation and other scientific fields.

The barriers to adoption are multiple and valid. Barriers include insufficient training and expertise among both industry statisticians and regulatory reviewers; perceived subjectivity in prior specification, concerns about consistency across submissions, regulatory standards, and legal precedents built around frequentist concepts; computational and documentation complexity; a historical lack of clear guidance that creates sponsor uncertainty; and organizational heterogeneity within the FDA.

However, converging trends suggest that adoption of Bayesian methods appears poised to increase in the coming years. The 2026 draft guidance provides explicit standards and examples, reducing regulatory uncertainty. Generational changes in training are expanding expertise in Bayesian methods. Modern development contexts-such as rare diseases, paediatric extrapolation, adaptive designs, and precision medicine-align well with Bayesian strengths. Technological advances have made Bayesian computational efforts widely available. As successful precedents accumulate, positive feedback loops should accelerate adoption.

For stakeholders aiming to improve drug development efficiency without compromising scientific rigor, the careful use of Bayesian methods-anchored in systematic prior construction, scenario-based evaluation of operating characteristics (often via simulation), transparent documentation, and reproducible computation with early regulatory engagement-offers an increasingly practical pathway. Bayesian and frequentist approaches are now widely viewed as complementary toolkits, each better suited to different questions and development contexts. As regulatory practice codifies this pragmatic stance, the evidentiary framework for drug development is becoming more flexible and nuanced, opening additional opportunities for innovation in clinical trial design and evidence synthesis.

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All authors have contributed to the scientific content and writing of this review.

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