# The Trajectory of Pharmacometrics to Support Drug Licensing & Labeling

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## Abstract

The field of pharmacometrics has been responsible for countless advancements within the drug development space. In recent years, we have witnessed the implementation of both new and revived analytical methods to increase clinical trial success and even supplement the need for clinical trials all together. Throughout this article we will explore the path of pharmacometrics from its inception to present day. At this point in time, the target of drug development has been the average patient, and population approaches have primarily been utilized to support just that. The challenge we are now facing involves the translation from treating the typical patient to treating the real-world patient. For this reason, it is our opinion that future development efforts should account more for the individual. With advanced pharmacometric methods and growing technological infrastructure, precision medicine can become a development priority rather than a clinician’s burden.

## Introduction

Pharmacometrics is one of the most transformative applied sciences in drug development history. The field started as a theory conceived over 60 years ago and has now cascaded into a practice that is heavily relied upon today. As with any successful idea, there is a natural path taken from its birth to its wide-spread use. This course can be described in five phases: (1) Inception and growth, (2) Implementation met with hesitation, (3) Legitimization and acceptance, (4) Reliance, and (5) Expansion. Throughout this article we are going to explore this trajectory, analyze its impact, and ultimately make an inference on where we are headed next.

## Historical Overview

### *From Inception & Growth to Implementation & Hesitation (1960 – 1990)*

The birth of pharmacometrics dates back to the 1960s, when the methodology of this applied science was the primary focus. Methods to quantify the fate of drug molecules in the body were introduced, but we did not yet know how to implement this methodology to answer important questions. The challenge of quantifying dose-response needed to first be addressed. Dose-response assessments were initially performed in a pseudo-steady state condition, where scientists would incubate tissue at various drug concentrations, measure changes in the tissue at each concentration level, and ultimately construct a concentration-response relationship. This was a major advancement; however, it did not allow for the component of time to be quantified. The missing piece to this puzzle was how to collapse the delay between concentration and pharmacologic response, and it wasn’t until years later that we were able to handle the time course of pharmacokinetic (PK) and pharmacodynamic (PD) effects.

The name of this new field was first coined in the 1980s when the Journal of Pharmacokinetics and Biopharmaceutics introduced a new section called “Pharmacometrics” that focused on advanced PK/PD analyses.1 After this, we started to see pharmacometric methods being implemented to analyze observational data from clinical trials. Although this field had made big strides by this time, there was still some uncertainty and hesitation surrounding its application. Pharmacometric methods could analyze robust data with fair adequacy, but there was no accessible way to analyze instances where only sparse data could be collected. With the development of non-linear mixed-effects (NLME) modeling software, the issue of sparse sampling could be alleviated. Scientists had long recognized that the heterogenous nature of patients had an impact on PK, and many saw the accessibility of such software as a solution to characterizing these differences. The focus at this time was to address drug PK/PD at a population level and to bridge drug efficacy/safety across such diverse populations. By the 1990s pharmacometricians had identified this problem, proposed a potential solution, and now all that was needed was regulatory support and infrastructure.

### *From Legitimization & Acceptance to Reliance (1990 – 2010)*

In the U.S. the demand for pharmacometrics truly propelled once the Food and Drug Administration (FDA) started to endorse these approaches. First, the FDA began to publicly focus on how the concentration-response relationship was a better linkage from animals to humans and across clinical development, supporting the acceptance of pharmacometric methods. Then, the first written effort to introduce pharmacometrics using sparse sampling came in the 1994 FDA Guidance, Studies in Support of Special Populations: Geriatrics where they discussed the concept of pharmacokinetic screening.2 The FDA had identified a clear gap that needed to be filled because PK data was not routinely collected in geriatric patients. Therefore, the FDA proposed that Sponsors begin collecting sparse PK samples in geriatric patients during registration trials and then compare their PK with younger patients. This reinforced that there could be big differences in PK present, leading to necessary dose adjustments and further legitimizing pharmacometric methods. Although the FDA Guidance referred to this practice as “pharmacokinetic screening”, it was really the inception of population PK as we know it today. Following this in 1999 came the first ever FDA Guidance for Industry on the use of population PK modeling.3 This was vital for the field of pharmacometrics, and as a result population PK analyses have become a gold-standard within drug development.

This new acceptance was further reflected in 2004 by the FDA’s critical path initiative, which was intended to address the issue of reduced productivity in modern drug development.4 The need to strength this discipline was identified as a major solution to their proposed initiatives, such as improving evaluation tools and bridging across animal and human studies.5 After this initiative was announced, we started to see a true boom in pharmacometric methods. Modeling and simulation was used to address developmental challenges, such as highly variable PK, uncertainty in dose selection, and long approval times. For example, when tacrolimus was studied for its potential therapeutic benefit in ulcerative colitis, its highly variable PK and high trough concentrations in Phase II trials posed a major hurdle to development.6,7 By using logistic analyses of the PKPD relationship, the Sponsor demonstrated how trough concentrations were an adequate predictor of response and dose escalation simulations could be performed. This ultimately allowed the Sponsor to justify a Phase III dose in an otherwise unpredictable scenario. Similarly, during this time random-effects models started being implemented to demonstrate the predictability of the exposure-response relationship, such as with gabapentin.7,8 These models allowed for the gabapentin-pain score relationship to be adequate described, avoiding the need for replicate trials that would increase the duration to approval. A comprehensive overview of 198 other submissions during this time period has previously been published.9 By doing so, Lee et al. demonstrate the dramatic increase in reviews with pharmacometric analyses and their impact on both approval and labeling.

In addition to its benefit to industry, pharmacometric analyses were accredited for major policy changes. Pharmacometric methods helped identify pivotal bioequivalence criteria, compare recommendations included in FDA Guidances, and evaluate gold-standard analysis methods against alternatives.10 This new reliance by regulators was then further demonstrated in 2007 when the Division of Pharmacometrics was founded under the Center for Drug Evaluation and Research of the FDA. The expansion by the Agency to include this division was ultimately motivated by this growing number of pharmacometric analyses in submissions.

The final major landmark during this phase came in 2008 when the very first American Conference of Pharmacometrics (ACoP) was held.7 The purpose of this meeting was to recognize the need for an established community of pharmacometricians. The opening session was presented by leaders from 4 companies (Bristol-Myers Squibb, Eli Lilly, Novartis, and Pfizer) in which they discussed how model-based methods could be used in drug development. 7 They focused on how modeling and simulation can provide supporting evidence for key decisions, touching both on prior successes and failures. This was an important moment in history because it showed how essential pharmacometric methods had become for many different stakeholders.

### *The Final Phase: Expansion (2010 – Present)*

The observed growth during this final phase revolves around the expansion of pharmacometric capabilities, support, and infrastructure. In 2011 the American Society of Pharmacometrics (ASoP) was founded to promote and advance the field, later becoming the International Society of Pharmacometrics (ISoP) to reflect its multi-national network.11 There was this monumental interest and desire to further the discipline, as signified by the 600 members who joined in the first 6-months of its existence. Today, ISoP has over 1000 members from approximately 30 different countries.12 This organization serves as a place where pharmacometricians can learn, form partnerships, and advocate for the discipline. Its creation and continued growth during this period is a direct reflection of the growing need for well-trained pharmacometricians.

The expansion of pharmacometrics for other stakeholders, including regulatory agencies, has followed a similar trend. One major contribution was the FDA’s Model-informed drug development (MIDD) Paired Meeting Pilot program.13 The purpose of this pilot was to promote the use of exposure-based, biological, and statistical models during the development and review process. The MIDD Meeting Program information page states that, “MIDD approaches can improve clinical trial efficiency, increase the probability of regulatory success, and optimize drug dosing/therapeutic individualization in the absence of dedicated trials”. 13 The motivations and applications of this program truly highlight how we have now expanded pharmacometric applications from just improving clinical trials to supplementing them all together. This proved to be overtly successful, and as a result it has now transition into a permanent program.

Not only has the pharmacometric infrastructure expanded, but so has its utility. Prior to this point we had limited ability to address more complicated issues, such as with special populations and rare diseases. New and revived techniques, including quantitative systems pharmacology (QSP), physiologically-based PK (PBPK) modeling, model-based meta-analysis (MBMA), Bayesian statistics, and machine learning (ML), have each been explored to address these challenges. For example, Bayesian borrowing has supplemented statistical evidence in the case of pediatric rare disease trials where sample size is highly limited.14 PBPK has been widely used to assess drug-drug interaction potential based on both in vitro and in vivo observations.15 QSP has been assessed for its ability to better understand conditions related to medical countermeasures and predict the pharmacological response of medications unable to be tested in humans.16 Most all of these approaches have been leveraged to support dosing recommendations in the case of underserved populations. There is an abundance of new techniques such as these, each revealing the exponential growth of pharmacometrics over the last 10 years.

## Future Direction

Throughout its 60-year history, scientists have found new ways for pharmacometric methods to facilitate and expedite development; however, we have not yet fully harnessed its ability to disrupt the process as we know it. There are two major issues that we face today. The first involves the current structure and end-goal of most development efforts. The focus of drug development up until this point has been at a population level, with treatments being developed for the average patient. This poses a problem for clinicians when treating in the real-world, and often the burden of personalized medicine falls on them. The second issue is the under-utilization of real-world data. There has been a lot of excitement about real-world data, but its application and methodology of use has been unclear. We believe each of these issues should and will become the major focus of future efforts.

### *Precision Medicine*

Precision medicine has previously been described as, “an innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles”.17 This could be considered advanced gene therapies, dose optimization based on patient-related variables, or simply customized monitoring plans. We have made great strides in the approval of targeted therapies for specific genetic predispositions, but this is only one part of what precision medicine encompasses. Looking from drug discovery to market approval, we are primarily working in a retroactive space. The concept of precision medicine has largely defaulted to the clinical, post-approval setting. It is up to the clinician’s discretion to select and tailor treatments based on available data, prior knowledge, and trial and error. The consequence of this includes increased cost, potentially avoidable adverse effects, suboptimal efficacy of treatment, and increased time to therapeutic success. A notorious example is the treatment selection process within psychiatry, such as for major depressive disorder. It often takes several different drug trials before landing on the best option for a patient, and each antidepressant can take 6 – 12 weeks for full therapeutic benefit to take effect. There is limited information on why certain antidepressants work for some and not others, leaving patients feeling frustrated and distrustful. A comprehensive view on this dilemma and how precision medicine could rectify these treatment hurdles has previously been published.18 Incorporating precision medicine during development can help mitigate these challenges and improve patient care.

Prioritizing precision medicine during drug development has clear therapeutic benefits, but what would this entail? Clinical Decision Support (CDS) systems have shown great promise when individualizing patient care. These devices offer clinicians support when making key decisions about treatment and monitoring plans. There are many different types of CDS systems, and a detailed overview of their functionality has been compiled recently.19 Currently, CDS systems are developed by a third-party post-approval. They are then accessed by clinicians as either an extension to commercial electronic health record (EHR) software or as a web- or mobile-based application.20 If the creation of CDS systems was streamlined during development, rather than retroactively from outside parties, clinicians and patients would reap the benefit of this technology quickly and consistently. Simply put, the potential exists to one day operate in a space where most drug approvals are accompanied by the development of these devices.

To go from idea to reality requires advanced pharmacometric methodologies, such as Bayesian approaches. Like CDS systems, Bayesian statistics is in no way a new concept, but its application to drug development is still maturing. These approaches are notorious for their ability to leverage prior information and answer critical go/no-go decisions, ultimately saving time, money, and resources. Currently, we use Bayesian methods to predict trial outcomes, determine the probability of achieving efficacy or safety endpoints, and even infer the likelihood of market success. What we should now consider is how Bayesian methods can be harnessed for the benefit of precision medicine. Bayesian predictive frameworks to personalize treatments have already been proposed.21 This field is ever evolving, and it wouldn’t be far-fetched to say that methodologies such as these have the capability to revolution drug development as we know it.

### *Real-World Data*

Real-world data (RWD) includes patient information, such as outcomes, demographics, and laboratory findings, that are collected in a real-world setting. This is distinctly different from real-world evidence (RWE), which is the clinical evidence of treatment efficacy or safety that is derived from RWD.22 This data is collected from sources like electronic health records, insurance claims, and even wearable devices, and therefore emulates the true heterogenous nature of our patient population. RWD has the potential to provide information that clinical trials are not designed to generate. Pharmacometric analyses of RWD can be used to optimize dosing, personalize treatments and monitoring plans, and even provide supporting evidence for drug repurposing. Many feel that RWD will one day bridge the gap between drug development and clinical practice, however this has not yet been the case.

One FDA impact story discusses how clinical trial design can even be positively impacted by RWD.23 The authors discuss how RWD is particularly of interest to support the evaluation of drugs intended to treat rare and life-threatening diseases. In both of these instances it is either challenging or unethical to conduct gold-standard randomized controlled trials. As a result, scientists have been actively conducting research to design innovative trials that incorporate such RWD. The impact story further discusses the potential applications of RWD to drug development, including assembling an external control arm, dose finding in smaller patient populations, and addressing the issue of high placebo response rates. 23 These concepts are further reflected in a recent FDA guidance on the use of RWD to support regulatory decision making.24 We believe that with further investigation and validation there will be a major shift in the design of clinical trials for such scenarios.

As one can imagine, there is an abundance of RWD. The sheer volume and complexity of its compilation has been an undeniable barrier. Only in recent years have we had the ability to access, store, and analyze what is referred to as “big data”, but there are still improvements to be made. We need a way to systematically store and handle such a mass amount of information. For this reason, we have witnessed the scaling of computational infrastructures and an increase in tools equipped to analyze big data, such as machine learning (ML) methods.

One major application of ML is in the context of drug repurposing. Real world data can be effectively leveraged to support both the addition of labeling in under-studied populations and the addition of new indications all together. We have previously proposed one strategic goal related to this effort, stating that by 2030 renewed pediatric labeling of 15 drugs without patent and/or exclusivity should be achieved.25 ML methods are likely necessary to analyze RWD efficiently, otherwise goals such as these may not ever come to fruition. Although there have been many studies regarding the use of RWD for drug repurposing, ML techniques have not been utilized to their full potential. One article that reviewed the current use of RWD and ML methods found only 16 prior assessments for drug repurposing in the last 20 years.26 It is our hope that the number of these cases increases as the infrastructure to support ML methods and RWD expands.

## Conclusion

Pharmacometrics has come a long way since its inception. The field started as an applied science without an established role in drug development. Now, pharmacometric analyses are included in nearly every drug program. History often repeats itself, and that is no exception here. Pharmacometricians will continue to grow in both numbers and capabilities, and in another 60 years it may very well transform drug development as we know it.

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## *Conflict of Interest Statement*

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