Predictive Modeling: The New Imperative for Pharmaceutical Innovation in a Capital-Constrained Era

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The economic environment for biotech and pharma drug developers today is challenging, marked by tightening financial pressures and rapidly evolving regulatory landscapes that are redefining development strategies. Biotech IPO activity has plummeted over 75% from its 2021 peak, with only 20 global offerings completed in 2024 compared to 104 three years earlier1. The Nasdaq XBI index declined by over 60% from its February 2021 peak, signaling broad valuation compression and investor risk aversion 2. Many early and mid-stage companies are resorting to bridge or extension financings at flat or reduced valuations to extend their runways.

This capital scarcity is forcing sponsors into 12 to 18-month funding cycles rather than the 30-36-month runways of previous years, with investors demanding value-creating milestones, IND filings, clinical readouts, strategic partnerships, before supporting follow-on investment. The escalating cost of capital is driving companies to prioritize cash conservation and operational efficiency, resulting in widespread pipeline rationalizations and workforce reductions across the sector3. Capital productivity pressures extend to venture capital funding, where investors are notably more selective. There is a prevailing expectation that VC-backed ventures demonstrate compelling regulatory strategies, clear manufacturability, and commercial viability far earlier in their lifecycle 4. Simultaneously, Contract Development and Manufacturing Organization (CDMO) costs are rising, while access to high-quality manufacturing slots is increasingly competitive. This has forced innovators to fine-tune development plans earlier under stricter resource constraints.

The Perfect Storm: Financial Pressure Meets Regulatory Opportunity

Yet this financial pressure coincides with a remarkable regulatory shift. The FDA's 2025 draft guidance outlines a structured, risk-based framework for AI and in-silico evidence in regulatory submissions 5, explicitly encouraging early engagement with regulators, robust validation plans, and transparent lifecycle management of predictive models. The FDA's Model-Informed Drug Development (MIDD) Pilot Program has engaged over 80 industry sponsors, creating clear pathways for modeling submissions through its seven-step credibility framework.

The EMA's 2022 physiologically based pharmacokinetic (PBPK) guidance formally supports modeling to waive clinical studies, while ICH guidelines increasingly endorse model-based approaches for pediatric extrapolation and lifecycle management.

This confluence of maturing regulatory frameworks and intensifying capital constraints is creating a “perfect storm” that compels drug sponsors toward smarter, more efficient development pathways. Regulators’ increasing openness and, in some cases, encouragement for sponsors to use digital evidence in place of costly, time-consuming experiments is now a powerful catalyst. In this environment, advanced in silico modeling and predictive analytics are rapidly transitioning from optional tools to essential capabilities for competitive survival and scientific progress. By leveraging these technologies, drug developers can conserve capital, reduce program risk, and accelerate achievement of the technical and regulatory milestones needed for sustained investor support and value creation. This convergence of scientific innovation and regulatory openness marks a turning point in how new therapies can be developed, scaled, and approved worldwide.

The Economic Imperative: Quantifying the Value Proposition

Traditional pharmaceutical development follows a costly, sequential experimental approach where each phase builds incrementally on the previous one. Process development alone can consume 18-24 months and $5-15 million or more, before reaching manufacturing readiness, with stability studies adding another 12-18 months of real-time data generation.

In-silico modeling fundamentally rebalances this equation. By shifting from **experimental-first** to **predictive-first** approaches, sponsors can achieve dramatic reductions in development burden across the entire lifecycle. In CMC and formulation phases, digital twins, process simulation, and kinetic modeling can reduce experimental effort by 60-70%. Early molecule design benefits from AI/ML platforms that eliminate trial-and-error work, delivering 50% or more time and cost reductions. Even preclinical and clinical phases see 30-40% efficiency gains through dose optimization, toxicity prediction, and bridging strategies, while tech transfer and manufacturing achieve 50% + reductions through mechanistic simulations and real-time release strategies.

These improvements concentrate experimentation where it adds maximum value while reducing effort where

models provide faster, more cost-effective insights. Most critically, this enables sponsors to "fail faster" and pivot earlier, unlocking significant capital efficiency in today's constrained funding environment.

Regulatory Framework: From Acceptance to Encouragement

Global regulatory authorities have evolved from cautious observers to active promoters of predictive modeling. The FDA's MIDD framework provides a clear pathway for model-based submissions, emphasizing context of use definition, systematic validation, and transparent documentation. Model credibility, defined as demonstrated trustworthiness for intended regulatory applications, is now assessed through established protocols rather than ad hoc review.

The EMA and FDA co-lead joint MIDD initiatives are fostering cross-agency alignment, while ICH guidelines increasingly integrate model-based approaches across the product lifecycle. This regulatory evolution reflects a fundamental recognition: when properly validated and scientifically justified, predictive models are no longer experimental, they are regulatory enablers which derisk evaluation by regulators.

Success requires robust model credibility frameworks addressing data governance, validation protocols, and uncertainty quantification. First-principle and mechanistic modeling offer particular advantages by embedding established scientific relationships directly into model structures, providing interpretable, causally linked predictions that extend beyond available training data. These approaches align with ICH Q8(R2) and FDA continuous manufacturing guidance while supporting regulatory submissions with higher scientific justification.

This maturation has been fueled by three converging trends: the exponential growth in high-quality pharmaceutical data, the refinement of mechanistic and hybrid models, and regulatory willingness to accept model-based justifications when built on scientifically sound and validated frameworks.

AI and machine learning models are now routinely used for target identification, de novo molecule generation, high-throughput screening, formulation optimization, and synthetic route scouting. More critically, these models increasingly simulate complex biological and manufacturing systems supporting or replacing wet-lab experiments in areas where testing is expensive, slow, or difficult to perform. In process development, digital twins can simulate manufacturing behavior across scales, reducing the need for multiple process scale-up runs and increasing confidence in the final design and control space. For stability studies, in-silico models incorporating kinetic and environmental variables can forecast long-term product behavior, helping to justify accelerated stability strategies and providing drug sponsors and regulators with a de-risked framework that can defer the need for extensive real time data collection.

In synthetic route design, i.e., the process of identifying optimal pathways from available starting materials to target molecules, AI tools can evaluate feasible approaches and prioritize them based on yield, cost, impurity profile, and environmental impact well before laboratory work begins.

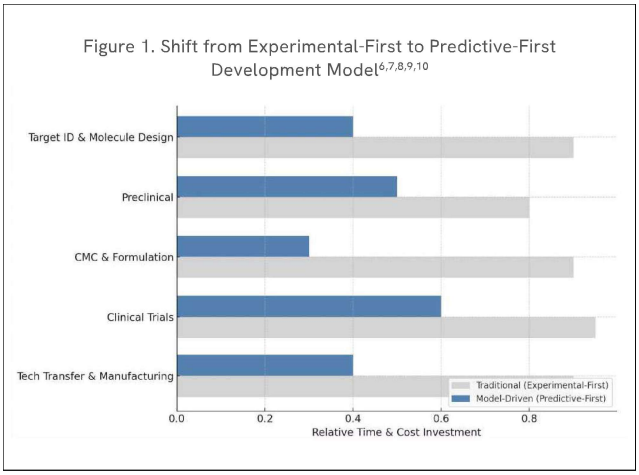
These tools no longer operate as black boxes. There is growing emphasis on explainability, validation, and contextual alignment, particularly in regulatory settings. Hybrid models that combine first-principle understanding with AI-driven pattern recognition enable higher confidence in predictive output, making it easier for sponsors to defend modeling results in regulatory submissions.

The FDA’s seven-step framework for modeling credibility reflects this shift. It encourages companies to define model scope and risk, verify and validate with relevant experimental data, and transparently document assumptions and uncertainty. As a result, predictive models are increasingly being accepted in lieu of experiments where real-world testing is not feasible or would introduce unnecessary delay. At a minimum the additional data from in-silico modeling affords regulators and drug sponsors with greater assurance that the data in a submission is correct and, most importantly, defensable.

This shift is not just theoretical. In several recent NDA and ANDA approvals, predictive models have been key components of control strategy justification, comparability assessments (e.g., batch vs. continuous manufacturing), and stability waivers often shaving months off development timelines and reducing development costs by orders of magnitude.

Figure 1 compares traditional experimental-first development with a predictive-first principles approach. The model-driven workflow shows reduced time and cost investment in preclinical, formulation, and CMC phases; modeling is used to direct experimentation rather than follow it:

Figure 1. Shift from Experimental-First to Predictive-First Development Model[6,7,8,9,10]



Note: Values shown reflect relative time and cost burden in each development phase. Predictive-first estimates are based on industry case studies, FDA pilot data, and published reductions in experimental workload due to in-silico and AI-driven approaches

In the CMC and formulation stage, predictive modeling tools such as digital twins, process simulation, and kinetic stability models can reduce experimental effort by up to 60–70%, resulting in a relative burden of around 0.3. Similarly, in early molecule design, AI/ML platforms can eliminate large swaths of trial-and-error work, enabling up to a 50% reduction in time and cost. Preclinical and clinical phases show more modest but still significant reductions—typically 30–40%, where modeling is used from everything for patient recruiting to optimizing dose selection, or to support clinical bridging strategies. The tech transfer and manufacturing phase also benefits from predictive modeling through the use of mechanistic simulations and real-time release strategies, allowing reductions of around 50%. Predictive modeling basically rebalances the development lifecycle, concentrating experimentation where it adds the most value and reducing effort where models can offer faster, more cost-effective insight.

Redefining Pharmaceutical Innovation and Manufacturing

Predictive modeling is transforming multiple critical domains, streamlining drug development and manufacturing to enable faster, more cost-effective, and higher-quality outcomes. This revolution spans from the earliest stages of research and development to advanced manufacturing, generics formulation, and chemistry, manufacturing, and controls (CMC) optimization. As regulatory agencies, investors, and manufacturers align around these capabilities, predictive modeling is shifting from a promising tool to a regulatory and commercial imperative and a foundational strategy for building competitive, capital-efficient pipelines.

R&D and Molecule Design

At the forefront of innovation, predictive modeling, powered by artificial intelligence and machine learning, is reshaping how new drug candidates are discovered and validated. By simulating molecular interactions and biological responses in silico, researchers can identify non-viable candidates early. The hope is as the data supporting these relationships continues to build, it will substantially reduce costly failures during later stages. AI algorithms attempt to integrate complex biological data to validate therapeutic targets more accurately and prioritize those with the highest potential impact.

Some leading companies have reported reducing discovery phases to under a year, an impressive leap forward facilitated by digital twin simulations that even model disease progression to optimize clinical trial design. AI is also enabling adaptive clinical trial planning by simulating enrollment patterns, dropout rates, and endpoint variability, allowing sponsors to design more efficient, better-powered studies. The rise of hybrid modeling, blending mechanistic understanding with machine learning is adding interpretability and robustness, further increasing regulatory confidence in these approaches.

While the opportunity here is to improve upon our industry's woeful track record of only one in nine products actually making to market. For drug sponsors and investors, the biggest opportunity for time- and capital efficiency lies in applying modeling as you move down the drug development lifecycle.

Foundational Elements for Successful In-Silico Modeling in Pharmaceutical Development

The adoption of in-silico modeling across pharmaceutical R&D and manufacturing marks a fundamental shift in the approach to drug development. The biggest barrier often lies in the fact that the necessary expertise, systems, and organizational capabilities do not typically reside within traditional drug development frameworks. A deliberate strategy is required to acquire, build, or integrate the expertise and digital infrastructure needed to fully leverage modeling and predictive analytics, one that requires disciplined foundations to ensure scientific integrity, regulatory acceptance, and demonstrable business impact, built on a capable framework.

Data Integrity, Quality, Sufficiency

Viewing data as a product rather than a byproduct of drug development is at the core of preparing an organization to leverage modeling. Data should be managed, curated, and enhanced continuously to deliver ongoing value, much like a digital product, rather than viewed as an artifact of experimental and operational activities across siloed and fragmented systems. Robust data governance is essential, and should include validation, traceability, version control, and lifecycle oversight. The complexity and organizational inertia associated with implementing these frameworks within an organization is significant. Many pharmaceutical and biotech companies face the challenges of fragmented legacy systems, talent shortages, or the need to shift workflows and culture to support rigorous, end-to-end data management.

To overcome these barriers, some drug sponsors partner with or outsource to a specialized solution provider. Such providers offer turnkey expertise, infrastructure, and validated processes, accelerating the adoption of advanced modeling without requiring the sponsor company to immediately take on the full organizational transformation or development of in-house competency. Outsourcing to a qualified provider can serve as a bridge or even a long-term strategy for leveraging in-silico modeling, reducing the burden of acquiring, developing, and maintaining sophisticated data governance and analytics in an environment where time, capital, and resources are constrained.

Model Credibility and Overfitting Mitigation

There has been a lot written about AI model error due to overfitting and "hallucinations." The FDA has defined model credibility as the demonstrated trustworthiness of a model's outputs, substantiated by systematic evidence, for its intended regulatory application. Model credibility is always assessed in relation to its "context of use" (COU), meaning the specific role and decision it is intended to support, such as in nonclinical, clinical, post-marketing, or manufacturing applications. Robust model credibility and the mitigation of overfitting are at the core of successful in-silico predictive modeling. As advanced analytics and in-silico tools become increasingly central to drug discovery, process optimization, and regulatory submission, organizations must anchor these efforts in a foundation of technical, procedural, and cross-disciplinary best practices.

The journey begins with rigorous data governance and quality control. Ensuring that modeling efforts draw upon high-quality, diverse, and representative datasets is non-negotiable. This means curating data from across all relevant chemical, biological, and process domains and putting in place protocols for validation, traceability, and version control, so the provenance of every data point can be tracked and scrutinized. Proper data splitting into training, validation, and test sets further protects against data leakage and ensures that performance metrics reflect true generalizability, not just fit to historical patterns. The good news is regulators have shifted from caution to collaboration. FDA and EMA guidelines now support model submission, provided models are transparent, validated, and risk-aligned. Early engagement, clearly defined COUs, and documentation that addresses overfitting, uncertainty, and data sufficiency are essential for streamlined review and innovative pathways.

What Modeling Approach is Best?

As regulatory expectations evolve toward model transparency, validation, and risk alignment, organizations must also consider the type of modeling framework best suited to their needs. While empirical and AI-driven models draw strength from large, diverse datasets, they are hampered by lack of data and the need for proactive data hygiene and governance. Many questions in drug development require deeper mechanistic understanding, rooted in physical laws, biochemical pathways, and systems biology.

This is where first-principle and mechanistic modeling offer clear advantages. By embedding established scientific relationships, such as mass transfer, kinetics, and molecular interactions directly into the model structure, mechanistic approaches provide interpretable, causally linked predictions that extend beyond the range of available training data. Unlike purely empirical models, they allow simulation of system behavior under novel scenarios, supporting process scale-up, optimization, and regulatory submissions with a higher degree of confidence and scientific justification. Mechanistic models, grounded in physical laws, offer unmatched interpretability and regulatory defensibility. First-principles approaches align with ICH Q8(R2) and FDA guidance on continuous manufacturing and are increasingly complemented by AI-driven hybrid models to reduce experimental burden while maintaining predictive power (Zhang et al., 2024)[10].

Real-World Impact: Three Transformative Case Studies

To better understand the transformative potential of in-silico modeling, we turn to three distinct case studies where in-silico modeling approaches have been successfully deployed as alternatives to conventional experimental methods. Each case highlights measurable time and cost savings achieved by leveraging virtual simulations in key stages of drug development,from API route scouting to process optimization and stability prediction.

Case Study 1: AI-Driven API Route Scouting

The process of selecting and optimizing synthetic routes for active pharmaceutical ingredients (APIs) is a critical, yet resource-intensive phase in drug development. Traditionally, route scouting relies on sequential, trial-and-error experimentation in the laboratory, a method that is time-consuming, costly, and often reactive in nature.

CHALLENGE:

A leading pharmaceutical developer faced bringing a generic stomach acid reducer to market under exceptional timeline pressure. Traditional route selection and process development for this complex multi-step chemistry typically requires 12-18 months and substantial resource investment.

SOLUTION:

The team implemented comprehensive in-silico modeling as their primary route scouting strategy, deploying CFD-based equipment characterization for reactor sizes from 1,000-5,000L alongside virtual testing of multiphase processes and material addition sequences. Simulation-driven optimization targeted yield, cycle time, and cost parameters while evaluating atom economy, mass balance, and environmental impact to eliminate unviable routes before experimental commitment.

RESULTS:

The transformation delivered timeline compression from concept to manufacturing in just six months, 50-66% faster than conventional approaches, while eliminating high-cost catalytic chemistries and specialized materials through virtual screening. Process simulations identified and resolved scale-up issues before pilot investment, enabling higher yields per batch with minimized rework and consistent product quality.

This transformation shifted route scouting from sequential, resource-heavy experimentation to parallelized, data-driven decision-making, enabling market entry within competitive windows even for complex, low-margin molecules.

These computational approaches integrate modeling of scale effects and unit operations, providing early visibility into how chosen routes will perform through scale-up and manufacturing. A key advantage is the enhanced safety profiling that in-silico models afford by flagging unsafe or unstable reagents upfront, thereby reducing the likelihood of hazardous scenarios and streamlining regulatory compliance. Sustainability is baked into these models, with the capability to estimate Process Mass Intensity (PMI), waste generation, energy usage, and toxicity, empowering greener process development aligned with modern environmental and corporate responsibility goals. In today's capital-constrained, competitive environment, this type of modeling approach can determine whether a program meets its launch window or misses the market entirely.

Case Study 2: Accelerated Stability Modeling

In pharmaceutical development, real-time stability studies are one of the most time-consuming aspects of drug development for establishing expiration dating and assuring product quality throughout storage for regulators and drug sponsors. While regulators want to see real-time data, ICH has always allowed predictive stability modeling as part of the expiration dating argument.

CHALLENGE:

A late-stage developer needed to extend frozen product shelf-life from 18 to 24 months but had only nine months of real-time stability data. Traditional approaches would require waiting for additional real-time data, delaying market access.

SOLUTION:

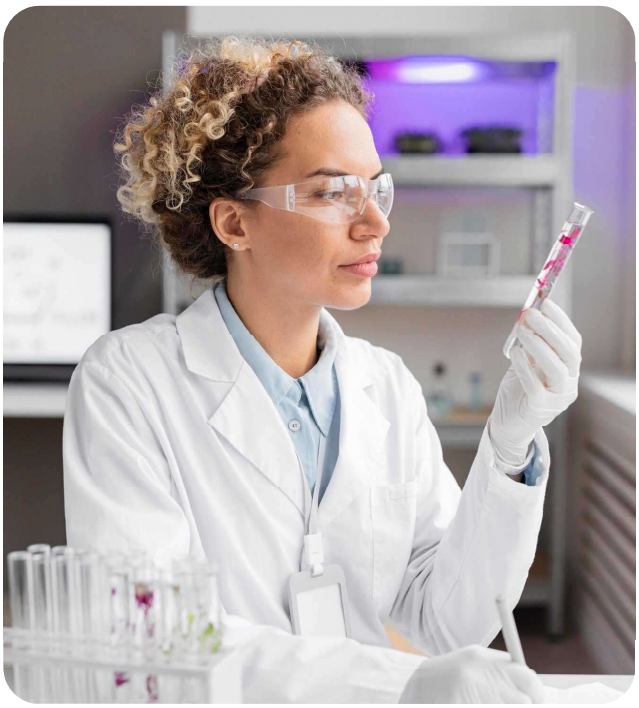
Accelerated Predictive Stability (APS) modeling was deployed using targeted studies under aggressive conditions, 25-50°C at 35-80% relative humidity for 14 days, combined with mechanistic degradation pathway modeling for key impurities and ICH-aligned validation protocols demonstrating model-data correlation.

RESULTS:

Both target markets accepted modeled stability packages without queries, enabling the desired shelf-life extension without waiting for real-time data. This approach reduced experimental burden by 70% compared to traditional stability programs while unlocking market opportunities six-to-nine months ahead of conventional timelines.

Regulators are increasingly open to incorporating well-validated in-silico stability models to complement conventional ICH testing and accelerated testing, enabling sponsors to reduce dependence on extended real-time studies, accelerate decision-making, and mitigate risk all without compromising product quality or patient safety. This approach is transforming stability assessment from a bottleneck into a strategic advantage, compressing development timelines while maintaining full compliance without adding regulatory risk.

Both target markets accepted the modeled stability package without inquiry, enabling the sponsor to secure the desired shelf-life extension without waiting for additional real-time data.



Case Study 3: Biologics Process Optimization

In biopharmaceutical manufacturing, process optimization has traditionally relied on iterative, experiment-driven development. In-silico modeling enables developers to virtually simulate process parameters, equipment configurations, and scale-up conditions before committing materials, resources or facility time.

CHALLENGE:

A late-stage biologics program faced downstream purification bottlenecks limiting throughput and increasing cost of goods. Traditional optimization would require extensive scale-down experimentation over 4-6 months.

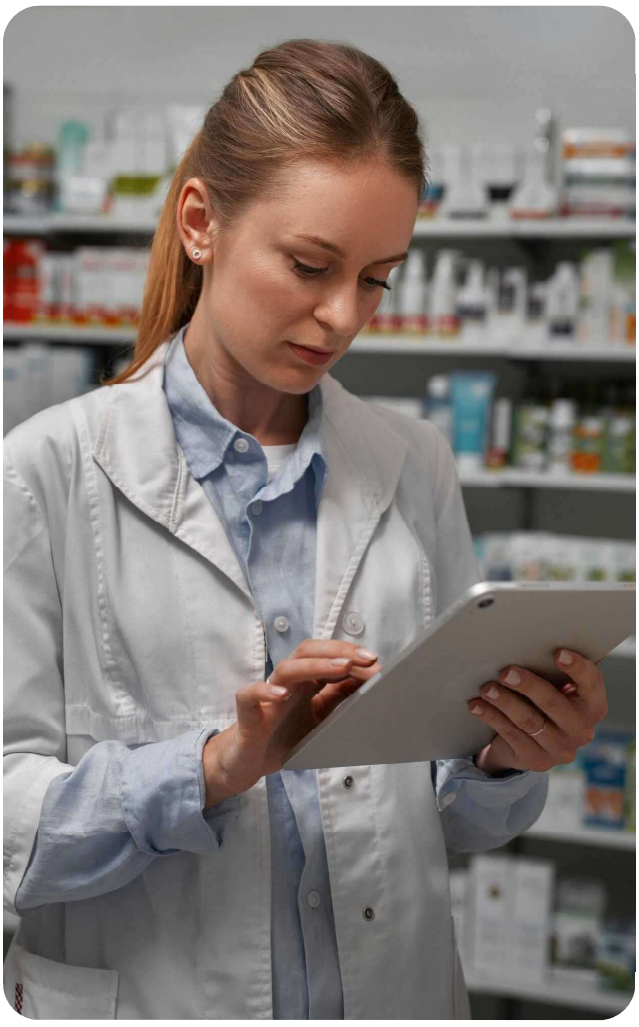
SOLUTION:

Process modeling based upon first principles calibrated with existing data-enabled parallel evaluation of multiple operating modes and resin configurations, virtual optimization of resin utilization, cycle time, and buffer consumption, and predictive assessment of scale-up performance and quality maintenance.

RESULTS:

Optimization was completed in three weeks versus the traditional four to six months, delivering a 25% increase in batch yields along with a 30% reduction in consumable costs. The science-based rationale aligned with FDA expectations for process control while enhanced equipment utilization and lower manufacturing costs created immediate commercial impact.

This process delivered higher batch yields, improved equipment utilization, and lowered consumable costs. More importantly, the in-silico work also provided a regulatory-ready rationale for the changes, aligning with FDA expectations for science and risk-based process control.



Implementation Framework: Building Predictive Capabilities

Successful deployment of in-silico modeling requires deliberate organizational strategy addressing four critical foundations. Organizations must first shift from viewing data as an experimental byproduct to treating it as a strategic asset, implementing robust validation, traceability, version control, and lifecycle oversight. For this, many sponsors find value in partnering with specialized providers to access turnkey expertise and validated platforms while building internal capabilities over time.

Model credibility and validation represent the second pillar, where the FDA's context-of-use framework demands systematic evidence demonstrating model trustworthiness for intended applications. Proper data splitting, cross-validation, and uncertainty quantification protect against overfitting while ensuring regulatory defensibility.

Model approach and structure selection forms the third foundation, where first principles and mechanistic approaches offer advantages in interpretability and regulatory acceptance by embedding established scientific relationships without being constrained by the quantity of data. Hybrid models combining mechanistic understanding with AI-driven pattern recognition provide optimal balance of predictive power and scientific justification.

Finally, organizational change management requires workflow modification, talent development, and cultural adaptation toward data-driven decision-making. Early engagement with regulators, clearly defined contexts of use, and transparent documentation addressing uncertainty are essential for streamlined review.

Predictive modeling and AI-driven analytics are fundamentally reshaping how pharmaceutical science and manufacturing operate. These tools are no longer just about speeding up timelines; they are about reducing failure risk, improving regulatory clarity, and maximizing the impact of every dollar invested.

As regulatory agencies, investors, and manufacturers coalesce around data-driven approaches, predictive modeling is shifting from competitive differentiator to baseline expectation. Companies and their investors that embrace this transformation will not only accelerate product development but also de-risk their pipelines, improve supply resilience, and increase the value of their assets in the eyes of regulators and investors alike. The future of pharmaceutical innovation will not just be faster it will be smarter.

Questions & Answers

Questions and Answers section with De Facto [DF] Team and Bikash Chatterjee [BC] to try and predict short, medium and longer term implications

De Facto team: Adoption & Standardization: how much of the industry do you predict will have transitioned to a predictive-first development model looking 5-years ahead, and what will be the tipping point that drives widespread adoption?

BC: *"To date we have been involved in more than 80 in-silico drug development applications with more than 25 different use cases, with large and small pharma/biotech. Within the next five years, I expect 15-20% of the industry to have meaningfully shifted to a predictive-first development model, with the deepest adoption in large pharma and well-capitalized biotechs. Smaller and mid-size firms will likely leverage "outsourced modeling" through CRO/CDMO or consulting partners rather than building full internal capabilities. The tipping point will come when regulatory normalization (FDA/EMA pathways like ETT and the M&S roadmap) converges with hard ROI, and a few headline approvals show models replacing bench work, the market will flip, triggering cascade adoption."*

De Facto team follow-up: What signals should we watch for that this shift is accelerating?

BC: *"I would watch for a convergence of language from major Health Authorities around the use of modeling as core component of product development."*

De Facto team: First Movers & Competitive Advantage: who are the early adopters of predictive modelling today, and do you expect they will establish a competitive advantage over the next 3–5 years—or will the rest of the industry catch up quickly?

BC: *"Large and mid-size Pharma and Biotech and large CDMOs that are productizing pieces of modeling are getting some attention. First adopter advantage compounds across assets and tech transfers. However, catch-up will accelerate as vendors/consultancies/CDMOs productize modeling and regulators normalize targeted application."*

De Facto team: Regulatory Trajectory: Which development stages or use-cases will that happen in first?.. or how do foresee the regulatory sphere continue to evolve?

BC: *"In silico modeling adoption in drug development is expected to progress in a phased manner aligned with regulatory acceptance and technical maturity. CMC and model aided clinical trial design present the opportunity for significant time reduction and capital efficiency. The move away from small animal testing will push the industry to look at surrogates. QSAR is already part of many molecule selection processes with PBPK and ADME modeling already a part of many R&D programs. The earliest and fastest adoption occurs in CMC, where in silico tools simulate manufacturing processes, formulation, stability, and scale-up, significantly reducing capital and time requirements and facilitating regulatory approvals. In silico methods are already increasingly being used as part of clinical development through model-informed drug development approaches that optimize trial design, dosing regimens, and patient selection; these models include synthetic control arms and virtual patient cohorts which have already gained regulatory traction for reducing trial size and duration.*

"Overall, regulatory position within US and Europe has reached a state of maturity where industry knows what is expected of them. Over the next decade, in silico methods are anticipated to become a foundational pillar across drug development stages, enabling faster, less costly, and ethically improved development processes while progressively replacing some human or animal studies."

De Facto team: CRO & CDMO Implications: what does the rise of predictive modelling mean for CROs and CDMOs over the next 2–5 years? Will their business models need to shift? Will this affect the non-clinical CROs most and might it help see early stage work return from China and India? [who – despite the domestic drug development rhetoric – have done very well in terms of non-clinical research services in the last 2-years] And similarly what you advise them to be doing in 2026 to prepare for this change – and/or due to see any players moving early

BC: *"Larger CDMOs are moving to productize modeling, selling model development and digital-twin deliverables that narrow wet-lab loops, speed tech transfer, and de-risk scale-up. Expect bundled pricing (development + twin), subscriptions for twin upkeep, and "model credibility" packages aligned to Q14/USP <1220>. However, model development works against the capital-intensive business of experimentation and tech transfer of most CDMOs so adoption will be slow in this sector. This is their bread and butter.*

"Traction in New Approach Methodologies (NAMs) + in-silico (PBPK/QSP, organ-on-chip, AI safety screens) will trim certain animal studies and pull modeling into tox/ADME and BE questions. Large non-clinical players are expanding NAM portfolios, and regulators' push to reduce animal testing is accelerating demand but there is a need for clarity as to what constitutes an acceptable surrogate to these studies. When the standard for tox assessment, i.e. small animal models, is universally recognized as poor, how does a better solution compete? It requires regulators to shift their paradigm for evaluation."

De Facto team: Capital & Investment Dynamics: if VC/PE and IPOs mean capital scarcity continues as expected, do you predict predictive modelling could become a gating criterion for forward looking VC or investors in the next year?

BC: *"Yes among forward-looking VC/PE, predictive-first plans will become a de-facto gating criterion within the next 12-18 months, especially at Seed/Series A and for CMC-intensive assets. Capital is tight, IPOs remain below long-term norms, and many biotech's have significant cash constraints, so investors are prioritizing capital-efficiency and faster time-to-value as a gating criteria for funding, exactly what credible modeling delivers."*

De Facto team: How could this really shift the investment market… maybe even restart it.. as better models will ultimately mean greater numbers of winners and potentially faster wins (development)?

BC: *"If underwriting standards migrate to include a "predictive-first" plan, more programs must hit earlier with cheaper inflection points (e.g., IND/BE/CMC readiness), improving portfolio hit-rates and opening the exit window via selective IPOs/M&A sooner, even in a scarce-capital regime. Expect more tranched rounds tied to modeled milestones (MIDD alignment achieved, model-credibility package completed, twin-validated scale-up) rather than time-based burn."*

De Facto team: Technology Evolution: what is your prediction for hybrid models and digital twins in 202627 - will they remain development tools, or will they start influencing commercial manufacturing and real-time release strategies?

DF Note: if this timeframe is too short – how quickly do you see this taking hold with wider adoption

BC: *"By 2026–27, hybrid models and digital twins will start to influence commercial manufacturing, not just development. We are already seeing it being integrated as part of downstream biologic process development. The enablers are already in place: ICH Q13 has standardized CM lifecycle expectations, EMA's Annex 17 and RTRT guideline give a clear legal path, and FDA's Emerging Technology Program now explicitly lists a "model-based control strategy for continuous manufacturing."*

De Facto team: Long-Term Vision: looking ahead to 2030 [and beyond], how do you see predictive modelling reshaping drug development timelines, costs, and risk? Will it fundamentally alter the success rate of drug programs?... and by how much in terms of a percentage or even dollar returns.

DF Note: we ask all of this, as with capital so constrained, many analysts think we need a new 'trigger' to start the metaphorical gold rush in biotech again

BC: *"By 2030, predictive-first programs should deliver significant end-to-end R&D cost reduction, and meaningfully shorter timelines (≈9–18 months faster to key inflection points) for portfolios that integrate MIDD in clinic plus model-centric CMC (predictive stability + mechanistic/digital-twin scale-up).*

"While AI companies often command higher MOICs [Multiple on Invested Capital] due to rapid scaling and market enthusiasm, biotech investments offer valuable risk mitigation through clinical validation, durable intellectual property, and long runway for blockbuster success, making them an attractive complement or alternative for investors seeking balance in a risk-return portfolio."

De Facto team: Can you a statement/prediction something along the lines of this example?

BC: *"I expect – my best guess – is that by end-2026, ~20–30% of mid-to-large pharma programs and ~10–15% of VC-backed early programs will use predictive-first workflows for at least one major development decision; by end-2027 that rises to ~30–40% and ~15–20%, and by end-2028 ~40–50% and ~20–30%, respectively. As regulatory pathways and the vendor/CDMO ecosystem mature, adoption at some level should reach ~60–70% of large-pharma programs by 2030 (and ~35–45% of VC-backed early programs)."*

De Facto team: How will predictive modelling reshape the economics of drug development by 2028; could it make today's traditional experimental-first model economically obsolete?

BC: *"By 2028, predictive-first stacks will be the financial default for CMC and biopharmaceutics decisions reducing ~10–20% per-asset R&D cost and shaving off ~6–12 months to key gates (formulation/pack, IND/BE readiness, tech-transfer). Experimental-only won't be "obsolete," but it will be an economically uncompetitive outside niche. Regulators have already set the permission structure (FDA MIDD program; ICH Q13 for CM; ICH Q14 and USP <1220> for model lifecycle; EMA's PBPK guideline), and vendors/CDMOs are productizing twins now—so the ROI is becoming standard, not exceptional."*

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