IBM Global Business Services
Executive Report

Life Sciences and Consumer Products

IBM Institute for Business Value

Trusting the science that drives your business

A systematic approach to verify scientific claims

IBM Institute for Business Value

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By Chris Moore, Nathalie Conrad, Jörg Sprengel, Doug Dean and Fran Hancock

The time has come to verify that business decisions predicated on the conclusions of profoundly complex science are not putting excessive shareholder value at risk. Yearly, almost US$200 billion are spent on research and development (R&D) in science-driven sectors such as healthcare, life sciences, consumer products or chemicals.[1] Sixty percent of pharmaceutical R&D investments is spent on products that will never reach the market.[2] The past decade has seen a rising number of public health and environmental issues following incorrect scientific claims and a ten-fold increase in scientific paper retractions.[3] We believe that an independent, systematic and unbiased process for auditing scientific claims can help increase companies' confidence in scientific outcomes, reduce risks, pilot innovation and generate more value for consumers, the environment and businesses.

Introduction

Companies across sectors are feeling the pressures of a multifaceted, increasingly interconnected and highly unpredictable business environment.[4] Those that rely heavily on research and development (healthcare, life sciences, consumer products and environmental enterprises, for example) must also cope with ongoing advancements in scientific techniques, ever-increasing volumes of data and more intense regulatory scrutiny. Add to these factors the uncertainty inherent to scientific research – which has reduced the shareholder value of many organizations and left many to cope with high attrition rates, product failures, and litigation due to inaccurate claims. A case study of the pharmaceutical industry estimates that over 60 percent of industry R&D spending (approximately US$63 billion each year) is lost to unsuccessful product candidates.[5]

Not surprisingly, innovation has stalled.

Organizations must also face a structurally different environment. A new R&D model, dependent upon a network of collaboration, has emerged. Commercial processes, which traditionally focused on developing products, are now centered on producing innovative *solutions* that integrate products, services and expertise. The reliability of scientific claims has never been more crucial.

How much do you trust your science?

Traditional research practices are proving to be inadequate when it comes to impartially and systematically verifying the growing number and complexity of scientific claims.[6] Generally, the quality of scientific work is assessed by the researchers themselves and by their colleagues in the peer review process.[7] Within organizations, the R&D pipeline is often driven by people whose career advancement is bound to the success of their research. This can cause problems in several ways.

First, assuring **impartiality** is an issue, since current practices create a bias toward reputable scientists.[8] Moreover, expecting researchers to self-assess their methods often leads to information leaks and "over-fitting." An article in Molecular Systems Biology describes this phenomenon as the "self-assessment trap," in which researchers wishing to publish their analytical methods are required by "referees" or editorial policy to compare the performance of their own algorithms against other methodologies – thus being forced to be "judge, jury and executioner" with regard to their own research results.[9]

Second, coping with increasing **scientific complexity** presents another obstacle, since reviewers may lack the capacity and/or access to the underlying data needed to perform a comprehensive assessment of the work they review. This is particularly evident in emerging fields like personalized medicine, which is challenging the scientific community even more, and calling for new and better ways to verify scientific outcomes.[10] A quote from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research for the Food and Drug Administration (FDA), highlights the extent of over-optimism affecting computational biology: "Seventy-five percent of published biomarker associations are not replicable, due to measurement platform differences, specimen handling, data normalization and sample incompatibility between the original and subsequent studies."[11]

Third, and perhaps most important, the current review process has revealed flaws in terms of **reliability**, as shown by: the lack of replicability to confirm previous results; recent scandals related to fraud; high late-stage attrition rates in the R&D pipelines, and the increasing number of retractions.[12] While the pressure to "publish or perish" continues, there has been a ten-fold increase in retractions over the past decade, and publications have only grown by 44 percent.[13]

"We need new models to move away from science based on advocacy to science based on facts."
– Pharmaceuticals Senior Executive, U.S.

How confident are you that the scientific claims guiding your company's strategic decisions are accurate and impartial?

Numerous real-life examples demonstrate the severe implications of incorrect scientific claims in terms of public health, consumer exposure, environmental hazards and business decision churn (see sidebars, "The cost of failure" and "The impact of incorrect scientific claims"). Traditional reliance on peer-reviewed empirical science has lead companies to operate outside their preferred risk profile – putting their business value, shareholder returns, partnerships and reputation at stake.

The cost of failure

Worldwide, the pharmaceutical (Pharma) industry spends a total of US$105 billion each year on R&D.[14] A case study estimates that over 60 percent of those costs can be traced to unsuccessful product candidates, resulting in US$63 billion of misplaced investment.[15] Another US$4 billion is spent each year on safety litigation.[16]

These figures are sobering, and open the question of potential savings and value creation through a more reliable validation of safety and efficacy as early as possible in the R&D process.

As we move toward outcome-based pricing models, the importance of clinical evidence will only increase. It is a necessity if organizations are to survive, not to mention what is at risk for patients.

The impact of incorrect scientific claims

Patient harm, litigation, insolvency. Consider the case of an emerging biotech company. During the company's first Phase I clinical trial, all six trial participants who received the candidate drug suffered a cytokine storm and narrowly escaped death. Each of them has severe, lasting physical damage. Scientists debate whether the cytokine storm could have been foreseen ahead of the trial by reconciling available preclinical data and better predicting the activity of the first-in-human dose.[17] The company did not survive litigation and reputation damages and was forced to close its doors. The monetary losses totaled over US$2 million in legal costs. When the biotech company went insolvent, US$14 million in venture capital was lost.

Independent verification of the compound's biological impact on humans through predictive methods, species translational science and the aggregation of available data might have prevented this type of situation.

Fraudulent claims, reputation damage. In another incident, a scientist using findings based on data manipulation claimed to have discovered a diagnostic signature for predicting the progression of cancer and the effectiveness of treatment. His claims passed peer-review scrutiny, were published in leading high-impact journals and led to the launch of clinical trials.[18] During three clinical trials over several years, patients received therapy based on a fraudulent diagnostic signature. One patient died while taking part in one of these trials.[19] So far, 11 articles have been retracted and seven corrected, while more are expected to be.[20] The reputations of the scientist's numerous co-authors, his affiliation, a well-known scientific institution, as well as the journals that published the findings, were badly damaged. Litigation is ongoing.

This scenario could have had a better ending if a comprehensive and fully independent verification of the diagnostic signature, such as using an impartial test on an unseen data set, had been put into practice.

Assessing hazards and risks. The unknown, long-term impact of chemicals represents a high risk for the environment, wildlife and human health. The REACH program – Registration, Evaluation, Authorization and Restriction of Chemical substances – launched by the European Commission, requires the industry to demonstrate its ability to assess hazards and risks of chemical substances, and identify and implement measures to manage those risks.[21] Experts estimate that the implementation of these requirements is expected to consume up to US$14 billion and 54 million animals for testing.[22] Costs to date have reached US$2.3 billion (2012).[23]

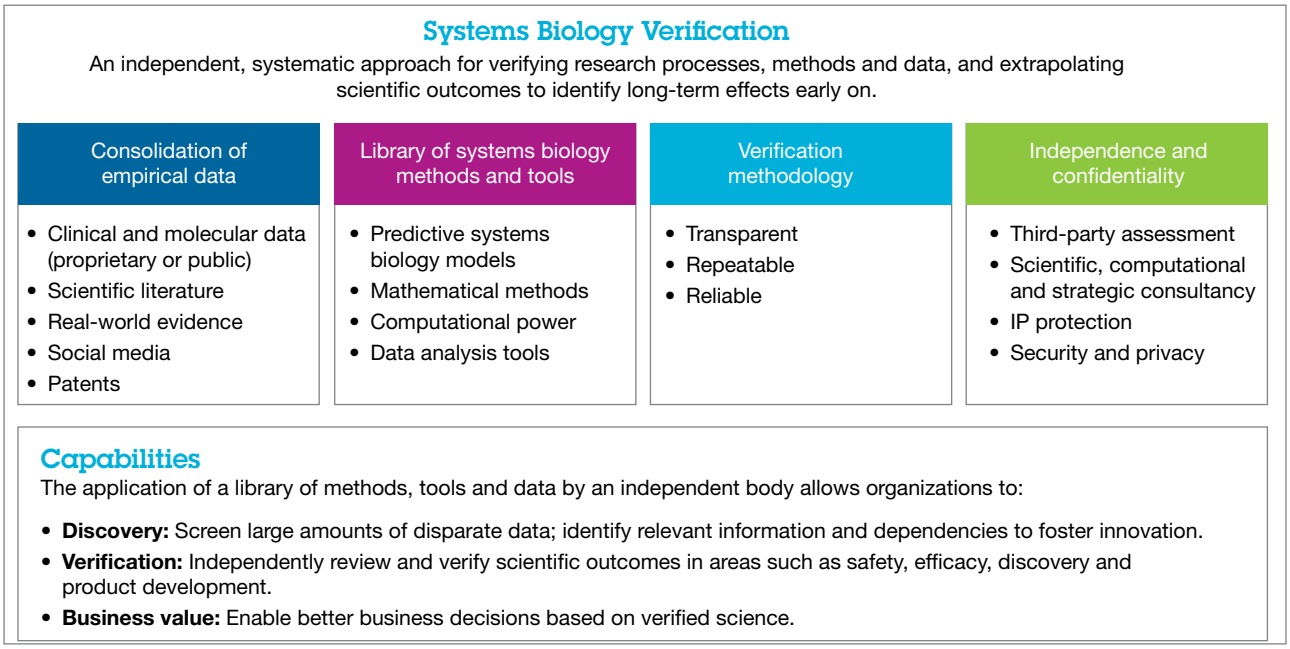
Using SBV, chemical businesses can prioritize the most suspicious chemicals, then create a complete picture of a chemical by verifying findings from empirical studies, aggregating information across multiple sources and companies, and using predictive methods to complement health and environmental impact analysis – and reduce the time and costs of regulatory approvals.

Consolidating existing knowledge, predictive models and independent assessment

By taking an independent, systematic approach to auditing research processes, methods and data, businesses can increase their confidence in science and help reduce risks in associated business decisions.

Today, this can be achieved through a deeper, more integrated view of biological systems, leveraging multidisciplinary research, mathematics and computational power to develop independent libraries of models, methods and data (see sidebar, "An integrated view of biological systems"). This approach leads to a new collaboration model, connecting all entities in the biological sciences eco-system by improving access to reliable scientific information. This connected eco-system is made possible by a set of advanced technologies that help broaden insights and build more trust in science. We call this **Systems Biology Verification (SBV)** (see Figure 1).

Systems biology aims to describe and understand the operation of complex biological systems and ultimately develop predictive models of biological processes, such as human diseases or plant growth mechanisms.[24] Rather than dividing a complex problem into its component parts, the systems perspective evaluates the problem with the use of computational and mathematical tools.[25] These models make it possible to target safety and efficacy to specific populations, and offer a way to evaluate long-term and cumulative effects of products – something that is currently impossible to achieve through empirical studies due to time and costs constraints (for example, confirming the effects of a statin over 30 years' intake).



Source: IBM Institute for Business Value

Figure 1: **SBV combines predictive capabilities and independent verification to increase confidence in science.**

An integrated view of biological systems

Systems biology is designed to describe, model and predict the behavior of biological systems using mathematical and computational tools. It is an interdisciplinary field integrating biology, clinical research, mathematics, engineering and computer science.[26] Systems Biology leverages high-throughput, experimental technologies to derive insights from genomics, proteomics and metabolomics data, and provide a deeper understanding of biological systems. Systems Biology has led to a paradigm shift in biology research – from being a descriptive and qualitative science to one that is quantitative and predictive.[27]

Systems Biology Verification (SBV) combines the predictive capabilities of systems biology data and models with an independent verification methodology to objectively assess and extrapolate the validity of scientific conclusions. Using an SBV approach, organizations can complement traditional research protocols to better gauge the safety and efficacy of their offerings – earlier, and with more reliability.

SBV combines systems biology data, models and advanced mathematical tools, which are applied by an unbiased third party to compare empirical findings against existing state-of-the-art knowledge and deduce their validity. This process addresses the issues of traditional research, in the following ways:

- **Impartiality** is made possible through **independent third-party** services comprising scientific, computational and strategic consulting, also preserving confidentiality and safeguarding intellectual property (see "Case study, "The MicroArray Quality Control consortium: Verifying reliability and reproducibility" on page 6).
- **Scientific complexity** is managed by comparing new scientific findings against established knowledge, such as scientific literature or clinical data from multiple sources and using a range of predictive models (see "Case study – IBM and Phillip Morris International: Leading in scientific verification" on page 6).
- A **central data platform** that consolidates and extracts insights from unstructured and disparate data sources will set the foundation of SBV. Data access and analytics capabilities are needed across disciplines: biology, statistics, medicine, computation; and information sources – clinical and molecular data (proprietary or public), scientific literature, real-world evidence, social media and patents. Screening large amounts of disparate data, and identifying relevant information and dependencies to foster innovation thus becomes possible.
- A **library of predictive models** – using systems biology, pattern discovery, mathematical tools and computer simulations allow for an in-depth analysis, as well as the extrapolation of long-term outcomes.
- Finally, a **reproducible and transparent verification process** helps assure the **reliability** of the assessment (see sidebar, "Overcoming uncertainty").

Overcoming uncertainty

The reliability of scientific outcomes is often challenged by the uncertainty surrounding the quality of underlying data. SBV helps overcome this uncertainty through:

Aggregation of data – Combining multiple sources helps even out inconsistencies and creates more accurate and useful data.

Consolidation of systems biology models and methods – The process of applying several predictive models, trained on different data sets and analyzing their predictions can reveal potential data inconsistencies.

Advanced mathematics, such as uncertainty quantification, robust statistics, optimization techniques, bootstrapping or fuzzy logic approaches address uncertainty and allow for more reliable insights.

Third-party assessment removes the inherent bias related to scientists being both defendant and judge of their theories.

Case study – The MicroArray Quality Control consortium: Verifying reliability and reproducibility

The MicroArray Quality Control (MAQC) consortium was set up as part of the United States Food and Drug Administration's (FDA's) Critical Path Initiative to medical product development. Its goal was to verify the reliability and reproducibility of predictive methods used to make a prognosis of preclinical and clinical endpoints from microarray gene expression data. In the MAQC-II project, 36 independent teams analyzed six microarray data sets to generate predictive models for classifying a sample with respect to several endpoints indicative of lung or liver toxicity in rodents, or of breast cancer, multiple myeloma or neuroblastoma in humans. In total, 30,000 models were built using many combinations of analytical methods. The teams generated predictive models and tested the models on data that had not been used for training. The project provided a unique opportunity to address concerns related to replicability of biomarker discoveries. The good modeling practice guidelines established by MAQC-II and lessons learned from this unprecedented collaboration provide a solid foundation from which other high-dimensional biological data can be more reliably used for the purpose of predictive and personalized medicine. The conclusions and recommendations from MAQC-II are useful for regulatory agencies, study committees and independent investigators that evaluate methods for global gene expression analysis.[28]

Case study – IBM and Philip Morris International: Leading in scientific verification

Philip Morris International (PMI) needed a way to verify its systems biology methods and results, and establish transparency and credibility within the external scientific community in performing state-of-the-art science. Given the traditional concerns with tobacco-industry science PMI wanted to put their scientific results out to review amongst the scientific community in a way that demonstrated that the results were beyond reproach. Researchers at IBM and PMI developed an independent systems biology verification methodology, **IMPROVER**, tailored to an industrial setting and leveraging key findings from **DREAM**, which uses crowd sourcing to verify R&D processes and outcomes. The project has established a sound verification method that views the involvement of the worldwide scientific community as an important component of science-based decision making. Scientific questions are defined, then published as challenges open to the global scientific community. Scientists from across the world submitted their solutions, which were evaluated by impartial scorers against an unseen data set to define the best-performing method, which would then be considered state-of-the-art in its field. This approach can better test the generalization of predictive methods, helping to minimize the limitations of traditional peer-review. The first challenge, delivered diagnostic signatures in four disease areas, verified the quality of empirical data and identified inconsistencies in histopathology. Trusted systems biology models and data benefit the entire scientific community and enables faster and more reliable safety assessment. The approach helps strengthen credibility toward the global scientific community, regulatory bodies and consumers.[30]

"This project will influence the scientific community, the regulators as well as the public, to rethink how science can be trusted and allow a more transparent assessment of complex scientific processes."
- Prof. Manuel C. Peitsch, Ph.D., Vice President, Biological Systems Research, Philip Morris International Research & Development

Auditing science

SBV offers a new way to evaluate scientific findings, allowing organizations to assess methods and data; evaluate safety and efficacy; and provide evidence of value.

Assess methods and data

Benchmark methods or models – by testing them on an unseen data set – as a new form of peer review, distinguished by an in-depth, fully independent and transparent process. Generate insights by identifying relevant information and dependencies from large volumes of disparate data.

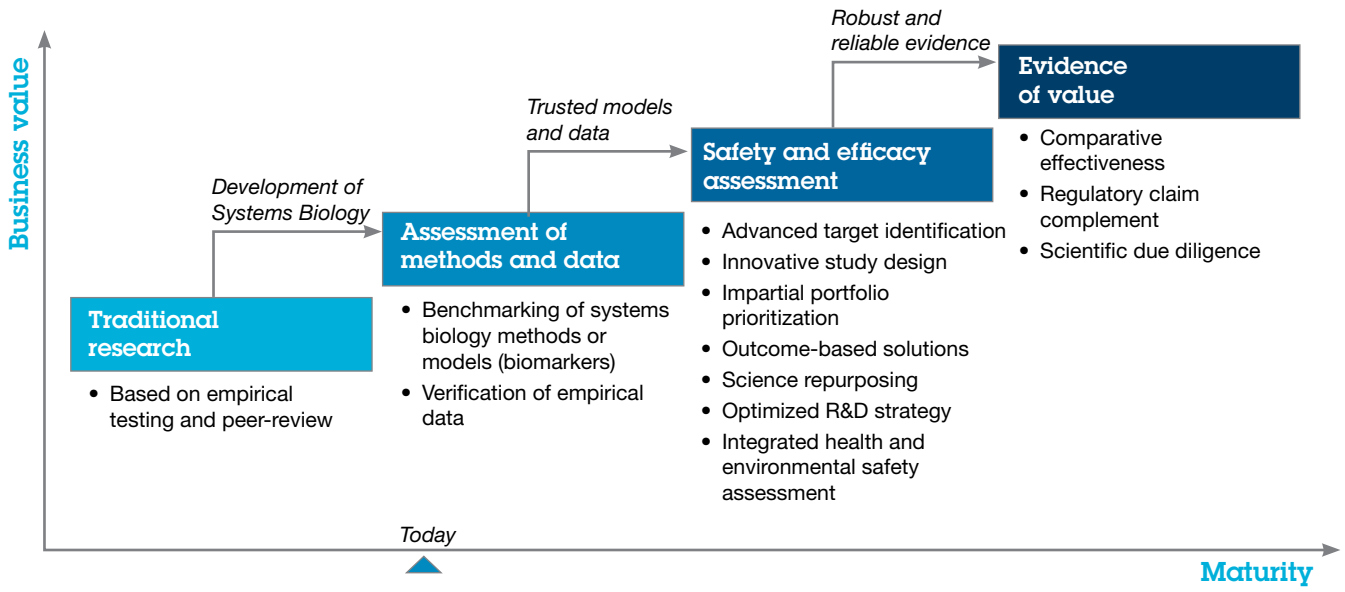
Evaluate safety and efficacy

Use proven systems biology models and data to perform a comprehensive safety and efficacy assessment of products, taking into account long-term, cumulative and environmental effects as well as genomic information. Such assessments can be used to create innovative study designs, optimize candidate selection, develop outcome-based solutions, repurpose existing science or improve R&D strategy and portfolio management (see "Case study –Safety Evaluation Ultimately Replacing Animal Testing").

Provide evidence of value

Employ an external audit of evidence to support traditional research data in regard to safety and efficacy. This can be used to compare effectiveness to drive growth in pricing, market size and market share. Complements to regulatory claims support traditional research in terms of reliability; long-term, cumulative or environmental effects; target populations; and/or optimal dosage. Scientific due diligence – for mergers and acquisitions, partnerships or licensing deals – helps organizations verify the value of a portfolio prior to acquisition.

SBV capabilities will grow and mature along with systems biology models and tools – moving R&D-focused companies away from traditional empirical testing and peer review to a more structured, independent and systematic model for assessing methods and data, and confirming the safety and efficacy of products with clear evidence of value (see Figure 2).



Source: IBM Institute for Business Value

Figure 2: **SBV capabilities will mature in parallel with systems biology models and tools.**

Case study – Safety Evaluation Ultimately Replacing Animal Testing

The vision of "Safety Evaluation Ultimately Replacing Animal Testing" (SEURAT) is to fundamentally change how the safety of chemicals is assessed, by superseding traditional animal experiments with a predictive toxicology that is based on a comprehensive understanding of how chemicals can cause adverse effects in humans.

The SEURAT-1 initiative, launched in 2011, comprises six complementary research projects that closely align with a common goal, and combine the research efforts of over 70 European universities, public research institutes and companies. The project will develop a long-term research strategy for the development of new non-animal test systems in the field of repeated-dose systemic toxicity to better assess human safety.

These achievements aim to provide a new basis for screening purposes and priority setting procedures that allow reductions in the use of animals. The results are likely to impact regulatory frameworks, and revolutionize both research and commercial models for the chemical and cosmetics industry.[30]

Building confidence and value across industries and organizations

An independent and comprehensive audit of science can help companies strengthen their confidence in scientific information and in associated business decisions – benefitting both research and business. Initially applied in life sciences, SBV is relevant in numerous industries, as well as to policy makers, research institutions and non-profit organizations.

For example, using SBV, **life sciences** organizations can discover viable products sooner by mining and analyzing volumes of relevant information – quickly, objectively and with greater accuracy. Equally important is lessening the risks of litigation and/or reputation damage through more reliable evidence of long-term impacts (see sidebar, "The impact of incorrect scientific claims").

For the **consumer products sector**, such as cosmetics and nutrition companies, primary objectives include building confidence in product claims (anti-aging creams or probiotics, for example) and assuring that products are safe and effective. SBV can assess a compound's viability in the long-term – results that cannot be obtained through traditional in vivo studies due to time constraints. Providing an external audit of evidence can increase the credibility of associated product claims – driving growth in pricing, market size and market share. The fact that SBV uses technology-based models also lessens the need for animal testing – supporting both good research practices and customer expectations.

SBV offers similar benefits to **environmental safety, chemicals** and **energy/biofuels** companies – enabling these businesses to quickly and more accurately assess the long-term impact of compounds on humans, wildlife and the environment, and assure that regulatory requirements are met.

Research institutions may benefit from SBV as a new form of peer review, with an in-depth, un-biased and transparent process. Successfully passing an SBV assessment is likely to enhance the credibility and the acceptance of scientific findings.

In search of clear evidence of products' safety and efficacy, **regulatory bodies** may embrace SBV to complement empirical data with external assessments – facilitating evidence-based health and environmental policy-making.

Finally, **not-for-profit organizations** can use SBV capabilities to develop innovative treatments for unaddressed health or nutrition needs in a cost-effective way; for example, by adapting established health treatments to genetic or body mass differences, as well as to social and environmental influences of developing countries. This can be achieved through dosing adjustments, repurposing existing drugs and assessing traditional medicines.[31] From a crop sciences perspective, SBV can help to improve yields and nutrient intake of plants or processed food.

Creating a trusted, value-based business model

SBV can play a transformational role in supporting new business models – enabling organizations to:

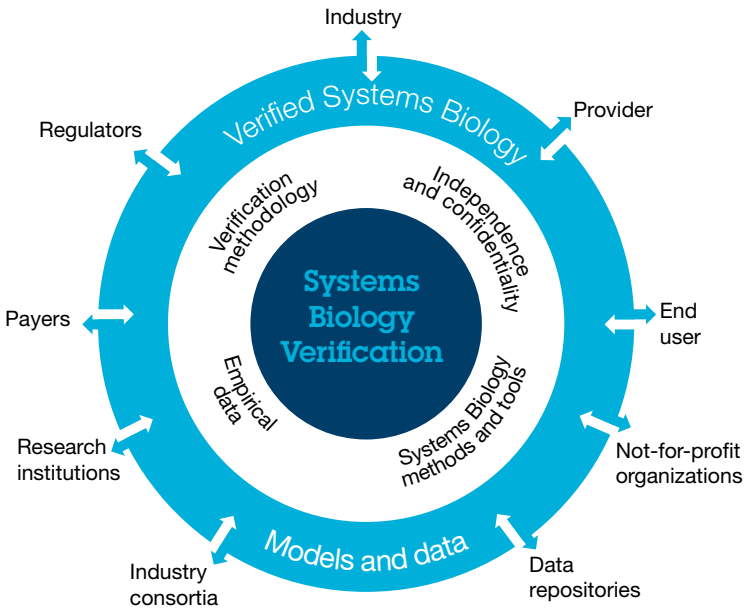
Mitigate risk by identifying potential or known product flaws, and verifying long-term and cumulative effects sooner in the development cycle.

Reduce costs and accelerate time to market by trimming cycle times and increasing the odds of success in the marketplace.

Build partnerships and foster collaboration by creating a trusted basis for working with non-traditional players, and sharing intellectual property and data to create more value.

Cultivate growth by supporting the development of innovative, outcome-based solutions that would be inaccessible through traditional research protocols, and providing clear evidence of value in terms of pricing, market size and market share.

SBV supports these initiatives by offering an independent, systematic way to verify value and embed that mindset into R&D and commercial processes (see Figure 3). Entities in the systems biology ecosystem can closely collaborate, and benefit from shared, reliable data and expertise.



Source: IBM Institute for Business Value

Figure 3: **The SBV business model foresees a central verification body coordinating data and expertise, and providing trusted evidence for all areas in the eco-system.**

Getting there from here

Realizing the potential of SBV requires more than a set of technologies and methodologies. It depends on objectivity, confidentiality and demonstrable capabilities – including extensive scientific and technological knowledge.

An independent third party with experience and expertise in SBV can remove scientists' responsibility for being "judge and jury" of their own theories, and help accelerate the R&D process while adhering to regulatory and industry demands. Access to empirical data, systems biology models and algorithms, and heavy-duty computing power, plus the ability to securely store massive amounts of data, are requisite.

An "SBV-platform" is needed to allow organizations to quickly and accurately gather, consolidate and interpret both proprietary and public data from multiple sources (such as clinical and molecular data, scientific literature, "real-world" evidence, social media and patents, for example). The insights gleaned from this information form the foundation for validating and benchmarking scientific conclusions across the R&D process.

Following a step-by-step approach – starting with a diagnostic assessment and progressively expanding scientific verification across R&D and commercial processes – can allow organizations to create more impact from SBV.

Where do you stand?

To manage and create more value from increasing scientific complexity, organizations need to challenge the way they approach science today. Answering a set of key questions can help you manage complexity, deal with uncertainty, produce evidence and create value (see Figure 4).

Complexity Are you ready to manage the increasing complexity?	**Confidence** How do you deal with uncertainty?	**Evidence** Can you demonstrate evidence of value?	**Value** Can you find new ways to create value?
• What impact do incorrect scientific claims have on your organization? • How does your organization address the increasingly complex and uncertain environment of discovering new science and proving it works?	• How confident are you that the facts guiding your company's strategic decisions are accurate and impartial? • How do you evaluate the validity of scientific claims of potential partners, collaborators or acquisitions?	• How do you demonstrate the cumulative effects of your products over long time periods? • Are your existing emprical testing methods sufficient to meet current and future regulatory, safety and efficacy requirements?	• Can increased evidence of value create differentiation, eminence or competitive advantage for your products or organization? • Would your organization benefit from an independent and in-depth verification of the science in areas such as product safety, candidate selection or scientific due diligence?

Source: IBM Institute for Business Value

Figure 4: **The path from complexity to confidence, evidence and value.**

Given today's increasing scientific complexity, organizations will need to revisit standard practices, acknowledging independent verification and evidence of value as key components of science-based decision making. The roadmap to scientific verification is comprised of five major steps:

1. Assess the organization's current state and identify value:
   - Examine current scientific verification processes in the organization
   - Define and quantify the value of increasing scientific reliability.

2. Develop a blueprint:
   - Analyze and prioritize gaps between the current and desired state
   - Define measurable targets and develop a scientific verification blueprint.

3. Set up capabilities and engage with partners:
   - Start small – using existing data, problems and models
   - Identify and engage with the right partners to execute the blueprint
   - Perform in parallel with traditional R&D initiatives.

4. Develop capabilities and drive adoption:
   - Establish trusted industry standards
   - Collaborate with all entities in the ecosystem to share data and expertise
   - Engage with the scientific community (regulators, payers, industry peers and users) to drive acceptance.

5. Expand scientific verification across the organization:
   - Integrate independent verification and evidence of value into R&D and commercial processes
   - Use trusted systems biology models to reduce costs, time and risk to market, and develop value-based solutions.

Conclusion

Every year, billions of dollars are budgeted and committed based on traditional peer review and empirical testing of scientific outcomes. This has resulted in several health and environmental issues, forcing companies to operate outside of their preferred risk profiles, contributing to poor R&D productivity or even legal actions – ultimately leading to the destruction of shareholder value. To address the increasing scientific complexity, organizations need to challenge the way they perform science today.

Are you ready to manage the increasingly complex and uncertain environment of discovering new science and proving it works?

Objectively and systematically verifying the growing number of complex scientific claims, and confirming the safety and efficacy of products early in the R&D cycle, are fundamental to an organization's credibility and success. Starting with an assessment of verification processes lays the foundation for an SBV roadmap. We recommend looking at examples of successful applications, and selecting a partner with experience and expertise you can trust.

By exploring new business models that set independent verification as a key part of scientific research, organizations across the life sciences ecosystem can create a reliable scientific basis, realize more value from R&D, reduce associated business risks and facilitate evidence-based policy making. SBV can transform how organizations validate scientific findings, assure the safety and efficacy of products, bolster scientific credibility, safeguard people and the environment, and drive innovation and growth.

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Doug Dean has 25 years of experience in the pharmaceutical sector and was until recently Senior Vice President of R&D at Philip Morris International. At PMI, his role was to transform both its R&D function and the way in which PMI science was regarded by the external scientific community. Under his leadership, a world-class capability in biological systems research was formed, and PMI embarked on a strategy to use mathematical modeling, systems biology and translational biology to show the harm reduction potential of next generation products. Doug has a BASc degree in Engineering Physics, and a PhD in Electrical Engineering.

Fran Hancock is a strategic consultant at Setanta AG. Previously, she was Vice President in Research & Development at Philip Morris International, where she was brought in as part of a small team to fundamentally transform the function. During her time there, she initiated and led several programs to restructure core R&D processes. She realized that a new approach to research was required to meet the challenges of assessing Modified Risk Tobacco Products, and so initiated and championed the need to build a Biological System Reseach unit. Before joining Philip Morris International, Fran was a partner and Vice President at IBM, and a director in PricewaterhouseCoopers. She holds a BSc. in Applied Science and an MBA.

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