

# Breaking the Constraints *of the Current Development Paradigm*

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## Our view on the future of biopharmaceutical research and development

Imagine a world where predictive tools for development planning scour development programs and pharmaco-epidemiological real world data to anticipate the response of patient populations. Where scenario analyses visualize strategic design trade-offs to optimize protocol design, and predictive assays select the right patients from integrated electronic health records across providers at a genome level. Where point-of-care data capture integrates trial evidence and real-world outcomes within clinical care systems, improving adherence and compliance to treatments. All this within biopharma's heightened operational performance with cycle times reduced by a third and development costs cut in half. Delivered by organizations aligned across research and development (R&D), commercial and external partner functions where there is full role clarity and seamless, harmonized integration.

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## The current R&D model is outdated

The current drug development paradigm was invented in the 1960s and persists, with minor modifications, to this day. Since then, investment in R&D has grown continuously. In the last 15 years alone, global biopharmaceutical investment in R&D has grown from \$54bn in 2000 to \$143bn in 2015.<sup>1</sup>

While the main external cost driver resided with increasing regulatory scrutiny, and reimbursement decisions were based on product innovation, biopharmaceutical companies were able to keep pace with the rising costs. This situation remained sustainable. Today's market is more competitive and treatments are more complex and costly to develop. In addition, historically, obtaining marketing authorization was the major hurdle. However, this is no longer the case. Macroeconomic pressures driving cost containment in established healthcare systems and the emergence of powerful reimbursement gatekeepers, including payers such as the National Institute for Health and Care Excellence (NICE) in the UK, Haute Autorité de Santé (HAS) in France and more recently G-BA (Gemeinsamer Bundesausschuss) in Germany, have changed the situation fundamentally. In today's healthcare environment an attractive reimbursement value is by no means guaranteed. Conditional approval is common and the importance of real-world evidence (RWE) to convince health technology assessment (HTA) bodies and payer organizations of a treatment's value is growing. As a consequence of all these contributory factors, the profitability of the fifteen largest biopharmaceutical companies has shrunk from an earnings before interest, taxes, depreciation and amortization (EBITDA) margin of 36% in 2010 to 32% in 2015.<sup>2</sup>

Leading biopharmaceutical players have rediscovered the patient as the true healthcare stakeholder. As a consequence, these players are exploring new ways to increase return on investment in R&D with emphasis on shifting to a more sustainable R&D model and with the aspiration to improve care for patients.

Many leading biopharmaceutical players have reacted with a strong focus on orphan and rare diseases benefitting from the high unmet medical needs in these indications and the less demanding regulatory framework. However, even this market is under pressure. While there is still a high unmet medical need in orphan and rare diseases with an estimated 7,000 rare diseases impacting 350 million people globally<sup>3</sup>, payers are increasingly worried about the budget impact of these rare diseases. New rare diseases are being added to the list so this global figure is expected to rise further. Recent HTA decisions demonstrate that even when there is a high medical unmet need, payers still require rigor in evidence generation. In April 2016, the Scottish Medicines Consortium (SMC) failed to recommend ataluren for Duchenne muscular dystrophy, a rare life-limiting disease in children, due to a lack of economic evidence. This follows other recent negative recommendations in life-threatening, orphan indications by SMC for elosulfase-alfa and a preliminary negative recommendation from NICE for sebelipase-alfa. However, the majority of patients live their lives challenged by other chronic diseases such as those of the cardiovascular system, intermediary metabolism, the central nervous systems, the respiratory tract, plus many oncology conditions that, with treatment, are now considered to be chronic diseases. Withholding the accelerated pathways restricted to orphan or rare diseases is neither ethical nor acceptable, especially since there is a trend towards developing treatments for chronic diseases for niche populations identified through biomarker or genome screening. One example is hepatitis. There are five types, A-E, and within these patients respond differently to the different treatment options. Leading biopharmaceutical players have rediscovered the patient as the true healthcare stakeholder. As a consequence, these players are exploring new ways to increase return on investment in R&D with emphasis on shifting to a more sustainable R&D model and with the aspiration to improve care for patients. Bringing innovation earlier to the world for a broader patient population represents a fundamental opportunity here.

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## The new reality has begun

What does early launch mean for the development paradigm? It was pioneered by the FDA in 2012 with the introduction of the breakthrough designation status for life-threatening diseases<sup>4</sup>. An accelerated development, review and approval process based on proof of concept (PoC) is the new normal for such indications with a focus on early consultation and ongoing dialogue between sponsor and regulator. The FDA approved 14 products in 2014 and 21 in 2015<sup>5</sup> with breakthrough designation status. In March 2016 the European Medicines Agency (EMA) launched the PRIME (PRiority MEdicines) pathway which treat conditions with high unmet medical need<sup>6</sup>. This means that, providing an asset meets the criteria, accelerated approval is now available in countries that represent more than two thirds of the global prescription drug market. The FDA breakthrough designation status and EMA PRIME pathway regulatory framework indicate that leading regulators envisage a more progressive change to the current clinical development paradigm. The EMA PRIME pathway has broadened scope beyond ultra-specialty conditions to accelerate

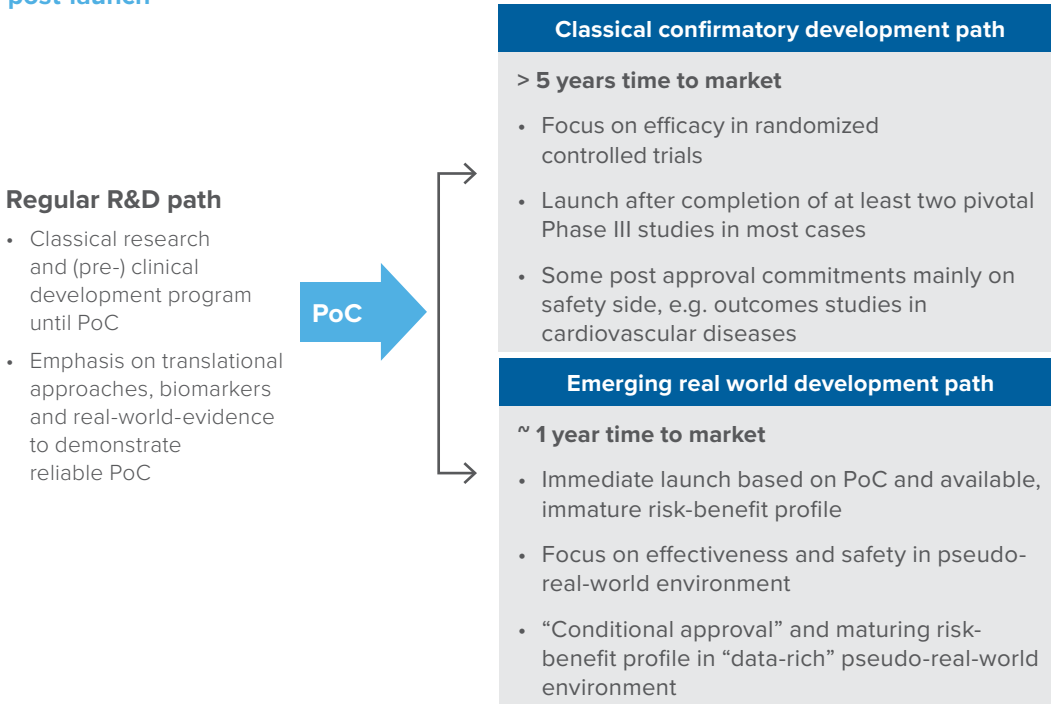


*Historically, conducting pragmatic trials with treatments that have no marketing authorization was not covered by the regulatory frame. The innovation of the pseudo-real-world environment is helping to change that.*

patients' access to a broader set of medicines that address unmet medical needs. This is a particularly important milestone and the first step towards a broad "launch at PoC" paradigm<sup>7</sup>. The Massachusetts Institute of Technology (MIT) Centre for Biomedical Innovation has taken this a step further by bringing together multi-stakeholder working groups of regulators, payers, patients and industry sponsors under the umbrella of the NEWDIGs (NEW Drug Development ParadIGMs) initiative to pre-plan evidence generation to meet the needs of all stakeholders and facilitate timely access to them<sup>8</sup>.

Leading biopharmaceutical players take advantage of emerging opportunities for earlier launches and smarter development strategies. In 2014, the FDA granted conditional approval to pembrolizumab for patients with advanced melanoma based on data from a surrogate endpoint (tumor size). At the time of approval there was no proof of increased survival or reduction in disease related symptoms; however, the sponsor committed to performing these confirmatory studies<sup>9</sup>. Another promising strategy is the use of patient registries, to match patients to treatments based on their genomic profile. The American Society of Clinical Oncology (ASCO) launched its Targeted Agent and Profiling Utilization Registry (TAPUR) study in March 2016<sup>10</sup>. The trial will evaluate molecularly targeted cancer drugs and collect data on clinical outcomes to inform additional uses of these drugs outside of indications already approved by the FDA. These types of study have the potential to inform resulting Phase III programs' inclusion/exclusion criteria, shorten the often lengthy patient recruitment times and improve patient retention in trials compared with the classical development approach. This accelerates the time to market. The next step from our point of view is integrating pragmatic trials into Phase III development programs. We define pragmatic trials, in this context, as trials that randomize patients to active treatment versus standard care in a care setting with significantly relaxed inclusion/ exclusion criteria and without a stringent study protocol. Historically, conducting pragmatic trials with treatments that have no marketing authorization was not covered by the regulatory frame. However, the Salford Lung Disease Study in chronic obstructive pulmonary disease (COPD) pioneered this transition. This study combined an approved active pharmaceutical ingredient (API) in a non-approved medical device and compared it to standard COPD care. The benefit and crucial feasibility driver of this pre-approval, pragmatic trial was the data density and high connectivity of the Salford provider system. Something that we call a pseudo-real-world environment. We believe the journey will continue with pragmatic trials as part of Phase II development programs and that the new normal will be conditional approvals granted shortly after PoC for a broad spectrum of therapeutic areas (Figure 1).

**Figure 1: Early conditional approval in a restricted population with active surveillance post-launch**

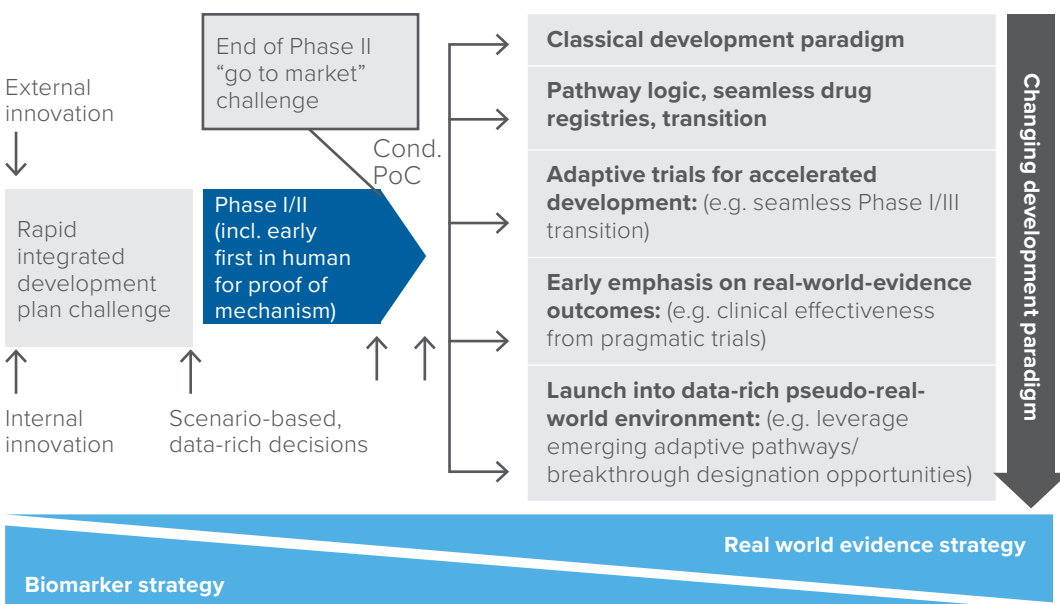


**Matching asset potential with optimal development pathway will make the difference**

The emerging opportunity to benefit from “launch at PoC” or similar regulatory frames forces drug developers to make strategic trade-off decisions about the optimal development path for an asset on an indication-by-indication basis. The options start with the classical development paradigm with options in incremental steps to the new data-rich pseudo-real-world environment option (Figure 2).

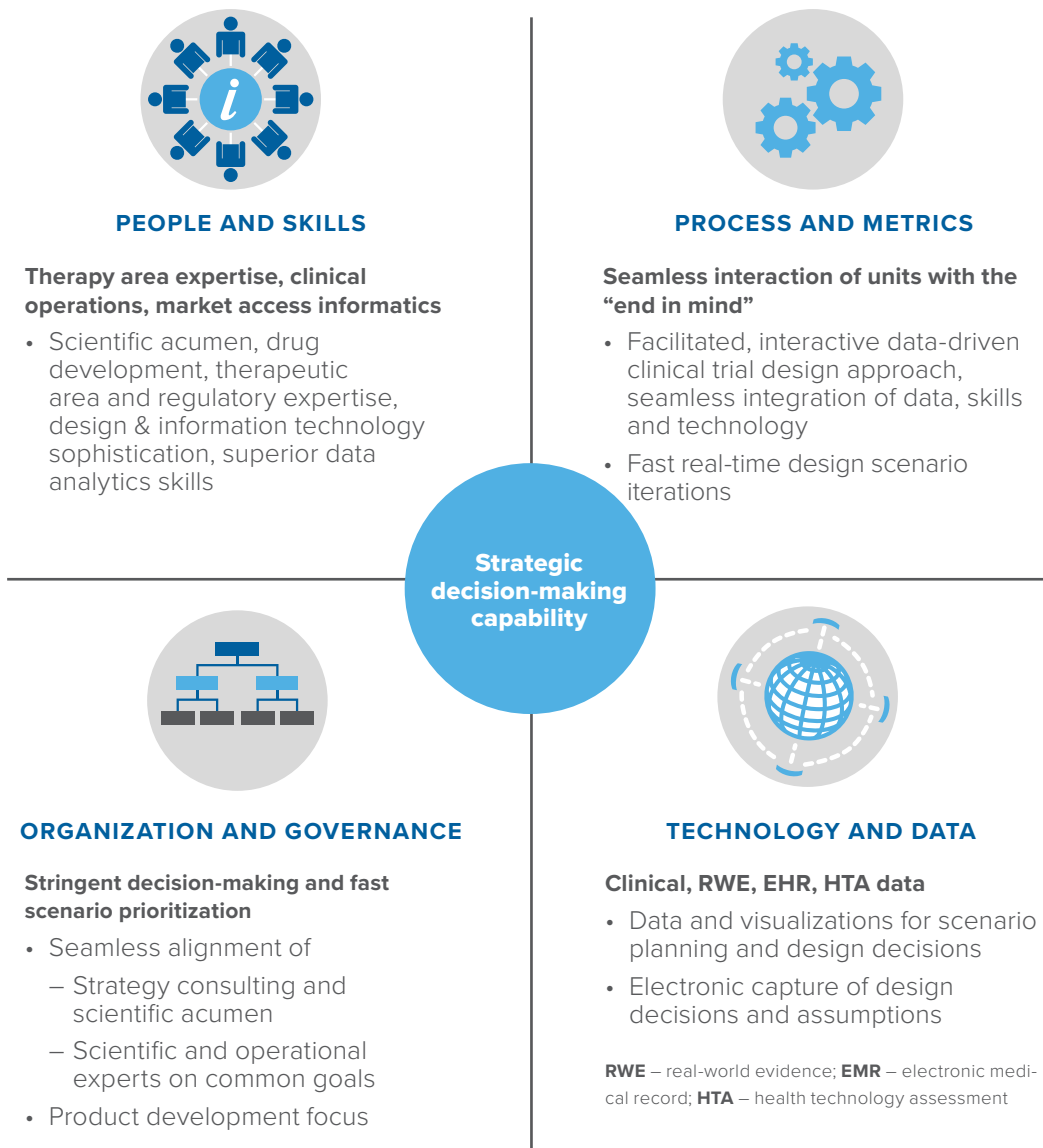
*A data-rich, scenario-based, decision-making capability is required to make conscious decisions for each asset and each indication to understand and manage the resulting benefit-risk profile.*

**Figure 2: Iterative trade-off decisions on therapeutic areas, disease indications for meaningful prioritization and end-to-end stewardship of priority projects**



An application for market authorization such as the piloted EMA adaptive pathways can reduce or eliminate the cost of Phase III. However, it still requires investment to fulfill the pre-approval and post-approval commitments to generate additional risk-benefit information. A data-rich, scenariobased, decision-making capability is required to make conscious decisions for each asset and each indication to understand and manage the resulting benefit-risk profile. We have built such a strategic decision-making capability internally by combining design best practices proven successful across other industries with the vast data resources of the world’s leading contract research organization (CRO). The approach is highly collaborative, bringing together knowledge in the form of internal and external data and expertise from Quintiles and biopharmaceutical companies (Figure 3). The process generates options with clinical and financial tradeoffs that inform management decisions about the best path forward. The result is a robust integrated development plan.

**Figure 3: Quintiles’ drug development decision making capability**



## Pseudo-real-world environments include a key risk mitigation mechanism

A robust PoC provides drug developers with an initial asset benefit-risk profile that should avoid unpleasant safety surprises. It is true that rare safety events only surface with larger treatment experience; however, the relatively small patient numbers in Phase III programs are not enough to detect them. Furthermore, our internal analysis has shown that asset failure in Phase III is generally driven by a lack of efficacy rather than safety. This provides a strong argument in favor of the “launch at PoC” paradigm into an environment where benefit risk is closely monitored. Conditional launch into a pseudo-real-world environment could be a powerful risk mitigation strategy here.

Such a pseudo-real-world environment is characterized by coherent implementation of electronic medical records (EMRs) and high connectivity between prescribers, caregivers, patients and other relevant stakeholders – for example, public healthcare trusts, private managed care organizations and regional/national public healthcare insurance. It allows early detection of expected and unexpected adverse events and is optimized for fast correction/remediation in a 24/7 setting. Data density is seamlessly enriched by increasing the number of mobile sensor devices and powerful platforms to integrate data and perform analyses in real time to identify trends in the data, such as early safety signals, and to inform and enhance care pathways/care delivery. Using mobile sensor devices and wearables also has the potential to fundamentally shift care delivery: bringing treatment to patients rather than bringing patients to treatment. Managed in the right way, mobile sensor devices and wearables encourage greater patient engagement and have the potential to revolutionize medical studies. We have already collaborated with Apple to build components for their platform that will enable a host of functions to promote patient engagement in clinical trials and registries<sup>11</sup>. We are also actively engaged in developing electronic patient reported outcomes (ePRO) tools, including participation in an ISPOR task force to provide recommendations on the mode of data collection using of PRO and ePRO data collection in clinical programs to support labelling claims<sup>12</sup>.

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## Conclusion

We have described a vision of the future development paradigm. The elements needed to turn this vision into reality are coming together. Regulators have created the frameworks needed to achieve early conditional approvals with close follow-up post launch. The technologies are available to collect real-world data from patients in a new type of study that generates the wealth of data required to detect safety signals and deliver patient-centric care. These studies are also more likely to generate the proof points required to demonstrate value to payers. Sponsors are already working collaboratively with regulators and payers in pilot programs. There is every reason to believe that our vision is the future development paradigm.



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## About the authors



### **Sarah Athey**

*Engagement Leader, Quintiles Advisory Services*

Sarah Athey has 25 years of industry experience and currently holds the position of Engagement Leader within Advisory Services.

She has a wealth of consulting experience with particular expertise in clinical development strategy, organization design, change management, performance management and process optimization. Since joining Quintiles, Sarah has led projects in clinical development transformation including partnership governance, pharmacovigilance and market access.

Sarah also has experience in global clinical development and was Clinical Lead for a number of successful regulatory submissions. She has also worked as a health economist developing market access / launch strategies in Europe and Asia. She won the GSK chief executive's award for innovation for her work with Seoul University and the Korean government.

Before joining Quintiles, Sarah spent ten years with PriceWaterhouseCoopers and IBM, following a successful global clinical development and health outcomes career at GSK. She has a BSc in Zoology and Pharmacology, an MBA and an MSC in Health Economics.

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## About the Authors



### **Volker Rönicke**

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Volker Rönicke has more than 20 years of experience in acting as senior strategic advisor to leaders in biopharmaceutical industry and being part of biopharma and biotech firms. His focus areas are business model innovation, operating model design, helping clients to build differentiated capabilities, and increasing effectiveness and efficiency of cross-functional working practices.

Volker spent the majority of his time supporting clients in market access, market entry strategies and to optimize the R&D Commercial interface, strengthening Medical Affairs capabilities, making better use of real-world evidence and ensuring earlier integration of payer needs into development programs.

Before joining Quintiles, Volker acted as Partner with Booz & Company (now Strategy&). He has earned an MBA from Heriot- Watt University Edinburgh, UK and a PhD in molecular biology and cell biology from Max-Planck Society and Philipps University



### **Anke van Engen**

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Anke van Engen leads Quintiles' HTA Solutions team, helping customers to maximize the commercial success of products through integrated market access strategy. She manages an international team of consultants based across Europe and the U.S. who deliver the full range of HTA and market access services. With more than 15 years of global market access experience and a proven track record in enabling companies to achieve greater commercial successes, Anke has led numerous HTA submissions and acted as client representative during NICE, NCPE AWMSG, as well as EMA-HTA scientific advice meetings.

An experienced professional in high quality consultancy, dedicated to helping life sciences companies, Anke holds an MSc from Leiden University.



### **Cara Willoughby**

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Cara Willoughby leads an international team of design and data scientists within Quintiles Advisory Services and is responsible for business development for Strategic Planning and Design services enabled by Infosario Design.

Cara has 18 years of pharmaceutical industry experience in clinical research program planning and reporting, interpretation and application of global regulations, medical writing, preparation of marketing applications, development of data interchange standards, and development and implementation of novel clinical technology solutions.

Prior to joining Quintiles, Cara was previously employed at Eli Lilly and Co. where she held leadership positions and consulted on a variety of strategic transformation and modernization initiatives across clinical development. Cara also led and influenced the development of clinical trial and healthcare data interchange standards as co-chair of Protocol Representation Group of CDISC and HL7.

Cara has a BA in Psychology and a BA in Zoology from Miami University of Ohio and an MSc in Reproductive Physiology, Cryobiology from Purdue University.