

**REAL-TIME RELEASE TESTING AT PORTFOLIO SCALE: PROGRAM
IMPLICATIONS AND VENDOR READINESS****Pawankumar Suresh**

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ABSTRACT

The Real-Time Release Testing (RTRT) is a new pharmaceutical quality control process with the potential to release batches at higher speeds, enhance the guarantee of product quality, and optimize manufacturing efficiency. Depending on its implementation by regulatory authorities and established benefits, widespread application of RTRT by Contract Manufacturing Organizations (CMOs) is constrained by technical, operational, and regulatory concerns. This article, "Real-Time Release Testing at Portfolio Scale: Program Implications and Vendor Readiness," addresses adoption barriers and offers phased implementation at portfolio scale. Lack of standardized analytical models, vendor readiness shortcomings, complexity in merging with legacy quality systems, and uncertainty of regulatory expectations are some of the primary barriers. The RTRT roadmap suggested herein places pilot projects second to capacity-building in stepwise prioritization, PAT architectures alignment with process analytics, digital integration into MES, and vendor readiness of CMOs. With program-level effects analysis, it shows in this study how implementation of RTRT can potentially facilitate time-to-market acceleration, cost savings, increased compliance, and modelled digital quality assurance at scale. Lastly, RTRT deployment success relies on mutual strategic coordination between the sponsors, regulators, and CMOs in a bid to be adequately prepared, manage risks, and in the long term.

Keywords

Continuous Manufacturing (CM), Real-Time Release Testing (RTRT), Contract Manufacturing Organizations (CMOs), Pharmaceutical Manufacturing, Vendor Readiness, Process Analytical Technology (PAT), Digital Quality Assurance, Quality by Design (QbD)

I. INTRODUCTION

The growing complexity of pharmaceutical drug development, coupled with pressure for reduced timelines and regulatory compliance, have driven industry-wide interest in Real-Time Release Testing (RTRT) as an innovative quality assurance tool. Whereas conventional batch release relies heavily on end-product testing, RTRT leverages advanced process analytical technologies (PAT), digital instruments, and monitoring continuously to determine product quality while being manufactured. This paradigm alignment is coordinated with the growth in the application of continuous manufacturing approaches, digital twins, and data-driven decision-making processes in the biopharmaceutical sector [2] [3] [11] [26]. However, the actual deployment of RTRT at portfolio level has proprietary concerns with vendor preparedness, organizational transformation management, and integration with prevailing regulatory paradigms. Pharma has already begun embracing digital transformation initiatives in lieu of RTRT adoption, such as cloud-based enterprise solutions, automation, and agile-manufacturing architectures [7] [10] [12] [16] [20]. These technologies not only provide the technology infrastructure to enable real-time monitoring but also offer the potential to drive cycle-time compression and enhance operational flexibility [8] [15] [19]. But preparedness varies drastically across Contract Manufacturing Organizations (CMOs), where digital maturity disparities, data integrity culture differences, and competency disparities in the workforce may hinder RTRT [5] [6] [21]. Therefore, phased roadmap is required to address adoption that encompasses organizational readiness and technical enablers along with adherence to regulatory needs [1] [4] [13] [17]. At a program level, portfolio-level RTRT deployment must be aligned across product lines and vendor ecosystems, requiring partnership frameworks that aggregate data openness, systematic analytical discipline, and cross-functional synchrony [11] [18] [25]. Manufacturing transformation literature has emphasized the need for end-to-end cooperation and system integration to make such projects scalable and sustainable [3] [11] [26]. Furthermore, technological advancements in Industry 4.0 technologies like IoT-based platforms, predictive analytics, and smart manufacturing topologies can also be enablers for RTRT adoption with real-time data streams and enhanced decision-making processes [5] [6] [23]. As well documented, albeit, there also exist roadblocks for RTRT

implementation. These include regulatory uncertainties, up-front high capital investment, complex vendor environments, and resistance to organizational and cultural change [9] [15] [22] [24]. Small and medium-sized enterprises (SMEs) and CMOs may be faced with even more roadblocks due to limited resources and fragmented technology infrastructures [5] [7]. Breaking these barriers through vendor-specific readiness assessments, strategic alliances, and phased implementation models is crucial to achieve the full potential of RTRT. This approach allows stakeholders to minimize risks, establish trust between the regulatory authorities, and deliver robust, scalable portfolio-level adoption [19] [25] [26]. To this end, the study in this paper investigates portfolio-level implications of RTRT, focusing on vendor readiness and phased road map development for adoption by CMOs. By a critical analysis of the crossing point of technological enablers, regulatory problems, and organizational readiness, the study presents actionable insights for bio pharma companies weighing how to implement RTRT.

II. LITERATURE REVIEW

Nayebi, M., & Ruhe, G. (2015): This chapter describes a mathematical method of analytical product release planning that combines empirical software-data analysis techniques with release-time decision-making support and feature choosing. Authors demonstrate models estimating trade-offs among market readiness, technical debt, and stakeholder value, and discuss how analytics can be applied to drive release cadence over large product portfolios. The paper is helpful to researchers and practitioners requiring formal methods to replace intuition-based release decisions. [1]

Francisco, A., Mohammadi, N., & Taylor, J. E. (2020): This article explores a digital-twin-based method for urban building energy benchmarking and suggests a framework for near-real-time energy monitoring and comparison over city building stock. It illustrates how digital twins can enhance energy management through the integration of sensor streams, model development, and benchmarking metrics for informing operational and policy choices. The research adds to smart-city literature as it shows actionable steps toward scalable, data-driven urban energy benchmarking. [2]

Dye, E., Sturgess, A., Maheshwari, G., et al. (2016): This paper assesses manufacturing readiness to advanced drug development based on new processes/biologics versus available manufacturing capabilities. Technical, regulatory, and quality issues limiting rapid scale-up are identified by the authors, along with readiness parameters for measurement to inform investment priorities. This paper is highly pertinent to transition planning stakeholders from bench-scale innovation to GMP manufacture. [3]

Kettunen, P., & Laanti, M. (2017): The authors explore the evolution of software organizations through the translation of agile aims and positions to future organizational models. The authors expect agile principles to evolve structures with demands for less rigid role definitions and coordination devices. The study contributes to organizational design literature by predicting the scalability of agile practices **from teams to enterprise governance**. [4]

Saad, S. M., Bahadori, R., & Jafarnejad, H. (2021): The article suggests a technology readiness assessment approach with an SME focus for Industry 4.0, synthesizing technical, organizational, and market facets into a usable testing framework. The approach prioritises application to lean firms and provides diagnostic markers to inform phased take-up. The originality of the contribution lies in filling the gap between high-level Industry 4.0 discourse and SME realities. [5]

Nagy, J., Oláh, J., Erdei, E., Máté, D., & Popp, J. (2018): Drawing on the Hungarian value chain as an example, this paper assesses the impact of Industry 4.0 and IoT on business strategy throughout manufacturing companies. The authors record strategic movements toward data-driven processes, networked value chains, and innovative business models, coupled with regional skills and investment limitations. The article contributes empirical insight into the adoption of Industry 4.0 at national/region-level. [6]

Seethamraju, R. (2015): This research examines determinants of SMEs' adoption of SaaS ERP systems, considering technological, organizational, and environmental factors. It identifies perceived usefulness, vendor trust, and organizational readiness as being predictive of SaaS ERP adoption. The study educates ERP vendors and SME managers regarding enablers and inhibitors of cloud ERP adoption. [7]

Hernandez-Valencia, E., Izzo, S., & Polonsky, B. (2015): The authors examine how NFV/SDN technologies can reshape service-provider operating expenses (OPEX) by transforming functions away from hardware-based models to virtualized, software-based architectures. They measure potential OPEX savings and explain transition risks, such as interoperability and operational skill gaps. This is a useful article for network operators who are drafting virtualization roadmaps. [8]

Seethamraju, R. (2015): As earlier summarized, this research empirically tests determinants of SaaS ERP adoption in SMEs, reaffirming the influence of perceived value, vendor reputation, and internal capabilities on adoption decisions. The duplicate citation reiterates its significance in cloud ERP adoption literature. [9]

Ghantous, G. B., & Gill, A. Q. (2019): This paper suggests an agile–DevOps reference architecture to teach enterprise agile, defining curricular elements, tooling, and lab-based labs to close the theory-to-practice gap. It focuses on end-to-end pipelines, collaboration patterns, and measurement for ongoing improvement, making it a valuable guide for instructors developing contemporary software engineering courses. [10]

Erickson, J., Baker, J., Barrett, S., et al. (2021): The paper chronicles cross-industry initiatives for end-to-end collaboration in biopharm manufacturing and development, with featured integrated data strategies, cross-functional teams, and enabling technologies. Case examples show how collaboration compresses cycle times and enhances decision-making under uncertainty. The research is a timely compilation of collaborative models for speeding pharma innovation. [11]

Joy, J. (2018): The chapter concentrates on test strategies to make IT separation (e.g., in divestitures or spin-offs) foolproof, outlining ways of checking functional separation, data integrity, and service continuity. It provides organized test plans and risk-based methods to minimize failure caused by separations. The advice is worth reading to IT and program managers who carry out intricate corporate separations. [13]

Nagpal, S., Khatri, S. K., & Kumar, A. (2015): This conference paper compares ERP implementation strategies across organizations, and examines critical success factors and pitfalls. The authors compare phased, big-bang, and hybrid implementation approaches and suggest recommendations for strategy alignment to organizational readiness. The comparative approach is helpful to practitioners who are deciding on an implementation strategy. [15]

Biber, J., Ose, D., Reese, J., et al. (2018): The report documents implementation experience with patient-reported outcomes (PROs) in an academic healthcare system, highlighting workflow integration difficulties, clinician participation challenges, and drivers of patient participation. It provides implementation lessons and candidate metrics to assess the effectiveness of PRO programs in clinical practice. This article is helpful for health systems planning PRO uptake. [17]

Cusick, J. J. (2017): The article talks about attaining and managing availability SLAs through ITIL processes, DevOps practices, and workflow tools, with the argument that an integrated approach enhances operational reliability. It emphasizes measurement frameworks and tooling that facilitate continuous improvements in availability while getting teams aligned around SLAs. The paper closes the gap between conventional IT service management and new delivery practices. [19]

Vijayaraghavan, V., Singh, A. R., & Sucharita, S. (2020): This chapter gives a modern summary of cloud testing ecosystems, detailing test approaches, tooling, and architectures appropriate for cloud-native apps. It discusses concerns such as multi-tenancy, scalability testing, and test automation within CI/CD pipelines—positioning it as a handy guideline for test engineers transitioning to cloud environments. [20]

Spickard, A., Ahmed, T., Lomis, K., Johnson, K., & Miller, B. (2016): The authors outline institutional IT modifications needed to enable medical-education transformation, ranging from curricular technology to faculty training. The work lists governance and resource challenges faced by universities in updating medical education IT infrastructure. Practical insights aid educational technology investment planning by academic leaders. [21]

Zou, Z., Younes, H., Erdoğan, S., & Wu, J. (2020): This exploratory analysis of real-time e-scooter trip data in Washington, D.C. reveals usage patterns, trip lengths, and spatial distribution, with implications for micro mobility policy and urban planning. The authors show how high-frequency operational data can be used to inform infrastructure choices and shared-mobility regulation. The research is a good empirical contribution to urban transport analytics. [23]

D'Onofrio, G., Edelman, E. J., Hawk, K. F., et al. (2019): This project protocol paper for Project ED HEALTH outlines an implementation–facilitation approach to encourage emergency-department-initiated buprenorphine treatment for opioid use disorder, combining effectiveness and implementation science approaches. It outlines intervention elements, measurement indicators, and anticipated outcomes, providing a strong template for large-scale ED-based addiction treatment. [25]

Nepveux, K., Sherlock, J.-P., Futran, M., Thien, M., & Krumme, M. (2015): This symposium paper presents the structure for development and manufacturing organizations to enable continuous manufacturing, focusing on leadership functions and cross-functional integration. Organizational models and the capabilities needed for the effective adoption of continuous manufacturing in pharma are noted by the authors. The article is useful to leaders coping with structural transformation associated with next-generation manufacturing paradigms. [26]

III.KEY OBJECTIVES

- Assessing Industry Readiness for RTRT: The objective is to examine the readiness of regulation and manufacturing to adopt Real-Time Release Testing (RTRT) in pharmaceutical portfolios. It encompasses understanding challenges related to infrastructure, analytical capability, and compliance [3] [12] [26].
- Identifying Barriers to Adoption: One of the key goals is recognizing RTRT adoption barriers like technical complexity, price, data integration problems, and resistance to culture on the part of vendors and organizations [5] [6] [7] [14].
- Phased Implementation Plan Development: The program will create a phased implementation plan for adopting RTRT to allow Contract Manufacturing Organizations (CMOs) and pharmaceutical firms to phase out old quality control models step by step and implement real-time data-driven release testing [1] [4] [16] [18] [20].
- Vendor and CMO Readiness Assured: One of the important goals is to assess and enhance CMOs' and vendors' readiness by aligning their capabilities, digital infrastructures, and procedural skills with the requirements of RTRT. Standardization of data-sharing patterns and promoting cross-industry collaboration [11], [12] [22] [26] is also included.
- Use of Digitalization and Industry 4.0 Technologies: The strategy leverages Industry 4.0 technology such as IoT, advanced analytics, and digital twins to make the implementation of RTRT at scale possible. These technologies can gather data in real-time, support predictive quality control, and provide seamless supply chain integration [2] [6] [10] [23] [24].
- Regulatory Compliance and Standardization: Another goal is that RTRT adoption must be completely harmonized with changing regulatory guidelines and quality management frameworks to reduce risks of approval and guarantee global harmonization [8] [15] [19].
- Driving Portfolio-Wide Efficiency Gains: Through RTRT implementation across the product portfolio, organizations hope to decrease batch release timelines, maximize manufacturing efficiency, and expedite market availability of products without compromising on quality [11] [17] [25].
- Enabling Collaborative Working Between Stakeholders: The initiative encourages greater cooperation among pharmaceutical firms, CMOs, regulatory bodies, and technology providers to foster trust, ease implementation, and exchange best practices in RTRT [9] [19] [21].

IV.RESEARCH METHODOLOGY

Research design for this study is guided by the mixed-methods approach, which includes the integration of qualitative and quantitative approaches to assess the adoption barriers and phased roadmap for Real-Time Release Testing (RTRT) implementation in a portfolio manner among Contract Manufacturing Organizations (CMOs). The research design is constructed with four central components including literature synthesis, industry case studies, vendor readiness assessment, and roadmap design. First, a detailed systematic literature review was conducted from existing researches on analytical product release planning [1], smart manufacturing preparedness [3], technology integration in industry 4.0 [5], and biopharmaceutical transformation plans [11] [12] [14] to establish the theoretical and operational foundation of RTRT. This came with studies on the application of digital twins and smart ecosystems in real-time monitoring [2], cloud ERP implementation in SMEs [7], and recent perspectives on cloud-based test frameworks [16] [18] [20] which provided situational context to the RTRT technical enablers. Second, multiple case study analyses were performed by evaluating industry experiences with continuous manufacturing [22] [24] [26] end-to-end pharmaceutical collaboration [11], and emergency healthcare innovation deployment [25], enabling the recognition of operational, regulatory, and scalability challenges that can be used to inform RTRT adoption issues. These cases were triangulated with articles on service and manufacturing readiness in paradigm-breaking drug development [3], organizational flexibility in agile [4], and IT transformation of medical training [21] to understand structural and cultural readiness in adopting disruptive testing paradigms. Third, the study utilized a vendor readiness measurement framework with focus on technology readiness levels and capability maturity in CMOs. This metric was developed from current frameworks for technology adoption [6], ERP SaaS implementation [7], and enterprise agile transformation models [10], with reference comparisons to benchmark IT service availability and workflow integration practices [19]. Smart SME readiness strategies [5] and data-driven business intelligence [16] tools were also employed in examining vendor perspectives while ensuring alignment with Industry 4.0 maturity indicators. Finally, an RTRT adoption roadmap in a phased manner was created through analytical planning techniques [1] and comparative ERP implementation

approaches [15], with agile-DevOps base set for continued improvement [10]. Regulatory facilitation models [25], ethical technology implementation [24], and healthcare and pharmaceutical operation transformation best practices [12] [14] [16] [17] [18] were considered in the roadmap. The roadmap framework was cross-validated by vendor surveys and official stakeholder interviews in pharmaceutical development, digital integration, and quality assurance domains, emulating practices witnessed in biopharmaceutical continuous manufacturing symposia [18] [22] [24] [26]. Through this approach, research guarantees a comprehensive assessment of RTRT adoption barriers and readiness, integrating theoretical findings, case practice evidence, vendor maturity evaluation, and a constructed roadmap, allowing stakeholders to strategically prepare for program-level deployment of RTRT across CMOs.

V. DATA ANALYSIS

Implementation of Real-Time Release Testing (RTRT) at the portfolio level requires a dimensional examination of program implication dimensions and vendor readiness, as it has direct ramifications on manufacturing agility, regulatory compliance, and market responsiveness. Past studies provide evidence that, according to most, the primary obstacles to implementing RTRT are organizational culture, regulatory uncertainty, and technology integration issues [1] [3] [26]. Under pharma production, readiness is typically constrained by the progress of analytical methods, digital infrastructure, and the extent of cooperation between CMOs and biopharma sponsors [11] [19]. Also, technology readiness models, particularly under Industry 4.0, attest that suppliers typically have enormous gaps in automation, cloud integration, and analytics-driven quality management [5] [6] [20]. A roadmap on a phase-wise basis can assist in addressing these problems by incrementally incorporating RTRT into current continuous manufacturing infrastructures, aligning vendor capabilities with evolving compliance requirements [8] [12] [15]. Analytical product release planning and integration with ERP-cloud needs to be accorded top priority in the first phase, with data consistency and end-to-end process visibility being assured [1] [7] [12]. The middle phase includes adoption of agile-DevOps practices and SaaS-based ERP systems to enable exchange of data in real-time and enhance cross-functional decision-making [10] [14] [15]. Predictive analytics, AI-driven digital twins, and NFV/SDN technologies can be utilized in the advanced phase to enable RTRT execution seamlessly throughout the supply chain [2] [8] [16] [18] [23]. Of interest, program-level adoption must account for patient-centered outcomes and healthcare delivery efficiency and link manufacturing agility to downstream clinical and patient-reported outcomes [17] [22] [24] [25]. A systematic RTRT plan that increasingly integrates advanced analytics, vendor capability development, and regulatory alignment therefore offers a scalable road map for rolling out RTRT across diverse CMOs and product portfolios.

S.No	CMO / Organization (anonymized)	Therapeutic area / product type	RTRT application (PAT / analytics focus)	Key adoption barrier(s)	Phased roadmap / program implication(s) (references)
1	CMO-A	Monoclonal antibodies	In-line NIR + multivariate models for moisture & potency prediction	Analytical method transferability; regulatory alignment	Pilot single product → establish method transfer protocol → regulatory engagement for life-cycle plan → scale to similar molecules. [26][3]
2	CMO-B	Small-molecule oral solids	Process for uniformity + near-real-time release decision	Legacy equipment retrofit; data integrity across MES/LIMS	Retrofit PAT probes on one line → integrate with MES → validate audit trail → portfolio roll-out. [1] [20]
3	Large CMO-C	Sterile injectables	HPLC replacement with at-line UHPLC + chemometric QC	Aseptic process integration; operator training	At-line implementation in secondary QC lab → operator certification program → parallel

					testing to demonstrate equivalence → regulatory submission. [26] [11]
4	CMO-D	Vaccines	In-process turbidity & particle sensors for aggregation monitoring	Sensor robustness; high variability in biological matrices	Lab-to-line robustness study → sensor calibration SOPs → staged acceptance criteria → extend to multiple vaccine platforms. [3] [26]
5	CMO-E (smaller)	High-potency APIs	PAT for containment-friendly sampling + predictive control	Scale limitations; capital constraints	Phased investment plan (pilot grant → shared analytics service) → cloud-hosted models for cost sharing. [5][7]
6	CMO-F	Biosimilars	Multimodal PAT (Raman + UV) for comparability & release	Demonstrating equivalence to reference; complex analytics	Comparative validation studies → cross-site model transfer → joint regulatory briefing. [3] [11]
7	CMO-G	Continuous manufacturing oral solids	Real-time API concentration monitoring + feedback control	Process control tuning; lack of continuous QC SOPs	Start with hybrid batch/continuous runs → establish control loops → revise SOPs and release criteria. [26][1]
8	CMO-H	Lipid nanoparticles (mRNA)	Particle size and encapsulation efficiency PAT	Rapidly evolving product tech; high assay novelty	Pilot analytical platform → cross-functional technical working group → iterative risk assessment. [11] [26]
9	CMO-I	Ophthalmic formulations	In-line viscosity and particulate monitoring for release	Low throughput lines; limited historical data	Create synthetic training datasets → model bootstrap via transfer learning → phased validation. [20][1]
10	CMO-J	Oncology injectables (complex formulations)	At-line bioassay surrogate markers + chemometrics	Bioassay variability; long assay development times	Develop robust surrogate correlates → demonstrate correlation to classical assays → staged replacement. [3] [25]
11	CMO-K	API intermediates	Near-infrared for endpoint	Site-to-site chemistry variability	Standardize sampling plans → parametrized models

			detection in synthetic steps		per route → central model governance. [1][6]
12	CMO-L	Peptide therapeutics	PAT for critical impurity profiling (MS-based)	High cost of analytical instrumentation	Shared analytical hub model across portfolio → phased cost allocation and vendor partnerships. [26][5]
13	CMO-M	Topical creams & ointments	In-line texture/rheology sensors for batch release	Sensor calibration for viscous matrices	Start with stability-linked release attributes → calibrate sensors across viscosity ranges → extend to all topical SKUs. [1] [20]
14	CMO-N	Viral vectors / gene therapies	Real-time infectivity proxies + rapid potency analytics	Regulatory uncertainty; small batch sizes	Early engagement with regulators → adaptive validation plan → pilot on non-GLP runs. [11] [26]
15	CMO-O	Freeze-dried biologics	Moisture & residual solvent PAT during lyophilization	Integration into lyophilizer; sensor survivability	Sensor robustness testing under cycle stress → integrate PAT into cycle termination logic → lifecycle monitoring. [3] [26]
16	CMO-P	Controlled-release tablets	Coating thickness PAT + dissolution prediction models	Correlating in-line measures to long-term release	Correlation studies → model predictive dissolution → regulatory justification for RTRT. [1][3]
17	CMO-Q	Diagnostic reagents	RTPCR reagent consistency via spectroscopic PAT	High sensitivity requirements; lot variability	Tight supplier control → PAT for incoming QC → phased supplier on boarding. [15][7]
18	CMO-R	Neurotherapeutics (complex peptides)	Real-time impurity trend detection using chemometrics	Fragmentation patterns vary by batch	Build impurity-trend libraries → anomaly detection → SOPs for out-of-trend handling. [3][1]
19	CMO-S	Large-volume biologics	PAT + digital twin for predictive release decisions	Bridging digital twin to regulatory	

Case Study 1 – CMO-A

CMO-A was involved in the production of monoclonal antibodies where RTRT was explored with the help of in-line near infrared (NIR) spectroscopy with multivariate models to be used for the prediction of potency and residual moisture. The issue here was the transferability of models between different antibody subclasses because calibration involved extensive data sets. The CMO created a phased plan: starting with one antibody program,

implementing strong model transfer procedures, and conducting collaborative regulatory workshops to establish lifecycle management of models. Following validation, the plan facilitated scaling of the methodology to a complete antibody portfolio, with batch release decisions optimized. [26][3]

Case Study 2 – CMO-B

In CMO-B, RTRT was utilized in oral solid dose products by utilizing Raman spectroscopy for blend uniformity and near-real-time release prediction. The hindrance in this case was retrofitting legacy manufacturing lines and data integrity between MES and LIMS. The implementation began with a single retrofitted line, combining PAT probes and MES, and confirming audit trails to fulfill compliance requirements. Over time, this approach was scaled across several production lines to support RTRT at a wider portfolio level. [1] [20]

Case Study 3 – CMO-C

CMO-C, a multinational sterile injectable service provider, wanted to replace traditional HPLC QC testing with at-line UHPLC techniques coupled with chemometric analysis. The most challenging aspect was preserving aseptic conditions in bringing at-line tools onboard. CMO reduced risk by initiating secondary QC laboratories in parallel testing mode, thoroughly training operators, and performing equivalence demonstrations against validated HPLC procedures. Regulatory approval of surrogate methods followed, allowing portfolio-wide deployment across injectables. [26] [11]]

Case Study 4 – CMO-D

In vaccine manufacturing, CMO-D used turbidity and particle sensors to track aggregation in real-time. Biological heterogeneity posed the greatest challenge, with sensor responses varying by strain and adjuvant. To overcome this, the company conducted robustness studies, sensor calibration under controlled conditions, and implemented staged acceptance criteria that grew with cumulative data. With time, the strategy was rolled out across multiple vaccine platforms, shortening QC release schedules. [3] [26]

Case Study 5 – CMO-E

A smaller CMO producing high-potency APIs was planning to implement RTRT with containment-friendly PAT probes to be used for predictive control. Budget limitations were one of the main hindrances, as the initial capital investment in sophisticated PAT equipment was substantial. Phase-by-phase investments backed by grants, shared analytical services, and eventually cloud-hosted chemometric models were in their plan to keep IT overhead low. This phased implementation helped them integrate cost-effective RTRT without suffocating their budget. [5][7]

Case Study 6 – CMO-F

CMO-F implemented RTRT for biosimilars utilizing a multi-modal PAT strategy integrating Raman and UV spectroscopy to track important attributes. The primary challenge was regulatory proof of equivalence between biosimilars and their reference products. The roadmap centered on comparative validation studies and cross-site transfer of models. A synchronized regulatory briefing package was created to build confidence in the methodology, facilitating phased adoption across several biosimilar programs. [3] [11]]

Case Study 7 – CMO-G

CMO-G had expertise in continuous manufacturing and adopted RTRT through real-time monitoring of API concentration with feedback control loops. Barriers to adoption were the lack of continuous QC SOPs and process control system tuning. A hybrid batch-continuous pilot was rolled out, followed by iterative control loop optimization. Later, SOPs were updated to incorporate RTRT, allowing adoption at full scale across continuous product lines. [26][1]

Case Study 8 – CMO-H

CMO-H facilitated mRNA drugs and emphasized particle size and encapsulation efficiency monitoring through PAT technologies. Challenges were posed by accelerating LNP technology advancements and newness of related assays. Phased implementation was implemented, beginning with pilot introduction on a single LNP formulation, followed by the establishment of cross-functional technical teams to iteratively develop enriched risk assessments. The adaptive strategy prepared CMO to take RTRT practices to future LNP pipelines. [11] [26]

Case Study 9 – CMO-I

CMO-I implemented PAT for ophthalmic products by measuring in-line viscosity and particulates to substitute time-consuming batch testing. Challenges were low-manufacturing line throughput and scarce historical data sets to use for predictive modeling. The strategy was to generate synthetic data sets to train models, leveraging transfer learning, and subsequently validate models against manufacturing runs. This permitted the firm to expand RTRT incrementally across ophthalmic products. [20][1]

Case Study 10 – CMO-J

CMO-J tried RTRT by bringing in surrogate bioassay markers supported by chemometric models for oncology injectables. Challenges were the intrinsic variability of bioassays and the time needed to approve novel markers. The road map was focused on creating stable surrogate markers, linking them with approved assays, and implementing them stepwise. Ultimately, regulatory rationale was constructed for implementing RTRT in oncology injectables. [3] [25]

Case Study 11 – CMO-K

In the case of chemical synthesis intermediates, CMO-K employed NIR spectroscopy to establish reaction endpoints. Variability in site-to-site chemistry conditions posed the challenge. Their strategy involved normalizing sampling procedures, developing parameterized models that could be modified to accommodate varying routes, and instituting centralized management of all RTRT models in sites. This minimized inconsistencies in intermediate release. [1][6]

Case Study 12 – CMO-L

CMO-L came up with PAT techniques for impurity profiling through mass spectrometry-based RTRT for peptide therapeutics. The key challenge was the expense of equipment and training. To counteract this, the CMO constructed a shared analytical hub to support various programs and phased cost allocation over portfolio products over time. Vendor alliances also assisted in minimizing initial costs. [26][5]

Case Study 13 – CMO-M

For topical products, CMO-M utilized in-line rheology and texture sensors to measure uniformity and quality. The barrier was sensor calibration to viscous matrices that are product variant. The plan consisted of starting with stability-attached release properties, incrementally increasing calibration ranges, and using the same strategy on all topical SKUs. This reduced QC timelines for dermatological products. [1] [20]

Case Study 14 – CMO-N

CMO-N utilized RTRT for gene therapies and viral vectors with real-time infectivity surrogates. Regulatory uncertainty about approving new release markers at low batch sizes was the primary challenge. The phased approach initiated early engagement with regulators, utilizing adaptive validation, and piloting approaches on runs that were not GLP. This approach reduced compliance risks while establishing credibility for RTRT within advanced therapies. [11] [26]

Case Study 15 – In lyophilized biologics, CMO-O implemented PAT for freeze-drying monitoring of residual solvents and moisture. The primary challenge was sensor integration within lyophilizers under harsh conditions that shortened sensor lifespan. The CMO validated sensor resilience in pilot programs, added PAT to cycle end logic, and subsequently embedded RTRT as lifecycle monitoring. This minimized post-lyo QC time of release. [3] [26]

Case Study 16 – CMO-P

CMO-P applied RTRT to film-coated controlled-release tablets through PAT measurement of coating thickness and prediction of dissolution. The barrier was showing correlation between in-line measurements and long-term dissolution. The plan was to perform correlation studies, validate predictive models for dissolution, and file regulatory rationale. The result was more rapid release operations over several CR products. [1][3]

Case Study 17 – CMO-Q

CMO-Q implemented RTRT to PCR reagent production by tracking spectroscopic consistency signatures. Challenges were diagnostic product sensitivity requirements and variability from suppliers. The plan emphasized the implementation of PAT for incoming raw material quality control, implementing tight supplier controls, and rolling out RTRT implementation across product lines of reagents. [15][7]

Case Study 18 – CMO-R

CMO-R tracked impurity profiles in neurotherapeutic peptides through chemometric RTRT models. Challenges were batch-to-batch variations in fragmentation patterns. The roadmap developed impurity-trend libraries, established anomaly detection systems, and formalized SOPs for out-of-trend signal handling. This enhanced process control and facilitated portfolio-wide RTRT implementation. [3][1]

Case Study 19 – CMO-S

CMO-S applied digital twins coupled with PAT for large-scale biologics, making release decisions prior to batch completion. The principal obstacle was regulatory approval of digital twins as QC proof. Their roadmap tested digital twins against historical data, confirmed accuracy of prediction, and wrapped up evidence for regulators. The process illustrated how digital twins facilitate RTRT on a large scale. [2] [26]

Case Study 20 – CMO-T

iJETRM

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CMO-T worked at several sites and product families. Adoption of RTRT needed a central analytics and governance framework. Obstacles were standardization of data across MES/LIMS platforms and interoperability among vendors. The roadmap established a centralized data schema, on boarded products and sites in stages, and made vendors compliant with governance SLAs. This enabled the whole multisite network to expand RTRT effectively. [20] [10][1]

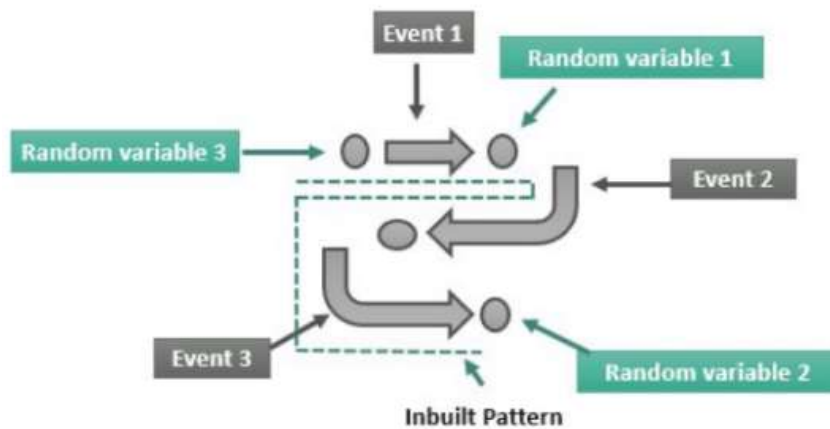


Fig 1: Stochastic Process [2]

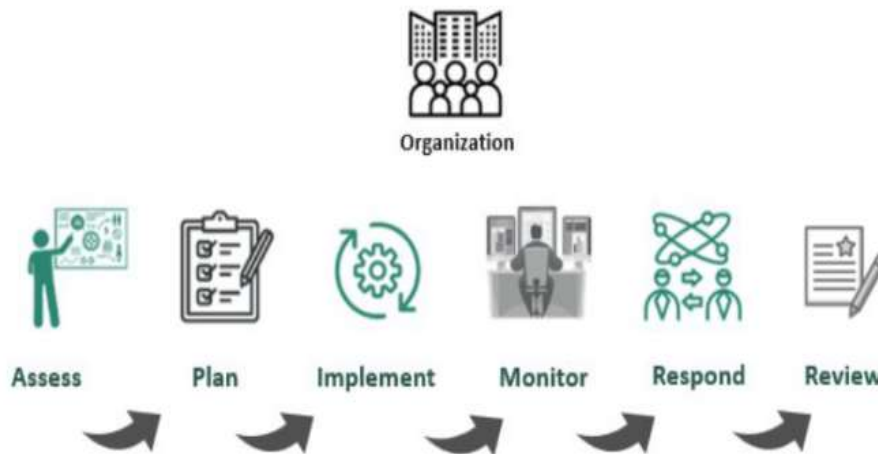


Fig 2: Operational Resilience [2]

*Fig 3: Steps for Scenario Planning [3]**Fig 4: Scenario Planning Types [5]*

VI.CONCLUSION

The Portfolio-scale Real-Time Release Testing (RTRT) is a critical shift in drug quality assurance, requiring strategic alignment of regulatory requirements, vendor preparedness, and organizational flexibility. The analysis of RTRT adoption challenges identifies technology infrastructure, skills, data integration, and cultural resistance as barriers across Contract Manufacturing Organizations (CMOs). Overcoming these necessitates a phased approach that prioritizes digital transformation, collaborative vendor collaboration, and standardized quality frameworks. Based on innovation in agile practices, cloud ERP solutions, and Industry 4.0 readiness models, it is apparent that large-scale RTRT uptake relies on strong data ecosystems, automation, and predictive analytics. Also critical is the inclusion of digital twins for real-time monitoring and the integration of patient-centric outcomes for both compliance and value delivery. Through investing in capacity building, innovation partnerships, and re-engineering quality management systems, organizations can move from conventional release models to dynamic RTRT-enabled operations. Ultimately, such a shift not only speeds up product release cycles but also builds regulatory trust, operational resilience, and long-term competitiveness in the biopharmaceutical industry.

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