BARRIERS TO INNOVATION IN PHARMACEUTICAL MANUFACTURING

Insights from Five Case Studies

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In April 2023, ISPE launched a survey to understand the sources of barriers to technological innovation within the pharmaceutical industry. This survey is part of an expansive and significant initiative by ISPE, Enabling Global Pharma Innovation: Delivering for Patients, which aims to promote consistent and harmonized interpretation and implementation of guidelines issued by the International Council for Harmonisation (ICH). The overarching goal is to improve global patient access to innovative medicines and technologies.

The survey consisted of three parts: multiple choice questions focused on demographic and summary-level innovation experience; specific examples of innovation development experience, and expanded case descriptions. The results have been published on ISPE's regulatory webpage [1], fulfilling the third component of the initiative's first phase by presenting more specific information in case studies that illustrate innovation experience and associated challenges.

The purpose of this ISPE initiative is to understand the circumstances and confirm the contributing factors that can present barriers to innovation, including the specific origins, extent, and magnitude of challenges and barriers that limit and reduce the development and implementation of innovative technologies [2]. Although regulatory authorities globally have embraced technological innovation to improve product quality assurance, accelerate product development, reinforce supply chain reliability, and increase patient access to medicines, there are still economic and regulatory barriers that discourage the development and implementation of new, innovative technology globally.

In fact, several regulatory authorities—including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the UK Medicines and Healthcare products Regulatory Agency (MHRA)—have actively promoted the adoption of innovative and advanced pharmaceutical manufacturing technology by introducing regulatory options that enable industry to develop and implement advanced manufacturing technologies. While it is incumbent on industry to modernize manufacturing processes to improve productivity and to strengthen confidence in product quality assurance, the conspicuous lack of global regulatory harmonization diminishes incentives for industry to invest in innovation, which indirectly limits access to safe, effective, and quality drug products to patients globally.

OVERVIEW OF CASE STUDIES

The five case studies described herein demonstrate individual company investments in new, innovative technologies that are designed for the manufacture of products intended for global markets. They also reflect the industry's enthusiasm to embrace the global regulatory challenges associated with implementation. While their specific experience and observations include a measure of success, particularly with respect to regulatory interactions, many challenges have been highlighted. These case studies reflect and exemplify findings from the ISPE survey, which include:

Regulatory Authorities

Interactions with multiple regulatory authorities take time and relatively large numbers of resources. Among regulatory authorities, the US FDA is considered the easiest to engage with because of its well-established Emerging Technology Program (ETP) and the Center of Biologics Evaluation and Research's (CBER) Advanced Technology Team (CATT) as well as its capacity to review and shepherd innovative proposals through the existing regulatory framework.

Industry Collaboration

While EU regulatory authorities are reluctant to discuss technological innovations without linking them to a specific product, which is considered a missed opportunity to enable and endorse platform technology. However, from time to time, they have entertained discussions about technological significance in the absence of specific product applications. This is an opportunity for regulatory authorities to reinforce the importance of collaborative engagements with industry by highlighting how they are working with industry to advance innovative technologies through the EMA's Quality Innovation Group (QIG), ETP/CATT. The QIG's Listen and Learn Focus Groups have been a welcome opportunity for engagement.

Duplicate and Redundant Manufacturing

There is concern with duplicate andredundant manufacturing and testing even after an innovation is approved in an application. Duplicative and redundant testing introduces unnecessary delays and increases resource demand. It has also been cited as a major barrier to investing in this new technology.

Transparency

Transparency of timelines for commercial implementation is necessary to fully realize productivity and return on investment (ROI) and it could be useful for regulatory engagement. Balancing the challenges associated with time constraints and resource requirements is particularly challenging in early research and development programs.

Innovative Technology

Innovative technology is typically intended to be global in scope even though it may be pursued and implemented incrementally from one region to another. For example, if global regulatory divergence dramatically increases the time and costs of developing customized applications for an innovative glass vial, that impact falls directly on patients and caregivers who will not benefit from reductions in broken vials that could result in drug shortages.

SUMMARY OF CASE STUDIES

Case Study 1: Azurra FAB

Case study 1 features a fully robotic aseptic filling line with mobile support robots (called "butler" robots). It is at an early phase whenrequests have been made to multiple regulatory authorities to introduce the concept. Due to high capital cost and long lead times, the concept has not been associated with any specific product; although, it should be widely applicable as a platform for aseptic products assembled into vials, syringes, and cartridges.

Thus far, only the US FDA has agreed to face-to-face discussions and accepted the concept into its Emerging Technology Program (ETP). The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom has provided written input and may interact and consult with the US FDA. The European Medicines Agency (EMA) and a specific member state's agency, Italy, have declined to discuss the project because it is not associated with any specific product. This indicates EU agencies are reluctant to discuss technology innovations without them linking to a specific product.

Table 1: Summary of case studies.

	CASE	DESCRIPTION
1	Azurra FAB	A fully robotic aseptic filling line with mobile support robots (called 'butler' robots)
2	Multi-Attribute Method (MAM)	A high-resolution, LC-MS-based, advanced peptide mapping analytical method designed to replace several current methods typically used for characterization and routine testing of biopharmaceutical products
3	Maholo Robotic Cell Culture Automation System	An adaptable cell culture automation system that can perform a series of cell culture operations, i.e., cell seeding, media change, passaging and harvest, etc. without human intervention
4	Application of Process Systems Modelling for Pharmaceutical Process Development and Manufacturing	A platform technology for process control strategy and design including use of digital twins and hybrid models
5	Valor® Glass	An alternative borosilicate glass vial that effectively reduces breakage and improves productivity, product quality assurance and supply chain reliability

CASE STUDY 2: MULTI-ATTRIBUTE METHOD

Case study 2 describes the adoption of the Multi-Attribute Method (MAM): a high-resolution, liquid chromatography/mass spectrometry (LC-MS)-based advanced peptide mapping analytical method designed to replace at least 4 methods typically used for characterization and routine testing of biopharmaceutical products. One product was selected for this project starting at the early clinical stage. This was a complex and resource-consuming project that required qualification, validation and compariison with existing methods.

The project was risk reduced by engagement with multiple health authorities, i.e., US FDA, Japan Pharmaceuticals and Medical Devices Agency (PMDA), and China National Medical Products Administration (NMPA) (formerly CFDA). This included direct meetings as well as iterative exchanges of information. The project was accepted into the US FDA ETP (because the CATT and QIG were not established when the innovation was initially proposed). The

sponsor has received health authority approval or "safe to proceed" for clinical trial applications in 32 countries, including harmonized criteria with respect to MAM.

During clinical development, the US FDA requested that the company maintain side-by-side testing of MAM and conventional methods for an extended period, This was despite extensive characterization data submitted for agency review. Side-by-side testing is resource intensive, undermines the impact of innovative approaches, and discourages industry investment in emerging technologies.

CASE STUDY 3: MAHOLO ROBOTIC CELL CULTURE AUTOMATION SYSTEM

Case study 3 focused on Maholo, a unique, novel, and adaptable humanoid dual arm robotic system that can perform a series of cell culture operations, including cell seeding, media change, passaging, and harvesting. By precisely and consistently manipulating peripheral equipment (i.e., centrifuge, microscope, digital pipettes, cell counter, refrigerator, and CO_2 incubator) within an unmanned environment, similar to or better than a skilled human operator. The system can also perform a series of cell culture operations. Maholo is intended to be implemented as a platform technology that has yet to be introduced for a product application.

Interactions with EMA QIG were timely and productive providing positive and supportive feedback on appropriate cGMP necessary for robotic automation as well as potential use with AI technologies. Considering this automation for highly selective gene and cell therapies significantly reduces human intervention and the potential risk for quality issues, the company is concerned that demand for comparability data will be required during the discussion of automation, which may pose a challenge. In addition, there will likely be divergent regulatory expectations for the implementation of this innovation globally. Therefore, it is important for major regulatory authorities and the pharmaceutical industry to actively promote and communicate future-oriented technology development and opinion consolidation. This is the entire pharmaceutical industry can progress towards innovative technology development for the benefit of patients.

CASE STUDY 4: APPLICATION OF PROCESS SYSTEMS MODELING FOR PHARMACEUTICAL PROCESS DEVELOPMENT AND MANUFACTURING

Case study 4 involved platform technology for process control strategy and design, including the use of digital twins and hybrid models.

While there are limited precedents and experience using model-based approaches for low-to moderate- risk product developments, the current intent is to focus on postmarketing applications for process control using digital twins and hybrid models (mechanistic and empirical) as a platform for a broad portfolio of products. These models improve process efficiency, product quality, use of prior knowledge, speed of development, and commercialization.

As such, for some well-established mechanistic "low-impact" models, development and implementation timelines are relatively short (1 to 2 years). For complex models and applications, current estimates are 5 tos7 years for development and initial commercial implementation. Timelines for subsequent deployment should be significantly improved; however, this is highly dependent on the initial success of the leading program.

Midway through the development stage, engagement with the US FDA and EMA through formal meetings served primarily as an opportunity to share information. Engagement with the EMA QIG was highly effective and led to substantive feedback that was then directly reflected in the "Preliminary QIG Considerations regarding Pharmaceutical Process Models" published by the Quality Innovation Group (QIG) of the European Medicines Agency (EMA). While no engagement with the US FDA ETP, the QIG is sharing information with the US FDA and PMDA on this subject area. Establishing a path for joint or parallel scientific input on emerging technologies across multiple major regulatory authorities would enable and expedite implementation of innovation.

CASE STUDY 5: VALOR® GLASS

Case study 5 featured an alternative borosilicate glass vial that effectively reduces breakage and improves productivity, product quality assurance, and supply chain reliability.

Valor®™ glass is an innovative glass vial substitute/replacement for Type 1 (USP) borosilicate glass vials. It is composed of elements used in Type I borosilicate containers (e.g., silica, alumina, etc.) with a boron-free formulation. This formulation eliminates delamination, improves overall extractables and leachables performance and eliminates in-line breakage that routinely results in product contamination and loss, disruptive and delayed manufacturing and drug shortages. The use of this innovative glass effectively improves productivity, product quality assurance and supply chain reliability. In addition, it reduces the potential for glass vials breaking during shipping, at pharmacies, hospitals, care centers, and in patients' homes.

The innovative glass vials were intended to be implemented as a platform replacement for an entire portfolio of innovative, approved, and generic products. Essential "DOE" risk assessment of the 75 products targeted for implementation was developed to demonstrate comparability/equivalence for each category of product families, which would limit the need to perform a complete battery of tests, including developing stability data on every product.

Interactions with the US FDA Emerging Technology Team (ETT), part of the ETP, were productive and largely supported the initial proposal to identify the appropriate sets of critical quality attributes that are representative of different categories of drug products and to develop an analytical strategy to demonstrate comparability and equivalence for each category of product families (the QIG and CATT were not established when the innovation was initially proposed). However, subsequent engagement with representative assessors from the US FDA triggered a relatively conservative response at the time of regulatory submission.

As a result, the regulatory strategy was revised to incorporate

several additional criteria and an expectation that stability results for all 75 products within the product family would accompany all post approval applications. This significantly increased the duration for implementation. Despite compelling comparative data provided by the glass vial manufacturer, the US FDA assessors remained concerned with "show us the product data" rather than extrapolating platform data. This experience is an example of the challenges of being the first to come forth with new technology.

The outcome was, for the US applications, a qualified success in that a measure of regulatory flexibility and reduced timelines for implementation was considered feasible, though the potential for maximum benefit was not realized.

CONCLUSION

In general, these case studies provide, confirm, and amplify the results from the recently published ISPE report, "ISPE Global Pharmaceutical Innovation Survey Findings: A Review [1]" which examines barriers to innovation. In general, return on investment is a critical factor in decisions regarding development and implementation of innovative technologies. Observations from these case studies indicate that even at the early stage of evaluating an innovation, global regulatory divergence is a consideration with an associated cost. Each case study projected that regulatory reliance and alignment among regulatory authorities could effectively offset the investment risk, and could facilitate global implementation of innovative technologies.

APPENDIX

Case Study 1: Azurra FAB

Project description

The innovative Azzurra FAB is a fully robotic aseptic filling line with mobile support robots (called "butler" robots). Several regulatory agencies are aware of the new innovation, so there is not an issue with ISPE sharing this information with other agencies. The purpose of this project, and the genesis of the Azzurra FAB, is to overcome the many current challenges with the existing aseptic filling technology; such as long lead times, high capital equipment costs and the extensive use of gloves at commercial scale. The intent is to deliver a paradigm shift in drug product manufacturing facility design and operation.

- The primary business drivers for the innovation were cost, lead time and a more robust quality solution that eliminates the risk of human interaction.
- The decision to proceed with the development and implementation of innovative technology was based on the challenges of long lead times and high costs with limited standardization experienced during the COVID-19 pandemic.
- The innovative technology was not developed with a specific product application or a post approval change/supplement.
- The innovation is intended as a platform for a range of product portfolios containing vials, syringes and cartridges.
- The development of the Azzurra FAB is ongoing, based on feedback from regulatory agencies, with some degree of complexity when removing the need for human interaction.
- The concept of the Azzurra FAB, including the collaborative approach with industry and regulatory agencies, has been presented at ISPE conferences in Asia, Europe and the US with some positive and encouraging feedback.

Engagement with regulatory authorities

- The MHRA, the US FDA, and the EMA were approached prior to the implementation of the Azzurra FAB in July 2023.
- The Azzurra FAB was accepted into the US FDA Emerging Technology Program (ETP) in October 2023 with an initial meeting with the ETT in January 2024.
- The MHRA provided a written response to on questions submitted to the Innovation Office November 2023. The MHRA was invited to the US FDA meeting in January 2024 and initially accepted the invitation but then had to decline at the last minute due to conflicting priorities.
- When it was clear the EMA Quality Innovation Group (QIG) was not going to respond to the application, an application was made via the local Italian Medicines Agency (AIFA) Innovation and Scientific Advice Office in March 2024. AIFA responded in April 2024 declining the opportunity to meet due to there not being a specific product to review as part of the application. AIFA instead decided the alternative scientific advice procedure would be a more appropriate route.
- The respective regulatory authorities have not issued approvals for the Azzurra FAB due to the continued development of the innovative technology.
- There have been no pre-approval inspections triggered by the innovative technology applications due to the continued development of the innovation technology and no specific products selected.
- The EMA and AIFA do not seem to be receptive to innovative technologies that do not come with a specific product to review. This is definitely a barrier to innovative technologies when trying to obtain feedback and support during the early stages of development. Fortunately, the MHRA and the US FDA are more forward thinking and understand the need for early engagement and support. The US FDA Emerging Technology Program (ETP) in particular seems to be the most advanced and effective program in this respect based on the interaction with several different agencies.

Opportunities and challenges

- For future innovative technologies, there is a reluctance to engage the EMA and instead to focus on other regulatory authorities.
- The EMA could adopt the same or similar approach as the US FDA by supporting and encouraging innovative technologies with or without a specific product. The EMA's position represents a missed opportunity that will not help develop and promote innovative technologies that have the potential to drive significant opportunities.

Case Study 2: The Multi-Attribute Method

Project description

Case study 2 involved method development and regulatory acceptance of the multi-attribute method (MAM): a high-resolution, LC-MS-based, advanced peptide mapping method [3-6]. The business drivers for this innovation included increasing the efficiency of drug substance and drug product release testing, and the introduction of an advanced analytical capability. The decision to proceed with development and implementation of MAM was driven by potential resource savings due to increased testing efficiency and a reduced number of test methods on the specification.

- MAM was filed as a new product application in clinical trial applications continuing through phase 2.
- It was intended for widespread use across the company portfolio, but one program was used to establish a regulatory precedent.
- The timeline for the project was driven by the goal of regulatory acceptance of MAM for the replacement of conventional methods.
- The level of complexity was high, with extensive characterization, side-by-side testing, and detailed method qualification performed to support the replacement of conventional methods with MAM.
- The project is viewed as a success with further assessment on-going.

Engagement with regulatory authorities

- The company applied to and was accepted into the US FDA CDER Emerging Technology Program (ETP).
- It met with the US FDA on multiple occasions during clinical development, including on-site.
- The company submitted extensive characterization data using MAM for Agency review, and it responded to written requests for information.
- Besides the US FDA, the company engaged with other global health authorities (including Japan's PMDA and China's National Medical Products Administration (NMPA) (formerly CFDA) through written correspondence and presentations intended to promote awareness of MAM and provide information on development.
- The interactions included direct meetings as well as iterative exchanges of information. The meetings and exchanges of information were very productive and health authorities, particularly the US FDA, provided significant feedback.
- To date, the company has received health authority approval or "safe to proceed," including harmonized criteria with respect to the MAM for clinical trial applications, in 32 countries: : Argentina, Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Greece, Honk Kong, Hungary, Italy, Japan, Korea, Latvia, Mexico, Netherlands, Poland, Romania, Russian Federation, Slovakia, South Africa, Spain, Switzerland, Taiwan, Turkey, Ukraine, United States.
- The process was extremely time and resource intensive. During clinical development, the US FDA requested that the company maintain side-by-side testing of MAM and conventional methods for an extended period of time, despite extensive characterization data submitted for agency review.
- Side-by-side testing is resource intensive, undermines the impact of innovative approaches, and discourages industry investment in emerging technologies.

Opportunities and challenges

- Establishing clinical trial application approvals for the precedent product took significant time and resources, especially with the expectation of side-by-side testing with the MAM and conventional methods, which was discouraging from a business perspective.
- Establishing clear near-term and long-term goals with a well-defined scope is recommended. In general, maximizing cross-functional alignment internally on the overall strategy and objectives for an innovative technology will improve and expedite the regulatory strategy globally. Based on the company's experience, no changes to the approach for application to regulatory authorities were warranted.
- Enabling innovation significantly depends on global harmonization among health authorities to offset the business risk. If a technology is accepted in some jurisdictions but not in others, a company is forced to maintain the GMP and regulatory status of both conventional and innovative technologies, which is resource intensive.
- Global regulatory reliance and harmonization will enable and de-risk adoption of innovative technology and encourage industry investment in modernization. Early collaboration amongst regulators to evaluate new technology should be encouraged to speed up the process. Successful global harmonization depends on industry commitment as well as regulatory authority acceptance.
- Industry should ideally support the concept of a single, global dossier, so as not to generate extensive variant submissions (e.g., with redactions for some jurisdictions) based on differing current regulatory expectations. This is difficult to do because the current regulatory expectations for new technology, including the data requirements for submission, are widely divergent.

Case Study 3: Maholo Robotic Cell Culture Automation System

Project description

Maholo is a unique and novel robotic system that can perform a series of cell culture operations consistently and precisely, similar to or better than a skilled human operator. This allows for manipulation of peripheral equipment within an unmanned environment. It is an adaptable cell culture automation system developed by Robotic Biology Institute Inc., Japan. Maholo consists of a dual-arm humanoid robot and equipment necessary for cell culture, including centrifuge, microscope, digital pipettes, cell counter, refrigerator, and CO_2 incubator. The system can perform a series of cell culture operations, such as cell seeding, media change, and passaging and harvest, with a flexible scheduling and without human intervention (i.e., higher process consistency, reproducibility).

Cell therapy manufacturing faces challenges with process consistency, extremely high cost of goods, and dependence on highly skilled operators for manual process operations. This makes it difficult to reproduce and transfer complex processing steps including an operator's motion. The replacement of human operators with Maholo will dramatically reduce the need for human

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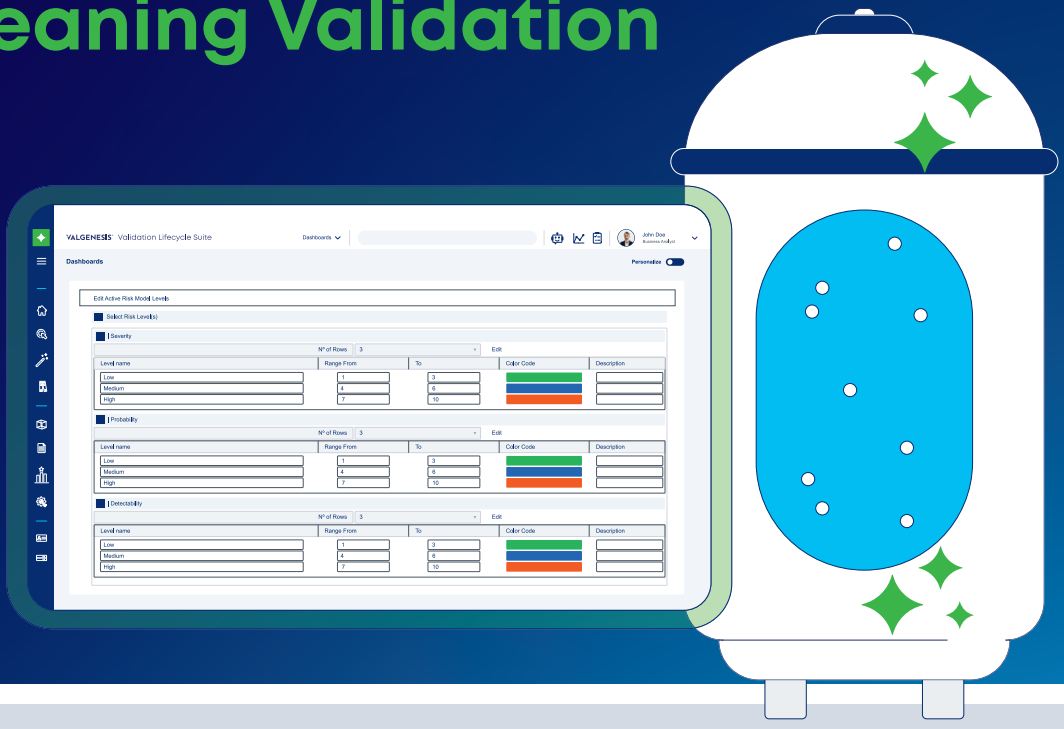

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intervention and thus reduce human error, leading to improved process consistency and decreased cost of goods.

Both the authorities and the industry understand the necessity of automation in the field of regenerative medicine, but there are many challenges that have hindered its progress. Because Maholo is skilled at imitating humans, it can cover everything from research to manufacturing on a single platform. Therefore, it can ensure consistency in development acceleration and quality assurance.

- The challenges and motivations for business arise from the complexity and difficulty of controlling cell-based products, resulting in long development periods and high development costs. The current manual processes that rely on existing know-how are not sustainable for future commercial manufacturing.
- Compared to traditional cell culture automation systems, Maholo can replicate cell culture processing with dual arms and 15-axis construction that (i) flexibly performs delicate cellular differentiation process, (ii) does not require complicated technology transfer, and (iii) enables design and performance of a simple, versatile and sustainable automation system, including use of Maholo software with minimal process-specific optimization of parameters.
- Cellular differentiation process from stem cell starting material requires highly skilled, often complex, and sensitive manual operations within a desired timeframe. Maholo can handle multiple culture procedures suitably and flexibly with highly precise, digitally controlled, sub-millimeter-scale arm motion.
- Maholo can imitate human operations using its dual arms, thereby minimizing process development. This means that a process developed with human operators can easily be translated to an automated process performed by Maholo. Once an operational motion by Maholo is created, the motion is saved and becomes transferrable digital data. Therefore, manual process steps do not require specific process transfer routinely required for training and qualification of human operators. This leads to reduced risk of human error and operational failure during process development and process technology transfer.
- General closed equipment and conventional automation systems are typically "custom" designed for specific/targeted products and are often limited with respect to broad applications and use. Additionally, for GMP manufacturing, conventional automation systems require "locking" manufacturing processes and then conducting a detailed, customized, design for hardware use. This approach is often not feasible for cell therapy products, especially in the early development stage. With the Maholo system, a customized hardware design is not necessary and operators can simply generate culture processes by combining commands of motions.
- Improvement in the rate of cell production will clearly reduce the manufacturing cost. The process was digitally made for the automation and will contribute to the reduction of technical transfer from research to manufacturing. This leads to shortening the development period for cell therapy. In addition to the return on investment (ROI) at the device level, this platform is being developed taking into consideration various related investment effects. This includesdevelopment acceleration and mitigation of potential quality risks, as it serves as a consistent platform connecting research to production.
- Maholo is intended to be implemented as a platform technology. If this platform is realized, it is expected to contribute to the acceleration development timelines and expand the product portfolio including improvement of the success rate of seeds that might be previously be terminated due to tech-transfer issues.

Engagement with regulatory authorities

- The EMA QIG and the US FDA CATT meetings were granted and conducted. It is acknowledged that both authorities have strong interest on this type of technology and digital innovations.
- Interactions with the EMA QIG were timely and productive. They provided positive and supportive feedback on the facility design and GMP understanding regarding utilization of robotic automationand Maholo's potential use with AI technologies. Interactions with the US FDA CATT were more educational and informative and helped to improve their understanding. Although limited resources were used to engage the US FDA, the firm had expected and hoped for more specific feedback from the US FDA CATT.

Opportunities and challenges

- Although the discussion is ongoing, in the field of regenerative medicine, there is often a demand to provide comparability data through process changes. We are concerned that similar data and opinions will be required during the discussion of automation.
- It is necessary to proceed with innovative new technologies, even in the absence of sufficient knowledge within the company, the pharmaceutical industry, and regulatory authorities. To obtain understanding and support for internal activities and the application of development themes, we would like to proceed in a manner that allows us to utilize the advice and collaboration of the pharmaceutical industry and regulatory authorities.
- Patients waiting for medicines and treatments exist all over the world, so ideally, they expect this type of innovative technology to be developed globally and promptly. However, due to the current state of regulatory affairs, it is anticipated that opinions may differ by region, which can also cause delays. Therefore, it is important for major regulatory authorities and the pharmaceutical industry globally to actively promote and communicate future-oriented technology development and opinion consolidation, so that the entire pharmaceutical industry can progress towards innovative technology development for the benefit of patients.

Case Study 4: Application of Process Systems Modelling for Pharmaceutical Process Development and Manufacturing

Project description

The primary business drivers for this innovation are improvements in process efficiency, product quality, use of prior knowledge, speed of development and commercialization.

- The organization has estimates of the benefits from a ROI standpoint, however, there is broad awareness that these targets are significant approximations that are subject to technical challenges and the external landscape (i.e., barriers to commercialization globally). It is too early to be able to provide specific breakdowns of business metrics for this broader initiative.
- For process model-based development studies, the company has implemented in limited cases for initial marketing applications. For process control schemes, the company has experience with commercial filings for continuous manufacturing (CM). However, there has not been a broader implementation for other commercial programs. The company's current intent is to focus on post-marketing applications for process control using digital twins and hybrid models (mechanistic and empirical).
- There is a long-term understanding that successful use of this technology would open the doors for greater platform application, particularly across a given modality (e.g., monoclonal antibodies or oligonucleotides). This could lead to very significant application across the company's portfolio (likelihood >50%).
- This area of focus is more of a portfolio of applications broadly comprised under "process modeling." As such, for some well-established mechanistic models being applied for development (i.e., "low impact" models), the development and implementation timelines are quite short (1 to 2 years). For the more complex models and applications, current estimates are on the order of 5 to 7 years for development and initial commercial implementation. The timelines for subsequent deployment should be significantly improved. However, this is highly dependent on the initial success of the leading program.
- The company has already had numerous successful deployments of process models for "low-impact" applications (i.e., process and control strategy design, process monitoring and operator training applications). For higher impact models, it is still too early to make a conclusion on the overall success of the initiative.

Engagement with regulatory authorities

- At mid-stage development, there was engagement with the US FDA and the EMA, both through formal meetings (e.g., project type C in the US) or by other paths (e.g., QIG Listen and Learn (L&L)/closed-door interactions focused meetings of the EMA's QIG).
- The project was accepted by the EMA QIG. We have not formally applied for entry into the US FDA ETP, but have kept the US FDA informed through the QIG, as they are sharing information on this subject area.
- The EMA QIG is a very promising vehicle for interaction. The listen and learn forums are effective at pulling in regulators outside of the EU (e.g., PMDA, US FDA) to ensure general awareness and current industry pain points. Closed door interactions with the QIG were highly effective and led to substantive feedback that was then directly reflected in a published EMA concept paper.
- For medium- and high- impact models other than CM, approvals have not been received or requested for Pre-Approval Inspections (PAIs) for our innovative technology applications.
- While no excessive requests have been received from regulatory authorities, there is some awareness that interpretations on GMP may play a role in divergent requests for Pharmaceutical Quality System (PQS) documentation on audits for low and medium impact models.

Opportunities and challenges

- The commercialization roadmap could be more well-defined in advance, with specific time points for regulatory engagement. This is an industry-wide challenge, with earlier research and development programs and there is always difficulty balancing the degree of timeline and project management with the resource requirements.
- It seems more likely that companies will need to have some regulatory staff to serve as emerging technology liaisons to regulators to maximize the use of the growing repertoire of regulatory tools authorities are offering. In addition, the ability to shepherd the technology through the regulatory process early on will greatly improve the success rate and timelines for successful implementation.
- A key area here is to establish a path for joint or parallel scientific input on emerging technologies across multiple major regulatory agencies. There appears to be some potential for International Coalition of Medicines Regulatory Authorities (ICMRA) to act in this capacity.
- It is often a challenge for industry to balance the need for early regulatory engagement with the overall odds of success within the organization. There is a strong desire to avoid wasting regulators time with projects that have a low likelihood of success. Some of this risk is mitigated by external joint working groups, such as ISPE, where a broader industry agreement on priority can trigger broader engagement with regulators on a specific area of technology.

Case Study 5: Valor® Glass

Project description

Case study 5 featured innovative glass vial substitute/replacement for Type 1 (USP/Ph. Eur.) borosilicate glass vials that significantly reduce\s in-line breakage that routinely results in product contamination and loss and disruptive and delayed manufacturing. The use of this innovative glass can significantly reduce drug shortages.

The innovative glass vials are composed of a proprietary, tempered aluminum/boron borosilicate and coating that imparts increased tensile strength to withstand product fill, lyophilzation, capping, and sealing. The composition of Valor®® glass maintains a glass network of elements used in type I borosilicate containers e.g., silica, alumina with a boron-free formulation that eliminates delamination and improves overall extractables and leachables performance. The use of this innovative glass will effectively improve productivity, product quality assurance and supply chain reliability. In addition, this innovative glass will reduce potential for glass vials breaking during shipping, at pharmacies, hospitals, care centers, and in patients' homes.

- The primary business drivers for the innovation were improved productivity and reduced manufacturing and inventory costs, improved quality assurance, and increased supply chain reliability and patient access.
- The estimated ROI was projected based on short-term adoption and implementation for more than 75 approved innovative and generic small molecule products (see Table 1) and long-term introduction for several innovative small and large molecule products including vaccines. Several anticipated cost savings factored over 5 years were generally estimated.
- The innovative technology was submitted as post approval supplements for approved innovative, and generic products.
- The innovative glass vials were intended to be implemented as a platform replacement for an entire portfolio of innovative, approved and generic products. An essential Design of Experiments (DOE) of the critical attributes representing the 75 products, where extreme, functional categories, reflecting different chemistry, pHs, buffers, etc., was the basis for assessment. Five conditional categories were identified, and extreme representative products were selected from each category family and evaluated under accelerated and extended stability conditions. This approach provided the context and basis for demonstrating equivalence for all other products within each category family to be able to justify applications for CB30s with 3 months of stability data.
- The original anticipated timeline from development of data to demonstrate product comparability and\/equivalence in the innovative vials to actual approval of the first application was approximately 1.4 years and approval of applications for all 75 products was approximately 2 years. This estimate was based on an approach that relied on identifying the appropriate sets of critical quality attributes that are representative of different categories of drug products and developing an analytical strategy to demonstrate comparability and equivalence for each category of product families. The primary goal was to be able to demonstrate comparability and equivalence for each category of product families that would limit the need to perform a complete battery of tests, including developing stability data on every product.
- Science- and risk-based approaches were used to demonstrate application of a platform technology for significant reduction in data requirements and application submission categories. The outcome was, for the US applications, a qualified success in that it allowed for a measure of regulatory flexibility and reduced timelines for implementation.

Engagement with regulatory authorities

- US FDA ETT was engaged through a formal application once the proposed post approval regulatory strategy to develop and implement the platform innovation for multiple products was established and endorsed by multiple internal disciplines. The cross-disciplinary team met with the US FDA ETT initially to present the technical and regulatory approach and subsequently with a team from the US FDA that was represented by several assessors from the Office of Pharmaceutical Quality and representatives from the Office of Generic Products. Additional interactions with specific regulatory assessors were engaged prior to submitting applications.
- The US FDA and EU EMA were contacted. The QIG was not in place at the time this innovation was being developed. At least two interactions with the US FDA were direct, whereas several others were iterative. The primary interaction with EMA Quality Working Party was direct and no further interactions were required thereafter as the EMA largely accepted the proposed regulatory strategy.
- The US FDA ETT accepted the application for innovative technology. The CATT and QIG were not established when the innovation was initially proposed.
- Interactions with the US FDA ETT were productive and largely supported the initial proposal to identify the appropriate sets of critical quality attributes that are representative of different categories of drug products and develop an analytical strategy to demonstrate. The ETT supported, in principal, the plan to demonstrate comparability and equivalence for each category of product families that would limit the need to perform a complete battery of tests, including developing stability data on every product. The US FDA agreed to the proposed 5 product category family equivalence assessments.
- However, subsequent engagement with representative assessors from the Office of Generic Products triggered a relatively conservative response. As a result, although less than normal stability data was required, the regulatory strategy was revised to incorporate several additional criteria. This included an expectation that stability results for all 75 products would accompany all post approval applications. This significantly increased the duration and resource capacity for implementation. From the company perspective, scientific rationale and risk assessments indicated the additional data was unnecessary relative to the risks associated with the vial replacement. In particular, the need to demonstrate appropriate and adequate stability for every product could have been achieved for most products within a family of products through a stability commitment in accordance with the approved stability protocol criteria.

Table 1: Projected savings for 75 products over five years.

Savings Areas	Outcomes	Estimated Savings (US$Milllions)
Product Integrity	No product loss because of broken vials	~17.5
Manufacturing Productivity	No disruptions in manufacturing schedules or delays dues to potential contamination	~36.3
Inventory Control	No disruption of inventory supplies	~2.1
Customer Satisfaction	No broken vials provide assurance of product reliability and continuity	~8.8
Total estimated savings (75 products/5 years)		~64.7

Integration of legacy equipment is easy

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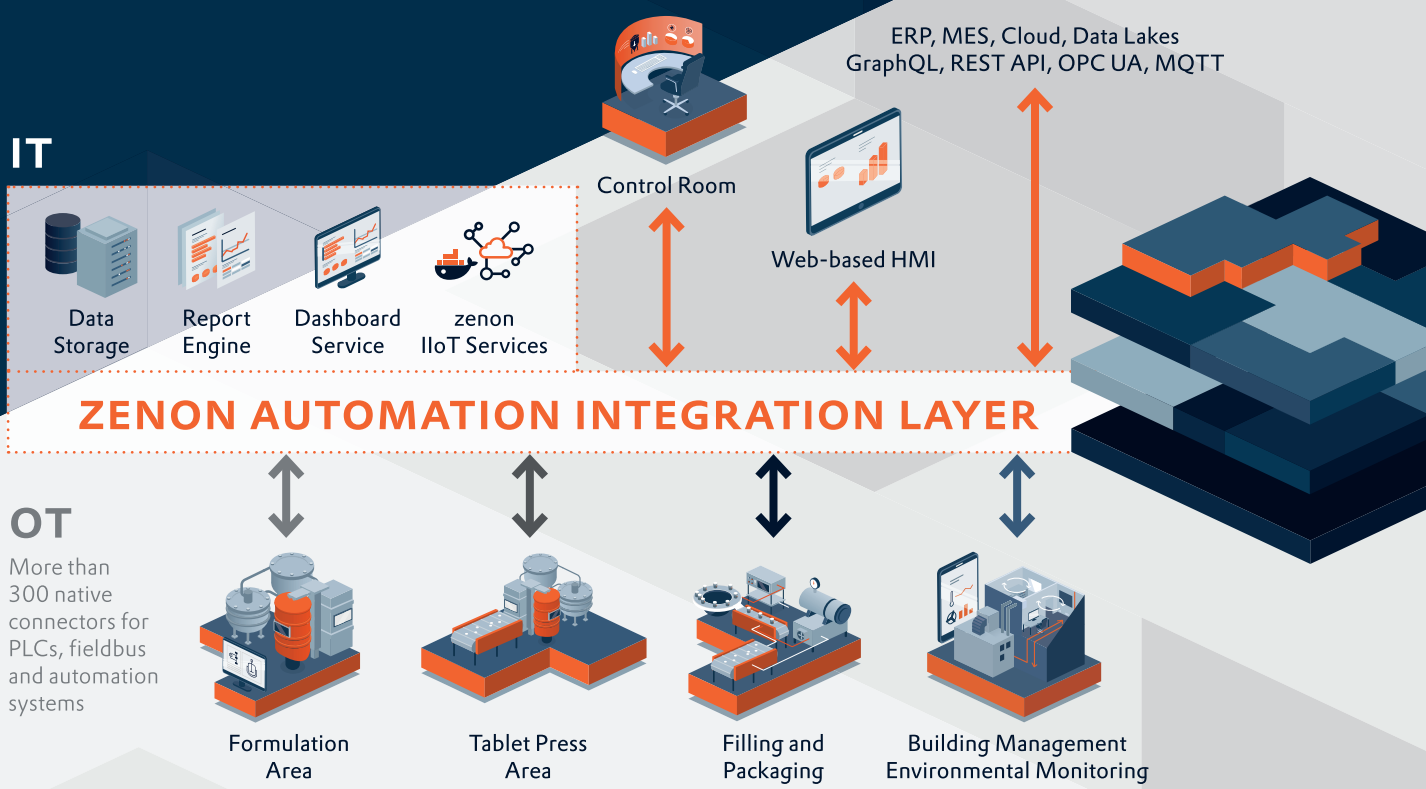

Integrating legacy equipment into existing IT systems is a challenge when it comes to maintaining accurate electronic batch records (EBR). zenon Automation Integration Layer (AIL) provides this missing link, enhancing **data integrity** and reducing time for **batch release**. Get ready for your digitalization journey in life sciences manufacturing.

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Opportunities and challenges

- The data for the new glass compared to borosilicate was compelling. Under all comparability conditions, the innovative glass vial and the traditional USP Type 1 borosilicate glass vials are superior. The importance of that comparative data provided by the glass vial manufacturer was not taken into consideration scientifically, as the US FDA wanted to see the product data and a demonstrated zero risk. This experience is a prime example of the challenges of being the first to come forth with new technology.
- An assessment of regulatory requirements in other regions indicated that additional studies and expectations would be required beyond those indicated by the US FDA. As a result, the approval timing for subsequent applications were incrementally scheduled over several years to avoid inventory management complexity.

CONCLUSION

ISPE's Enabling Global Pharmaceutical Innovation Initiative encompasses a broad spectrum of advancements, including technical innovations in pharmaceutical manufacturing and analytical technologies, the introduction of new medical modalities, novel delivery and administration methods, and digital transformation through Pharma 4.0™. The initiative aims to enhance product quality assurance, ensure consistent and reliable supply, improve product usability, and expedite global patient access to innovative therapies. Where applicable, it also supports improved productivity and reduced manufacturing costs.

The scope of pivotal objectives for this initiative include:

- Contemporize manufacturing technologies, i.e., advanced modeling and simulation digitalized technologies
- Reinforce globally harmonized interpretation and implementation of ICH guidelines necessary to advance innovative technology and industry approaches such as Pharma 4.0™, establishing criteria for a globally accepted drug product control strategy
- Identify sources of regulatory challenges that are barriers or create limitations in applicability across multiple therapeutic modalities
- Increase the level of clarity and consistency in harmonized approaches and identify and promote incentives for implementation of innovative technology
- Leverage relevant regulatory harmonization initiatives and convergent regulatory approaches in progress regionally, accelerate adoption and implementation of ICH guidelines and other harmonization proposals, i.e., mutual recognition/reliance, ACCESS Work sharing, WHO, etc.
- Identify incentives for regulatory authorities to collaborate
- Assess learnings from the COVID-19 pandemic global regulatory and supply distribution experience that can serve as a roadmap, i.e., mutual reliance, parallel development, regulator engagement.

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