Enabling Pharmaceutical Innovation: Delivering for Patients

A report on the Barriers to Innovation Survey

April 2024

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Executive Summary

Introduction

In 2023, ISPE launched an expansive and significant initiative, **Enabling Global Pharmaceutical Innovation: Delivering for Patients,** to address the barriers to technological innovation in the pharmaceutical industry. 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. Several regulatory authorities including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the United Kingdom's 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 upon industry to modernize manufacturing processes to improve productivity and increase confidence in product quality assurance by introducing novel technology and modalities, economic and regulatory barriers discourage the development and implementation of new, innovative technology globally. Perhaps most significantly, the conspicuous lack of global regulatory harmonization reduces incentives for industry to invest in innovations which indirectly limits access to safe, effective, and quality drug products to patients globally.

This initiative is consistent with ISPE's Mission and Vision and is aligned with the advancement of ISPE's Pharma 4.0™ program. This initiative aims to catalyze consistent and harmonized interpretation and implementation of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines to improve global patient access to innovative medicines and technology. "Enabling Pharmaceutical Innovation" comprises technical innovations in pharmaceutical manufacturing and analytical technology, the introduction of new medical modalities, modes of delivery and administration of medicines, and digital transformation (Pharma 4.0™). "Delivering for Patients" addresses improved assurance of product quality, supply consistency and reliability, improved product convenience and use, expedited patient access globally, and where applicable, improved productivity/reduced manufacturing costs. Seven pivotal objectives describe the scope of the initiative:

1. Contemporize manufacturing technologies, i.e., advance modeling and simulation digitalized technologies.
2. 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.
3. Identify sources of regulatory challenges that are barriers or create limitations in applicability across multiple therapeutic modalities.

4. Increase the level of clarity and consistency in harmonized approaches and identify and promote incentives for implementation of innovative technology.
5. Leverage relevant regulatory harmonization initiatives and convergent regulatory approaches that are in progress regionally, accelerate adoption and implementation of ICH guidelines and other harmonization proposals, i.e., mutual recognition/reliance, the Access Consortium work-sharing initiatives, the World Health Organization (WHO), etc. (See Section VI. Review of Regulatory Initiatives to Address Barriers to Innovation)
6. Identify incentives for regulatory authorities to collaborate.
7. Assess learnings from the COVID-19 pandemic, where global regulatory and supply distribution experience can serve as a roadmap, i.e., mutual reliance, parallel development, regulator engagement.

In late 2022 ISPE assembled a team of industry leaders with expertise in advancing innovative technology and products with experience in addressing regulatory divergence. This ISPE team developed a comprehensive survey to understand the circumstances and confirm sources that create barriers to innovation including the specific origins, extent, and magnitude of challenges/barriers that limit and reduce the development and implementation of innovative technologies.

The survey consisted of three parts with the option to respond to all or any of the parts. The first part was a list of questions requiring simple multiple-choice answers focused on demographics and summary-level innovation experience. The second part requested brief but specific examples of innovation development experience. The third part requested more detailed information and, where appropriate, anecdotal examples and case studies describing innovation challenges. The survey was launched in April 2023 and was closed on December 12, 2023, after 391 responses.

Summary of Findings from the Survey

Responses to the survey were relatively high (391 respondents) and reflected a representative sector of the pharmaceutical industry including a diverse mix of large to small pharmaceutical manufacturers, contract manufacturing and development organizations, component and equipment suppliers, and facilities and software service providers located in multiple countries and reflecting multiple product modalities.

While the majority of responses came from innovator (brand name) companies (23%), a small proportion of responses came from companies responsible for manufacturing generic products (6.1%) and biosimilar products (3.6%).

Respondents also identified a variety of product types for which they were responsible including large molecules, small molecules, combination products and vaccines, medical devices,

companion diagnostics as well as manufacturing and analytical equipment/components/facilities, digital software, process materials, and reagents.

From this broad cohort of companies, a large number and a wide range of innovations were reported. Biologics manufacturing (11.7%), continuous manufacturing processes (10.1%), and in-process monitoring Process Analytical Technology (9.1%) were the top innovations reported. Of these innovations, not all were submitted in regulatory applications for approval. However, a wide range of innovative technologies, most notably with respect to biologics manufacturing (13.5%) and novel product formulations (11.0%) were submitted in regulatory applications predominantly in the US (21.8%) and the European Union (EU) (18.3%) with fewer application submissions in the other geographic regions globally.

Respondents reported a range of experiences with submission of applications for innovative technologies. A number of responses indicated their applications for innovative technologies were approved (20.4%), however different regulatory expectations from individual regulatory authorities (28.5%) and delays in application assessments/inspections (15.3%) also were reported. A relatively low number of rejections (2.9%, 4 reported out of 152) indicate that regulatory authorities have generally accepted applications containing innovative technologies.

Respondents indicated that in general, economic factors were the primary drivers determining cost/benefit for capital investment in innovative technology. In particular, potential for long-term revenues and anticipated efficiency/productivity determine whether a company proceeds with developing and implementing an innovative technology. Improving assurance of quality along with global regulatory acceptability also were cited as major factors in those decisions. Respondents reported a range of business factors that led to discontinuation of innovation projects, such as economic, “fear of change,” levels of competence, including that of CDMOs and concern that short-term risks would incur delays in regulatory approvals. While certain improvements in manufacturing or analytics may be addressed directly by technical teams during development, decisions to invest in significant technological innovations are made at senior levels within organizations and tend to be based on short term Return on Investment (ROI) rather than long-term sustainability and ultimate timeliness of speed to patients.

In fact, regulatory challenges were reported as a significant factor influencing decisions to develop innovative technology. For a large proportion (48%) of respondents, these regulatory challenges were deemed most significant or significantly greater than other factors.

The top three concerns with regulatory acceptability were:

- Challenges during application review — regulator adherence to conventional expectations that do not apply.
- Lack of globally harmonized regulations.
- Guidance, challenges during application review — regulator understanding of innovative technology.

Responses to the questions in Parts 2 and 3 confirm and amplify these concerns and provide additional specificity.

While respondents indicated an overwhelming advantage in engaging with a regulatory authority innovation pathway, such as the FDA's Emerging Technology Program (ETP) or CBER Advanced Technologies Team (CATT) program, and the EMA's Quality Innovation Group (QIG), a significant proportion of respondents reported a relatively low level of engagement with both groups: 22.0% for the FDA Emerging Technology Team (ETT) and 14.5% for the QIG. In addition, divergent global regulatory expectations, based on previous experience, are a primary concern and create a concomitant challenge for a majority of respondents:

- Agreements at meetings with senior-level regulators do not always lead to the same interpretation and acceptance by reviewers and inspectors who perform the assessment and inspect facilities.
- Engagements with multiple individual regulatory authorities frequently lead to different regulatory expectations for innovative technologies, i.e., separate specification acceptance criteria, different operational process parameters and level of registered details, etc.
- Engagements with multiple regulators are a logistical and resource burden and generally extend over a long time.
- No regulatory pathway is available in any market to facilitate the review and approval of Chemistry Manufacturing Controls (CMC) platform technologies, for example, analytical methods that are developed as applicable to multiple products.

According to respondents, these differences in regulatory authority expectations ultimately result in:

- Increases in regulatory commitments and resource costs.
- Extended timescales due to delays to accommodate alternative or additional product development and characterization studies which adversely impact estimated ROI benefits.
- Increased compliance complexity and inventory management due to multiple control strategies for a single process or the most conservative control strategy governing a manufacturing process.

When the level of uncertainty associated with divergent regulatory expectations is relatively high, the potential value of an innovation relative to its ROI becomes difficult to estimate and justify and, according to many respondents, innovative approaches are subsequently postponed until the regulatory environment is more favorable or are simply terminated. Indeed, the factors associated with perceived and real regulatory barriers by which decisions to proceed with an innovative technology are made, have led to a "it's all too difficult, let's not change" or "we don't want to be the first to prosecute an innovative approach" mindset within the industry.

Conclusion and Recommendations

The survey confirmed that, in addition to developing innovative technology, the pharmaceutical industry is committed to continual improvement to ensure a reliable and sustainable supply chain, and to increase quality assurance and patient access to medicines globally. However, it is also clear from the survey feedback and responses that the current global regulatory environment poses a significant challenge to implementing continual improvement and innovative technologies. While several respondents indicated that regulatory pathways such as the ETP/CATT and QIG offer effective approaches that enable development and implementation of innovative technologies, globally divergent regulatory expectations remain a conspicuous concern and challenge. In fact, collective industry feedback clearly indicates that collaboration with regulatory authorities globally, either to revise existing regulatory options or introduce alternative global regulatory pathways, will undoubtedly enable and facilitate the introduction, development, and implementation of innovative technology.

The following suggestions summarize the survey recommendations:

- Establish an efficient system that connects regulatory authorities and fosters opportunities for companies and vendors to propose and establish innovations for global consideration, acceptance, and implementation.
- Align application review/assessment processes that cultivate a convergent approach to evaluate the merits of innovative technologies and produce a combined list of queries from global regulatory authorities.
- Adopt a single or limited GMP inspection schedule for assessing the implementation of innovative technologies per manufacturing facility (when required) in accordance with global inspection standards, i.e., Pharmaceutical Inspection Co-operation Scheme (PIC/s), and a focus on the requisite Pharmaceutical Quality Standards that support the innovative qualities of the product control strategy that is acceptable globally.
- Initiate global regulatory authority approvals that rely on mutual reliance/recognition. Several respondents emphasized that this conceptual approach, where appropriately established to reduce the chronic regulatory lag for global approval of post-approval changes associated with continual improvement, could serve as a key enabler to innovative technologies.
- Establish a predictable global regulatory authority review/assessment/inspection and approval schedule that ensures global supply chain reliability and patient access.
- Introduce a globally harmonized regulatory process to support review, inspection, and approval of platform technologies (e.g., analytical procedures) which may apply to multiple products.

A concerted globally aligned/integrated regulatory approach would undoubtedly increase the confidence within the industry to overcome regulatory risks and effectively enable the development of innovative technology. In addition, it would improve the industry's commitment to continual improvement, cultivating the curation of a lifecycle mindset. The unequivocal success with the introduction of the FDA's ETP/CATT programs and anticipated success of the EMA's QIG program* should serve as the basis for these recommended global regulatory approaches. It is worth noting the industry experience during the COVID-19 pandemic. The expedient regulatory assessment and distribution of vaccines could not have occurred without regulatory authority collaboration and mutual reliance.

Next Steps for the Enabling Pharmaceutical Innovation Initiative

1. A summary of the objectives of this initiative, the intent, design, and feedback from the survey on barriers to innovation will be submitted for publication in *Pharmaceutical Engineering*® magazine.
2. Data and information from the survey supported by in-depth discussion with several respondents who have direct experience developing, adopting, and implementing innovative technologies will serve as the basis for case studies and provide opportunities for potential solutions which could serve as substrate for engagement with regulatory assessors and inspectors globally.
3. ISPE's Enabling Global Pharmaceutical Innovation Initiative team will present proposals to multiple regulatory agencies at appropriate forums dedicated to advancing globally accepted regulatory approaches. These efforts are intended to promote practical incentives for the industry and regulatory authorities to address specific challenges to innovation and continual improvement initiatives.
4. The ISPE team will work with industry and equipment suppliers to understand the steps to introduce innovative technologies and develop a "points to consider document" of how to present these internally and externally to regulatory authorities.

* A unique challenge for the QIG is that it does not include representatives from every member state. In fact, a very small number of member states participate in QIG assessments. However, the regulatory application review and approval process through the Committee for Medicinal Products for Human Use (CHMP) or the Committee for Veterinary Medicinal Products (CVMP) includes all member states, who may raise objections or questions throughout the assessment process. The rapporteur and co-rapporteur, as well as the member states conducting inspections may not participate in the QIG. While top-level authority leaders encourage and support innovative approaches, receptivity and acceptance is not necessarily guaranteed through the regulatory process.

Origins, Background, and Goal of ISPE's Enabling Pharmaceutical Innovation Initiative

Problem Statement

Science- and risk-based approaches in pharmaceutical development were first explicitly described in ICH Q8[1] and further elaborated in ICH Q9,[2] Q10,[3] and Q11[4] as well as Q12[5] for post-approval changes. Conceptually, Quality by Design (QbD) is a prospective approach that increases process understanding, manufacturing robustness, and product knowledge to improve confidence in the quality of pharmaceutical products. The QbD approach is an important part of developing "enhanced knowledge of product performance"[6] as described in ICH Q8(R2). It was proposed in ICH Q8(R2) and Q10 that "Enhanced Science and Risk-Based Regulatory Approaches" could lead to regulatory flexibility.

However, during the last decade, the industry has experienced a proliferation of regulatory divergence with respect to the interpretation and implementation of ICH guidelines (and control strategies) across geographic regions. Rather than the adoption of globally harmonized regulatory criteria, localized interpretations of ICH guidelines have resulted in widely different regulatory expectations that have forced companies to adopt multiple control strategies for a single product using the same manufacturing process globally, or worse, diluting the control strategy toward the most conservatively harmonized common denominator. This has not only created manufacturing and supply chain challenges but has discouraged technical innovations that might otherwise provide increased quality assurance and expedite patient access to medicines globally, both at initial regulatory approval and for subsequent changes. These diverse regulatory expectations create additional burdens and challenges in carrying out continual improvement initiatives and, even the perception of divergence, hinders innovation in product development and lifecycle management while providing no improvement in product quality, safety, or efficacy. Global regulatory divergence has served as both a real and perceived barrier to developing innovative manufacturing technology, new medicinal modalities, and continual improvement initiatives that have, in some instances, created temporary drug shortages in some markets.

Several published assessments and a large body of anecdotal examples indicate that implementation of many concepts described in ICH guidelines, i.e. a single global product control strategy, are not currently achievable.[7]

Goal of the Enabling Pharmaceutical Innovation Initiative

The goal of the initiative is described in the following mission statement: "To catalyze consistent and harmonized interpretation and implementation of ICH guidelines to improve global patient access to innovative medicines and technology."

Scope

The scope of the initiative:

- "Enabling Pharmaceutical Innovation" comprises technical innovations in pharmaceutical manufacturing and analytical technology, introduction of new medical modalities, modes of delivery, and administration of medicines and digital transformation (Pharma 4.0™).
- "Delivering for Patients" addresses improved assurance of product quality, supply consistency and reliability, improved product convenience and use, expedited patient access globally, and where applicable, improved productivity/reduced manufacturing costs.

Objectives

The objectives of the initiative are to:

1. Contemporize manufacturing technologies.
    - Progress modeling and simulation, digitalized technologies.
2. Reinforce globally harmonized interpretation and implementation of ICH guidelines necessary to advance innovative technology and approaches.
    - Functionally necessary to advance innovative technology and approaches, i.e., Pharma 4.0™.
    - Establish criteria for a globally accepted drug product control strategy.
3. Identify sources of regulatory challenges that are barriers or that create limitations in applicability across multiple therapeutic modalities.
4. Increase the level of clarity and consistency in harmonized approaches by identifying and promoting incentives for the implementation of innovative technology.
    - Identify and promote incentives for implementation of innovative technology.
5. Leverage relevant regulatory harmonization initiatives and convergent regulatory approaches that are in progress regionally.
    - Accelerate adoption and implementation of ICH guidelines and other harmonization proposals, i.e., mutual recognition/reliance, the International Coalition of Medicines Regulatory Authorities (ICMRA) Pharmaceutical Quality Knowledge Management System (PQKMS), mutual recognition/reliance, the Access Consortium work-sharing initiatives, World Health Organization (WHO), PIC/S, etc.
6. Identify incentives for regulatory authorities to collaborate.
7. Assess learnings from the COVID-19 pandemic.
    - Global regulatory and supply distribution experience can serve as a roadmap, i.e., mutual reliance, parallel development, regulator engagement.

ISPE Actions

To deliver this initiative, ISPE assembled a multi-disciplinary, multi-national team of subject matter experts under the auspices of the ISPE Regulatory Steering Committee and chaired by Roger Nosal, Principal Consultant, PharmaCMC Regulatory Consultants. The project is sponsored by ISPE President and CEO Thomas B. Hartman.

ISPE Survey Scope and Methods: Identifying the Source of Barriers to Innovation

While the ultimate objective is to provide potential solutions to improve implementation of global regulatory expectations, the ISPE team started by designing and conducting a survey. The survey was designed to determine the extent and magnitude of challenges/barriers globally in developing and implementing innovative technologies. The survey was launched in late April 2023 and was open to both ISPE members and non-ISPE industry professionals. It closed on December 12, 2023.

Summary of Survey Design

The survey was divided into three parts.

Part 1 contained 13 multiple choice questions intended to gain an understanding of the demographics and overview of the respondents' experience concerning the development and implementation of innovative technologies and modalities.

Part 2 of the survey contained 14 short-answer questions focused on eliciting increased granularity of responses to questions focused on respondents' specific experiences with the development and implementation of innovative technologies and modalities.

In Part 3 of the survey, respondents were invited to provide anecdotal examples describing successful introduction of innovative technologies and/or challenges associated with the development and implementation of innovative technologies and modalities. Several respondents provided contact details for follow-up which will contribute to the development of case studies with particular interest in engagement with regulatory authorities globally.

Each part of the survey was distributed through ISPE to industry professionals throughout 2023. While responses to all three parts of the survey were encouraged, most respondents completed only Part 1, which afforded a compelling assessment of the magnitude of the concerns associated with barriers to innovation.

Survey Data, Interpretation, and Results

Data and analytics are provided in the Appendix. A total of 391 respondents completed one or more parts of the survey.

For each question, a summary of the responses is given here and in the Appendix. Additionally, interpretative and relevant comments have also been provided for several responses in this section.

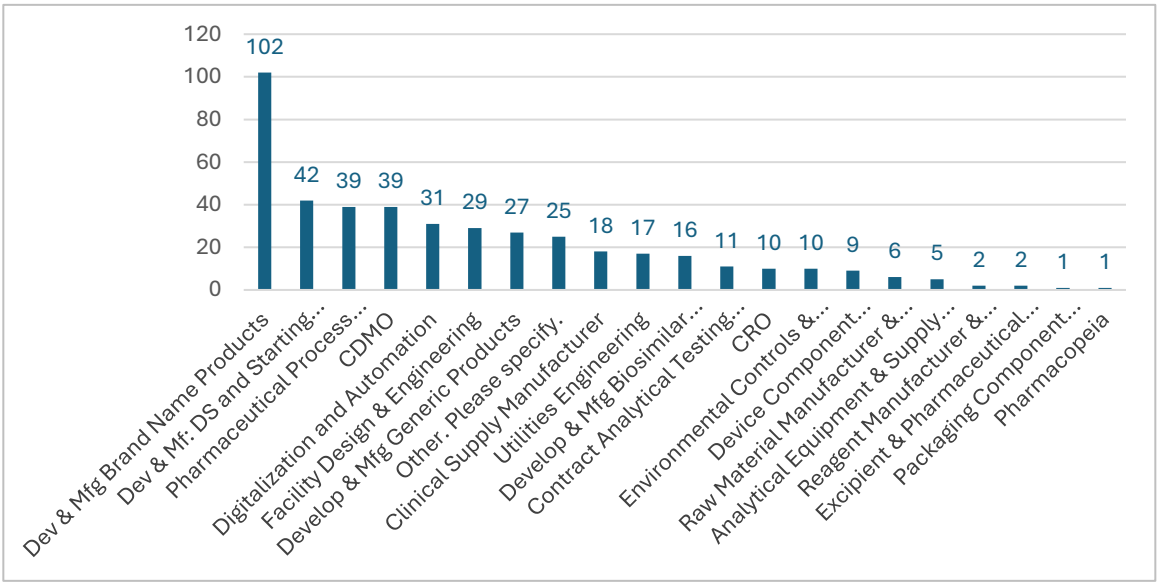
Survey Part 1: Demographics and Summary Level Innovation Experience

Multiple choice questions

Q1. What role(s) does your company/organization have within the pharmaceutical industry? (multi-select)

Summary of responses: Respondents were from a broad representation across pharmaceutical manufacturing, suppliers, and service providers. While most responses came from innovator product companies (23%), responses from companies that manufacture generic products (6.1%), and biosimilar products (3.6%) products were also represented.

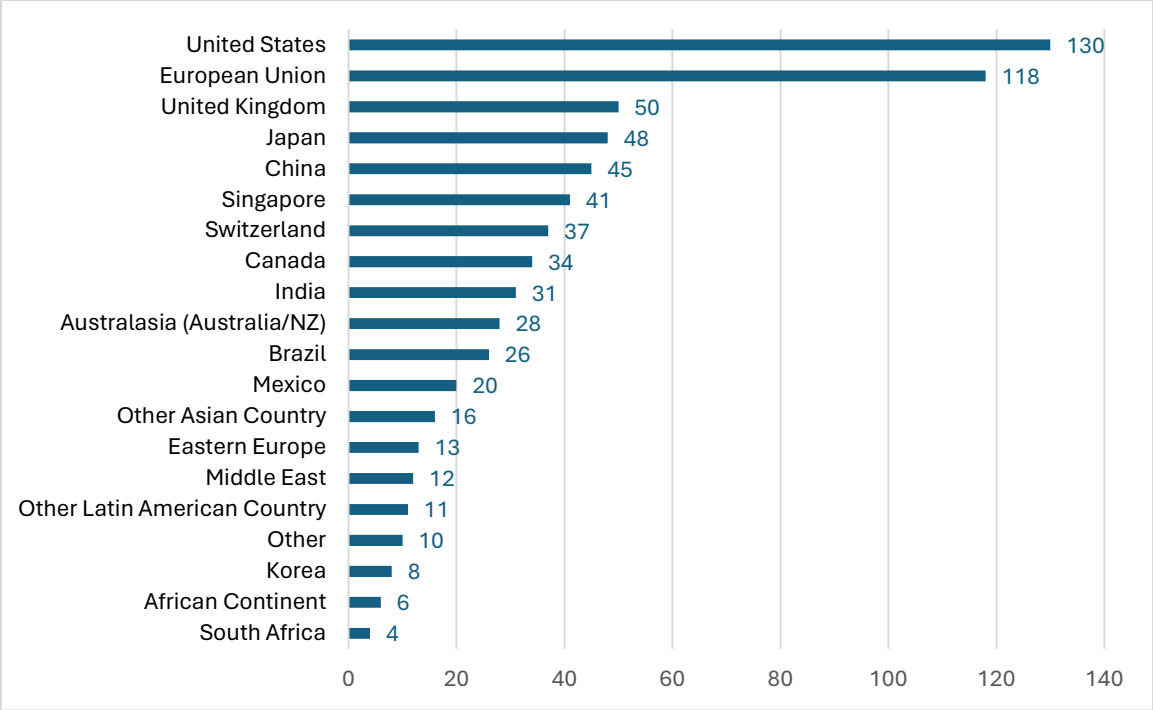
Figure 1: Role of Company



Q2. In which region(s) does your company have development or manufacturing facilities? (multi-select)

Summary of responses: Respondents identified a wide distribution of locations for development and manufacturing facilities, essentially global, with the majority of sites located in the US (18.9%) and EU (17.2%).

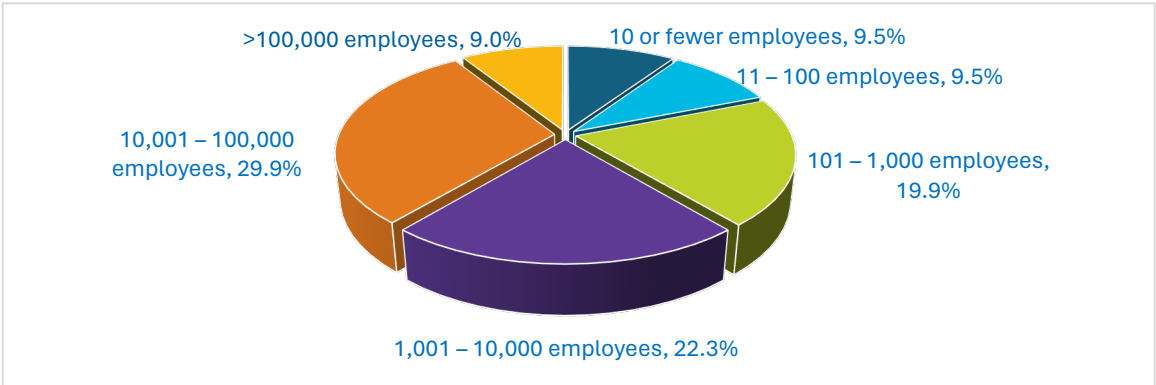
Figure 2: Regions for Development or Manufacturing



Q3. What is the size of your company/organization?

Summary of responses: There was a good balance of company size with a skew towards larger companies (>1000 employees).

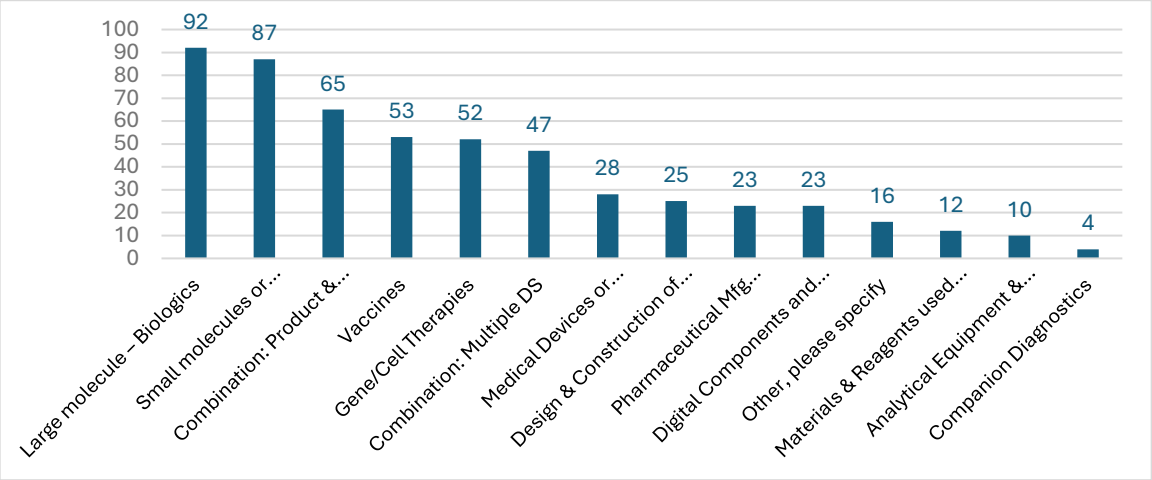
Figure 3: Size of Organization



Q4. What types of products does your company/organization manufacture? (multi-select)

Summary of responses: Respondents manufactured a wide range of products and combination products and included vendors of equipment, facilities, and software. Large molecules (17.1%), small molecules (16.2%), combination products (12.1%) and vaccines (9.9%) received the highest responses.

Figure 4: Type of Product for Innovation



Q5. What are the primary drivers for developing and implementing innovative technology? Please rate the most important (1) to least important (9) for each option that applies.

Summary of responses: The top five responses received first place rankings as summarized in the first column in the following table. Total percentage values of responses ranked first through fifth are shown in the second column. According to respondents, the top three reasons for introducing innovative technologies are to improve manufacturing efficiency/productivity, improve quality assurance, and reduce manufacturing/operating costs.

Table 1: Top Three Drivers for Developing and Implementing Innovation

Reason	Ranked first (%)	Total Percent ranked first to fifth
Improve Manufacturing Efficiency/Productivity	26.2	94
Improve Quality Assurance	22.0	88
Reduce Manufacturing/Operating Costs	16.2	91
Expand Business Opportunities	12.0	38
Establish an Innovative Technology Platform for Multiple Products	9.4	65

Q6. Which of the following concerns with regulatory acceptability has prevented your company/organization from proceeding with innovations? Please rate the most important (1) to least important (8) for each option that applies.

Summary of responses: The top five responses received first place rankings as summarized in the first column in the following table. Total percentage values of responses ranked first through fifth are shown in the second column. The top three concerns with regulatory acceptability were challenges during application review – regulator adherence to conventional expectations that do not apply, lack of globally harmonized regulations and guidance, challenges during application review – regulator understanding of innovative technology.

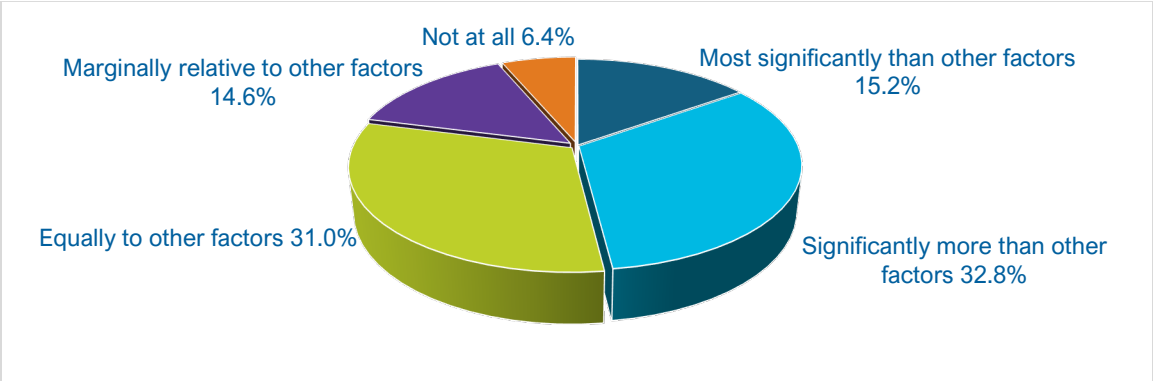
Table 2: Top Five Concerns with Regulatory Acceptability

Concern	Ranked first (%)	Total Percent ranked first to fifth
Challenges during application review - Regulator adherence to conventional expectations that do not apply	29.6	90.0
Lack of globally harmonized regulations and guidance	19.7	67.7
Challenges during application review - Regulator understanding of innovative technology	14.5	93.8
Challenges during inspections	8.6	41.4
Lack of implementation of globally harmonized guidelines, i.e., ICH	7.9	57.1

Q7. To what extent did regulatory challenges influence decisions to develop innovative technology?

Summary of responses: Respondents reported that regulatory challenges were a primary, if not equivalent, factor influencing decisions to develop innovative technology with 48% of responses indicating regulatory challenges are most significant or significantly greater than other factors.

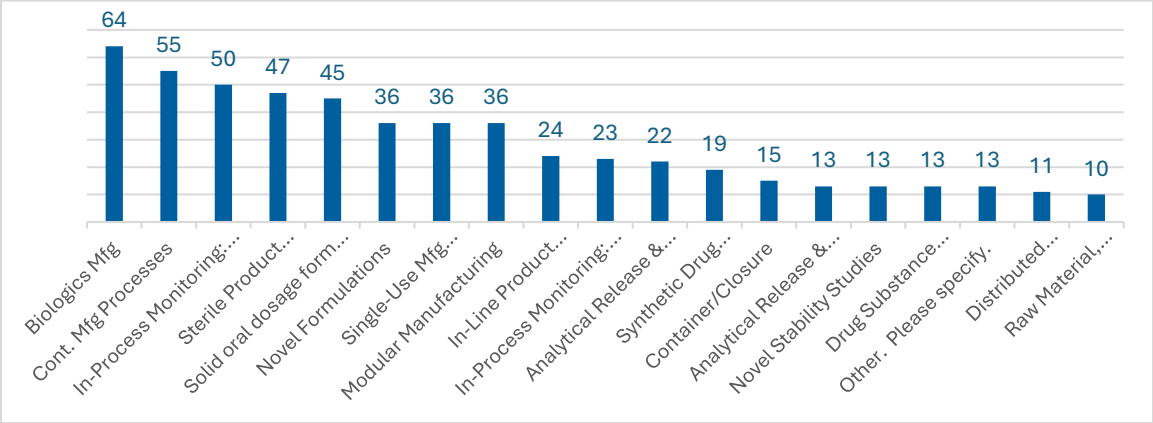
Figure 5: Regulatory Challenges Influencing Development of Innovative technology



Q8. Has your company/organization developed technical innovations for any of the following manufacturing and product control operations? (multi-select)

Summary of responses: Respondents reported developing a wide range of innovative technologies. Among the highest reported innovative technologies were associated with Biologics Manufacturing (11.7%), Continuous Manufacturing Processes (10.1%) and In-Process Monitoring: Process Analytical Technology (9.1%).

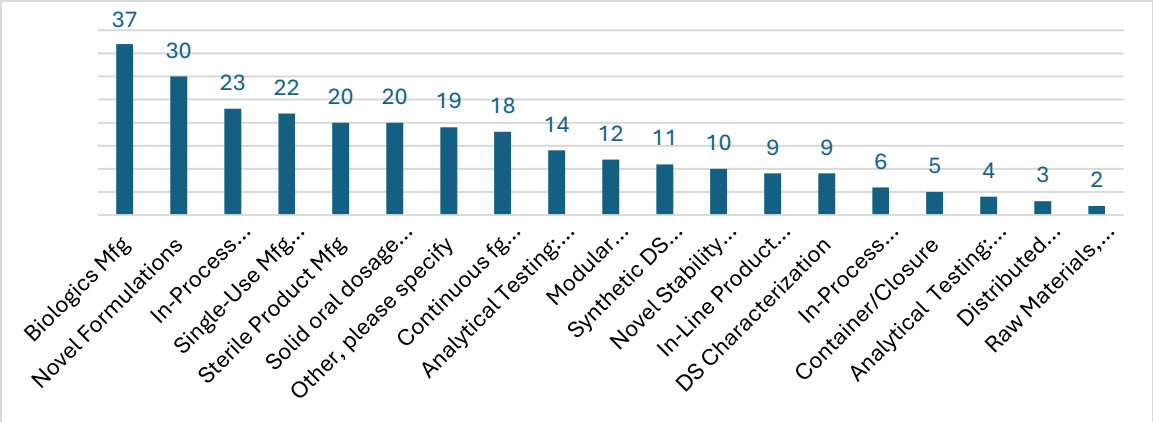
Figure 6: Manufacturing and Control Operations for Technical Innovations



Q9. Which of the innovations identified in question 8 above have been submitted in regulatory applications for approval? (multi-select)

Summary of responses: Respondents reported a wide range of innovations submitted in applications with those associated with Biologics Manufacturing (13.5%) and Novel Formulations (11.0%) leading the list of innovative technologies. However, of the innovations identified in question 8, not all have been submitted in regulatory applications for approval.

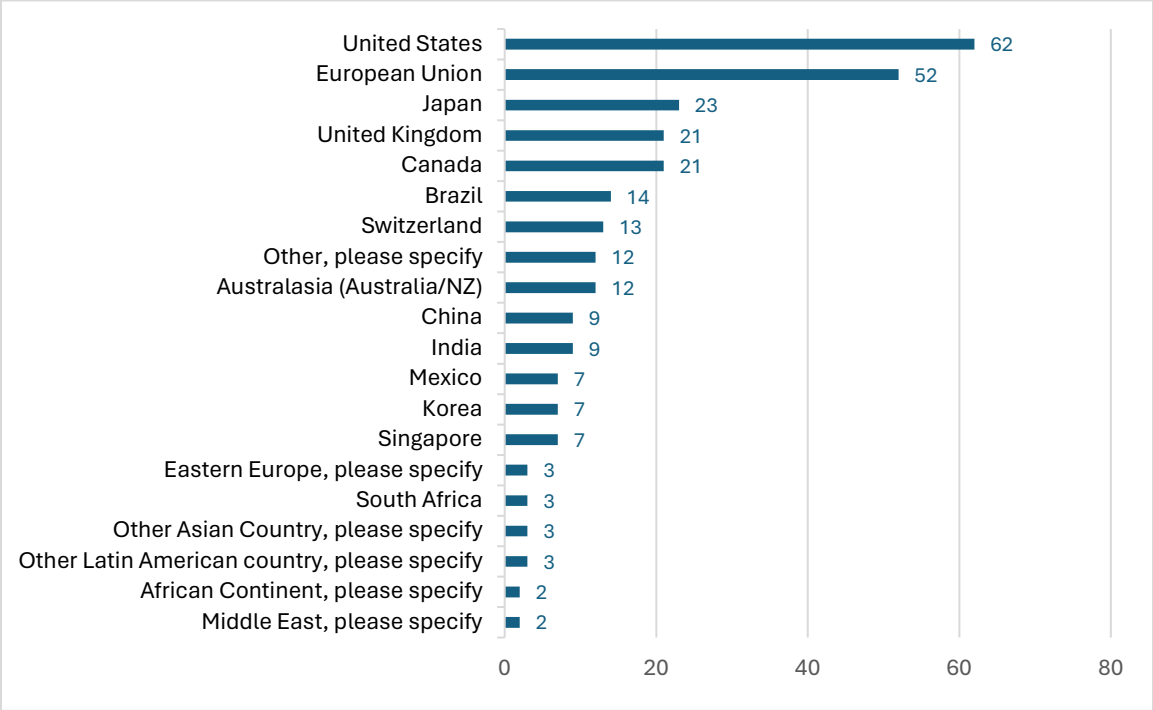
Figure 7: Innovations Submitted in Regulatory Applications



Q10. In which regions were regulatory applications submitted for those innovations identified in question 8? (multi-select)

Summary of responses: While respondents reported that a few applications which included innovative technologies were submitted in several geographic regions, most were submitted predominantly in the US (21.8%) and the EU (18.3%).

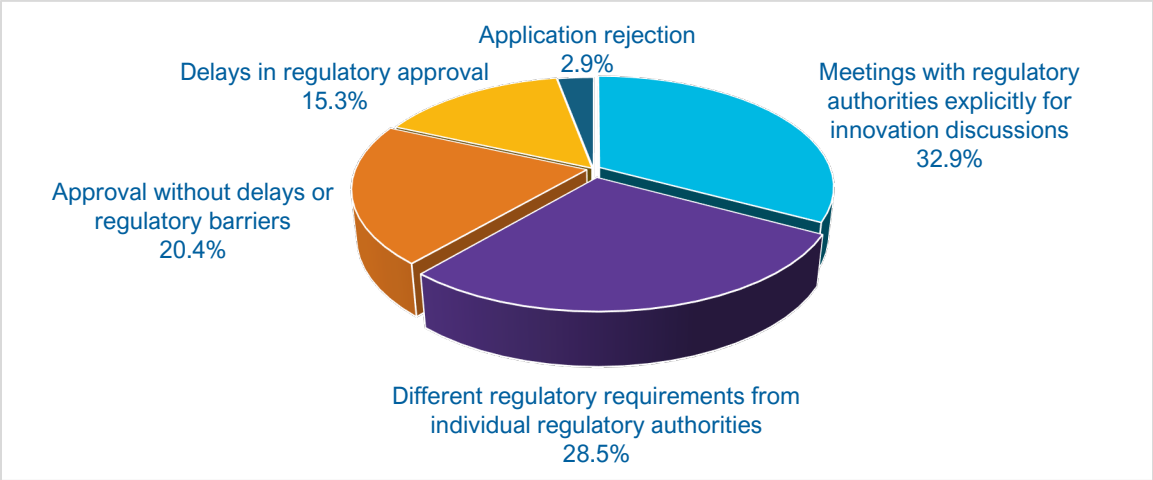
Figure 8: Regions Applications Made



Q11. For those innovations submitted in regulatory applications, which of the following outcomes did you experience? (multi-select)

Summary of responses: Respondents' experiences with the submission of innovative technologies show a range of outcomes, including approvals (20.4%), divergent regulatory expectations from individual regulatory authorities (28.5%), and delays (15.3%). Few rejected applications were reported (2.9%, 4 reported out of 152) suggesting, that, in general, initial receptivity to innovative technologies was positive, however different regulatory expectations may have been encountered, some of which are captured in the anecdotal responses.

Figure 9: Outcomes from Regulatory Applications



Q12. Which of the following critical factors are most important in determining cost/benefit for capital investment in innovative technology? Please rate the most important (1) to least important (7) for each option that applies.

Summary of responses: Respondents reported that economic factors are the primary drivers of determining cost/benefit for capital investment in innovative technology (Long term revenues and efficiency/productivity) as shown in the following table. While improving the assurance of quality was - a major factor, the need for global regulatory acceptability also was considered an important factor governing these decisions.

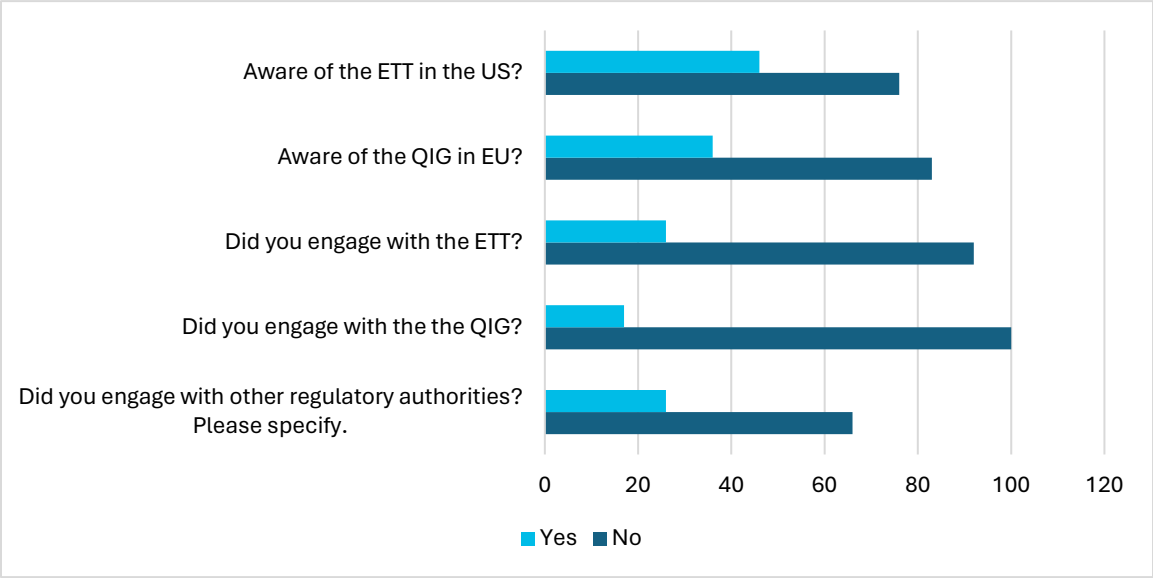
Table 3: Critical Factors in Determining Cost/Benefit for Investment

Option	Ranked first (%)	Total Percent ranked first to fifth
Long Term Revenues	33.6	89.1
Manufacturing Flexibility	18.5	95.0
Global Regulatory Authority Acceptability	15.1	61.3
Efficiency/Productivity/minimizing SKUs	14.3	90.7
Quality Assurance	10.1	95.9

Q13. In your plan to develop and implement innovative technologies were you aware of the: (multi-select)

Summary of responses: Respondents reported a surprising lack of knowledge and conspicuous lack of engagement with health authorities on innovative technology even when regulatory pathways for innovative technologies are available in the US and EU. A relatively large percentage of respondents apparently were unaware of the US Emerging Technology Team (ETT) (62.3%) and EU Quality Innovation Group (QIG) (69.8%), and this is reflected in the low level of engagement with both groups – 22.0% for ETT and 14.5% for QIG.

Figure 10: Regulatory Awareness



Answer	Minimum	Maximum	Mean	Std Deviation	Variance	Count
Quality Innovation Group (QIG) in EU?	1.00	2.00	1.70	0.46	0.21	119
Emerging Technology Team (ETT) in the US?	1.00	2.00	1.62	0.48	0.23	122
Did you engage with the QIG?	1.00	2.00	1.85	0.35	0.12	117
Did you engage with the ETT?	1.00	2.00	1.78	0.41	0.17	118
Did you engage with other regulatory authorities? Please specify.	1.00	2.00	1.72	0.45	0.20	92

Survey Part 2: Feedback from Specific Examples of Innovation Development Experience

Text entry questions, 250-character limit

Q14. In your company/organization experience, how receptive are major regulatory authorities to innovative manufacturing?

Summary of responses: 55 respondents gave relevant comments, and they reported a wide range of experiences with regulatory authority acceptability of innovative technologies. Responses indicated variability of experiences by single respondents with different regulatory regions, as well as different experiences between respondents.

32 respondents made positive comments summarized as "FDA especially with their ETT program, and EMA are very receptive," however, there were 22 responses that indicated that receptivity was lacking, particularly in regions other than US and EU. These comments could be summarized as "some regulators prefer to stick with what they know."

Q15. Is the same true for smaller markets?

Summary of responses: According to respondents (42 relevant responses), regulatory authorities in small markets seem to follow the pattern of regulatory authorities in large markets with a tendency for those in small markets to be more cautious than those in large markets with regard to introduction of innovative technologies.

Q16. In your company/organization experience, how receptive are partner companies (e.g., CRO, CDMO, co-development, co-marketing, etc.) to innovative manufacturing?

Summary of responses: Respondents (59) reported that, in general, many partner companies are receptive to innovative technologies. However, this is not universal, and decisions to proceed with innovative technologies are largely driven by economics and at a high level within an organization.

Q17. In your company/organization experience, are proposed innovative technologies supported by internal governance?

If Yes:

- **Which factors determine proceeding with development and implementation?**
  - Summary of responses: As identified in answers to Q12, economic and other business factors are the major factors which determine proceeding with development and implementation of new innovations.
- **At what levels in the organization are decisions to proceed and implement innovative technologies made?**

  - Summary of responses: Although titles and organizations differ among companies, decisions to approve and support new innovations generally are made at a very senior management level.

- **Is there organizational willingness to engage with regulatory authorities to discuss innovations?**
  - Summary of responses: While a majority of respondents (29 of 49) to this question reported a willingness to engage with regulatory authorities. Three respondents indicated there was not a willingness to engage with regulatory authorities, which may be related to responses to Q13 where a relatively low proportion of respondents (20–30%) indicated they did not engage with regulators.

If no:

- **Which factors determine discontinuing development and implementation of innovative technologies?**
  - Summary of responses: Respondents (28) offered a range of factors which led to discontinuation of innovative projects including business/economic drivers, lack of competence among partners, e.g., CDMOs, CROs, and concomitant appreciation of risk within organizations.

Q18. If you are a supplier or manufacturer of generic products, do your partners/clients embrace innovative technology? Why or why not?

Summary of responses: Generally, respondents (22) indicated that generic companies do not embrace new technology mainly due to economic factors and the risk of disrupting supply chains. Several companies and partners to generic companies indicated that some generic companies embrace new technology when the business case supporting cost reduction is strong.

Q19. Has your company/organization had the opportunity to engage in a dialog to discuss innovative technologies with regulatory authorities and has this improved regulatory acceptability? If so, please provide examples.

Summary of responses: Generally, respondents reported that meetings with a single regulatory authority are positive and appear to reduce concerns. Engaging with FDA's ETT was reported as being very positive, with the EMA QIG also mentioned as being helpful. However, specific respondent feedback indicated experiences where there were differences in outcomes from different regulatory authorities and disconnects between regulators reviewing the merits of innovative technologies with regulatory personnel involved in inspections.

Q20. Are meetings with multiple regulatory authorities to secure their agreement a significant obstacle?

Summary of responses: Although some respondents reported that interacting with multiple agencies (13 of 41 relevant responses) was not a problem, a significant proportion (21 of 41) did report meeting with multiple regulatory authorities as a challenge, indicating that the possibility of different regulatory expectations/outcomes was a deterrent to the introduction of new technology. In addition, several respondents highlighted the burden associated with preparation and conducting separate and multiple meetings. Relevant comments could be summarized as "there is lack of harmonization and meeting multiple agencies is burdensome."

Q21. Has your company/organization received divergent recommendations from different regulatory authorities regarding approval and implementation of innovative technologies and has this created a significant obstacle to implementing innovative technologies? Please provide examples.

Summary of responses: Similar to the Q20 responses, a significant number of respondents (14 of 38 relevant responses) reported not receiving different recommendations from different regulatory authorities. However, a larger proportion of respondents (18 of 38) reported receiving different regulatory expectations from different regulatory authorities and provided many examples. Divergent regulatory expectations were reported in both assessment and inspection criteria. Examples were not limited to specific issues or technologies but reflected differences in regulatory expectations for innovative formulations and devices, processes, and analytical methods.

Of particular interest was a response that difference for any COVID-related medicines was not a problem. However, for other projects such as new development approaches (QbD) and less common manufacturing processes, differences in regulatory divergence were observed that challenged implementation. Understandably, healthcare leaders and regulatory authorities desperate for certain therapies to address significant threats to local health are prepared to be more flexible than they might be for conventional therapeutic products. The responses to this question imply that where technological innovations can improve therapeutic platforms perhaps a similar level of regulatory flexibility may be warranted.

Q22. Have cGMP inspections from multiple regulatory authorities resulted in increased quality/regulatory requirements, i.e., implementation of excessive or duplicative controls due to a lack of global regulatory harmonization?

Summary of responses: Similar to Q20 and Q21 responses, a significant number of respondents (14 of 40 relevant responses) reported not receiving different recommendations from different regulatory authorities. However, a larger proportion (20 of 40) of respondents reported receiving different regulatory expectations from different regulatory authorities and provided many examples. While no direct correlation between divergent regulatory expectations and impact on

specific innovative technology applications can be established, divergence implicitly leads to increased costs and potentially to delays in approvals.

Q23. How would you characterize your experience(s) with respect to developing and implementing innovative technologies?

Summary of responses: There were many positive experiences reported (22 of 50), however, there were also many comments (25 of 50) relating to the cost and time burden and the many frustrations faced. Meetings with individual regulatory authorities were reported as generally positive and appear to have reduced concerns. Engaging with FDA's ETT was reported as being very positive with the EMA QIG also mentioned as being helpful.

Q24. How has your company/organization quantified the cost/benefit for developing, introducing and implementing innovative technologies? Can you provide examples of the estimated total costs associated with specific innovations, particularly those innovations that require customized equipment?

Summary of responses: Based on responses, most companies quantify the cost/benefit for developing, introducing, and implementing innovative technologies. Perhaps, as should be expected, respondents were reluctant or prohibited by company policy to share values for cost/benefit calculations.

Q25. Is innovative technology introduced as a post approval change rather than as part of a new product marketing authorization application?

Summary of responses: Responses show a balance between regulatory approaches with 8 pre-approvals, 15 post approval, and 17 introducing innovative technologies both ways.

Q26. In your company/organization experience, approximately how long has it taken to receive global approvals in major markets vs. smaller markets for an innovative technology?

Summary of responses: Approval times were reported as highly variable from a few months in major markets to multiple years. Generally, approval times were reported as approximately one year in major markets and two to three years for smaller markets. One notable and important respondent commented that long global implementation time is a significant hurdle to the adoption of new technologies as separate supply chains need to be maintained until global approvals are achieved. This concern is consistent with continual improvement via post-approval changes globally.

Q27. Based on your company/organization experience, does your organization have confidence in the cost/benefit to develop and implement innovative technologies?

Summary of responses: Among 45 respondents, 27 indicated confidence in their respective cost/benefit approaches to developing and implementing innovative technologies. In addition,

eight respondents reported qualifications to advancing innovative technology projects. A few respondents (18%) reported a lack of confidence in developing innovative technology.

Survey Part 3: Anecdotal Case Studies of Examples of Innovation Development

Text entry, no character limit

Q28. Please provide examples of innovative technologies that your company/organization has developed and prosecuted through regulatory approval and a Summary of responses of the experience and cost/benefit?

Summary of responses: A number of respondents (19) provided a wide variety of examples for the development of innovative technologies.

- One case study highlighted the benefits of early interaction with FDA, which led to optimized stability programs resulting in significant cost savings.
- In an example of an innovative introduction of equipment and software technology, the respondent was reluctant to make changes due to increased regulatory expectations.
- In an example that incorporated innovative rapid microbiological analytical methods, the respondent highlighted significant challenges with long global regulatory approval timelines.
- Other examples of innovations using Real Time Release Testing for biologics products and modular robotic fillers encountered different regional expectations that have proven to be a significant hurdle, requiring, at times, changes to equipment or methodology for one region that is considered unnecessary in other regions.

Q29. Are there innovative technologies that are cost prohibitive due to regulatory barriers to effectively implement? Please include rationale.

Summary of responses: Innovative technologies that are cost prohibitive due to regulatory barriers to effectively implement.

Respondents (19) identified innovative technologies that are cost prohibitive to implement effectively due to regulatory barriers that include improved analytical methods such as rapid microbiological test methods and multi-attribute protein characterization methods.

Q30. Would your company/organization be inclined to develop innovative technology for the manufacture and control of generic or biosimilar products? Please include why or why not.

Summary of responses: Respondents were split between those that do develop innovative technology for the manufacture and control of generic or biosimilar products (6/24 relevant responses) versus. those (5/24 relevant responses) that were reluctant. Of those reluctant to invest in innovative technology, three respondents indicated their reluctance was associated with their company business strategy and one highlighted cost barriers.

Q31. What suggestions does your company/organization have to improve the receptivity and effective implementation of innovative technologies by regulatory authorities?

Summary of responses: Respondents (25) provided a large number of suggestions to improve the receptivity and effective implementation of innovative technologies by regulatory authorities:

- More education/training, knowledge sharing and communication.
- Establish globally harmonized meeting opportunities and a rapid system to produce globally harmonized guidance for innovative technologies.
- Introduce a mechanism to "approve" a platform technology (across multiple products).
- Have a common plan with collaboration/mutual recognition of novel technology by different regulators. Have a common IT platform such that each regulator can see the plans for implementation and see each other's concerns.
- Greater effort by main health authorities (but also international regulatory organizations like ICMRA, WHO, etc.) for harmonization of expectations for new technology.
- Consider a shift of documentation requirements and life cycle management of new technologies in the dossier vs. in the PQS (assessment vs. inspection).
- Introduce opportunities for vendors such as equipment and software suppliers to have discussions with regulators.
- Have a mindset that innovative technologies are proposed which provide higher levels of assurance of quality and less risk than current technologies.

Survey Discussion and Conclusions

Demographics and Experience

The relatively large number of respondents to the survey (391 respondents) representing a broad variety of manufacturers, suppliers and service providers afforded a useful assessment of the sources associated with perceived and real challenges and barriers to innovation in the pharmaceutical industry. In addition, the technology and modalities that these respondents

represented, i.e., small and large molecule manufacturing, vaccines, gene/cell therapies, material and component suppliers, equipment/facilities engineering firms, digital and software companies, etc., as well as the breadth of geographical locations where their companies do business, not only reflects the complexity of the industry but offers a comprehensive perspective on innovation.

While the survey results have largely confirmed that there are regulatory challenges to developing, adopting, and implementing innovative technologies, appropriately characterizing short and long-term benefits in conjunction with concomitant investments and financial/resource costs are significant factors in developing and executing innovations.

From this very broad cohort of companies that contribute to pharmaceutical development and commercialization, a large number (545) and wide range of innovations were reported. While the number of innovations that have been advanced is a subset, the collective experience associated with the decisions, costs, benefits, regulatory receptivity. and implementation provide a valuable report on challenges associated with innovation.

Key Messages

- Economic factors such as ROI are the primary drivers for investment in developing and implementing innovative technology.
- Improved quality assurance is a major factor driving innovation.
- Regulatory challenges including divergence in global regulatory authority expectations and inertia in global regulatory approvals are the most significant factors in determining the development, advancement, and implementation of innovative technology.
    - Regulator adherence to conventional expectations that do not apply.
    - Lack of globally harmonized regulations.
    - Regulator understanding of innovative technology.
- Regardless of regulatory receptivity and outcomes the industry has continued to develop a variety of innovative technologies and is committed to doing so in the future.
- While a relatively large proportion of respondents did NOT engage with the FDA ETT (78%) or the EMA QIG (85%), there is a pervasive willingness to engage, leverage and expand these regulatory pathways globally. Those respondents who engaged ETT and/or QIG overwhelmingly reported these innovation pathways enabled innovations to advance and in most instances with positive results.
- Respondents indicated that engaging with an individual regulatory authority can be helpful in resolving issues and establishing optimum development programs leading to approval.
- Meeting individually with multiple regulatory authorities can be ineffective and inefficient. Experience has shown that differences in outcomes from different regulatory authorities

and disconnects between regulators reviewing the merits of innovative technologies with regulatory personnel involved in inspections have resulted in significant regulatory challenges.

- The range of experiences has provided a perspective on how to improve development and implementation and expeditiously enable advancing innovative technology as well as continual improvement.
    - Improve education/training, knowledge sharing and communication within regulatory authorities and with other global regulatory authorities.
    - Establish globally harmonized opportunities to meet with regulatory authorities and a rapid system to produce globally harmonized guidance for innovative technologies in accordance with international regulatory organizations, i.e., International Pharmaceutical Regulators Programme, ICMRA, WHO, ICH, etc.
    - Introduce a globally acceptable pathway and mechanism to "approve" a platform technology (across multiple products).
    - Cultivate a global mindset that innovative technologies and continual improvement ostensibly increase quality assurance for products and reduce risks compared with conventional technologies.
    - Establish a common plan (and shared IT platform) for collaboration/mutual reliance/recognition of novel innovative technology among global regulatory authorities, so that plans for implementation and quality concerns can be addressed collectively.
    - In accordance with a lifecycle management approach, consider a shift in regulatory governance where, in a Mature Quality Management program the Pharmaceutical Quality System serves as the primary source for regulatory assessment/inspection of continual quality improvement and innovative technologies.
    - Introduce opportunities for equipment, facilities, and software suppliers to engage with regulatory authorities on innovative technologies and approaches.

Conclusions

The industry has a broad interest and commitment to develop and implement innovative technologies in almost all areas of its operations. This desire is evident by the number of responses to the survey, the breadth of the respondents, and their collective experiences. Innovation is a reflection of scientific progress that the majority of survey respondents espouse. How expeditiously and effectively innovative technologies advance fundamentally determines industry commitment and investment. The clear message from survey respondents is that while ROI drives decisions to develop and proceed with innovative technologies, and for that matter

continual improvement initiatives, economic estimates are largely influenced by the costs associated with global regulatory acceptability and associated regulatory challenges.

For that reason, the ability to engage regulatory authorities through a program like FDA's ETT and EMA's QIG reduces unpredictability. Globalization of these programs could improve communication and consistency among regulatory authorities, reduce divergent regulatory expectations, align regulatory assessments with inspections and ultimately improve product quality assurance. A globally aligned approach that improves predictability will harmonize innovative control strategies, reduce delays in approvals, minimize resource commitments, and costs and improve capacity for both industry and regulatory authorities. In addition, global harmonization reduces supply chain complexity thereby increasing distribution flexibility that ensures adequate and appropriate patient access globally.

The results from this survey offer an opportunity for the industry and regulatory authorities globally to collaborate on approaches that will significantly reduce barriers to innovation and continual improvement and, most importantly, increase product quality assurance and patient access globally.

Review of Regulatory Initiatives to Address Barriers to Innovation

Multiple initiatives focused on eliminating/reducing barriers to innovation are currently being addressed by several organizations.

International Council for Harmonisation

Harmonization of global regulatory requirements has formally and informally progressed for more than 30 years under the International Council for Harmonisation. ICH is committed "to achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner."[8] Internationally, acceptable scientific guidelines, primarily applicable to commercial registration of new and generic drug products and drug substances have dramatically improved regulatory alignment for many technical approaches focused on safety, efficacy, and quality of drug products. ICH concentrates on the harmonization of technical requirements; change of regulatory pathways driven by local legislation and requirements is out of scope.

Over recent years, several regulatory agencies have established initiatives to promote pharmaceutical manufacturing innovation in specific regions.

United States

The FDA established the ETP in 2014 and has actively promoted the program. In his keynote presentation at the 2022 ISPE Annual Meeting and Expo, Dr. Michael Kopcha, Director of the

FDA Office of Pharmaceutical Quality, emphasized the FDA's commitment to promoting advanced manufacturing. The FDA's Center for Drug Evaluation and Research (CDER) established the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) initiative to prepare a regulatory framework to support the adoption of advanced manufacturing technologies that could bring benefits to patients.

The Duke-Margolis Institute for Health Policy has interest in promotion of advanced pharmaceutical manufacturing and innovation and is promoting advanced manufacturing as a factor in the goal of preventing or reducing drug shortages. Duke-Margolis has connectivity to influence US government policy and liaises closely with the FDA.

European Union

The National Competent Authorities (NCAs) of the 27 EU member states plus those of Iceland, Liechtenstein and Norway and including the EMA released the European Medicines Agencies Network Strategy to 2025. Two of the six strategic focus areas are "data analytics, digital tools and digital transformation," and "innovation." In line with this strategy the EMA established the Innovation Task Force (ITF), which is a multidisciplinary group that includes scientific, regulatory, and legal competences. It was set up to ensure coordination across the Agency and to provide a forum for early dialogue with applicants on innovative aspects in medicines development.

United Kingdom

The MHRA established the Innovation Office which is open to ideas for innovative medicines, medical devices and manufacturing processes.

Japan

The Pharmaceuticals and Medical Devices Agency (PMDA) established the Innovative Manufacturing Technology Working Group (IMT–WG) with the following objectives:

- To propose a new regulatory framework for the pharmaceutical quality control by the new technologies.
- To establish .PMDA's perspective on the latest technologies of pharmaceuticals quality control

International Harmonization

While the afore-mentioned regulator-sponsored initiatives represent opportunities to encourage and accommodate innovative technology, each is regionally focused. To date, there remains no effective mechanism to obtain consistent, globally aligned regulatory assessment for innovative pharmaceutical technologies or modalities. Investments in the development of these innovations is costly and is frequently technically and commercially risky, made even more so in the absence

of a regulatory landscape that does not provide for the prospect of a single, globally harmonized, approval for the implementation of that innovative technology or modality.

International Coalition of Medicines Regulatory Authorities

Many leaders from regulatory authorities across the globe are beginning to appreciate these challenges and the lack of a globally harmonized regulatory incentive to motivate pharmaceutical innovation. The International Coalition of Medicines Regulatory Authorities (ICMRA), consisting of Heads of Agencies of 30 medicines regulatory authorities, issued a policy statement in June 2021 recognizing "that pharmaceutical manufacturers seek agility to maintain robust supply chains and continually update manufacturing processes to incorporate changes and improvements as equipment ages, suppliers change, innovations are developed, and knowledge is gained." ICMRA goes on to state, "ICMRA recognizes that regulatory authorities can gain efficiencies by developing common procedures, guidelines, requirements, and interoperable infrastructure that would facilitate the timely sharing of information among regulators on changes occurring within the supply chain."[9]

ICMRA established a Pharmaceutical Quality Knowledge Management System (PQKMS) and as part of this strategy is commencing two pilot programs focusing on:

- collaborative assessment with initial focus on chemistry, manufacturing, and control (CMC) post-approval changes, and
- collaborative hybrid inspections.

The overall aim of these pilots is to improve manufacturing capacity for production of critical medicines and facilitate collaborative assessments and inspections by multiple regulatory authorities.[10]

World Health Organization

The WHO established with the EMA a collaborative registration procedure using stringent regulatory authorities' medicine evaluation.[11] Since its establishment in 2015, 59 approvals were granted to 16 medicines in 23 countries through SRA Collaborative Registration Procedures. This procedure is based on approval by a stringent regulatory authority, in this case, EMA and authorities apply the principle of reliance to improve the efficiency of their regulatory systems. The principle of "reliance" is, therefore, accepted.

Pharmaceutical Inspection Co-operation Scheme

The Pharmaceutical Inspection Co-operation Scheme (PIC/S)'s mission is to lead the international development, implementation, and maintenance of harmonized Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products.

Work-sharing Programs

In addition, regulatory work-sharing programs have introduced opportunities for regulatory alignment across multiple regulatory authorities that could serve as models for implementation of global regulatory harmonization.

- Project Orbis was started in May 2019 by the FDA's Oncology Center of Excellence (OCE) to enable faster global access to cancer treatments – as of April 2023, there are eight countries involved – Australia, Brazil, Canada, Israel, Singapore, Switzerland, United Kingdom (UK), and US. US FDA. Project Orbis.
- The Access Consortium is a collaborative effort between Australia, Canada, Singapore, Switzerland, and the UK (like-minded, medium-sized regulatory agencies).

Recommendations

The ISPE Enabling Pharmaceutical Innovation initiative team agrees with the output from the survey and supports progression of these proposals, which are given again below:

- Improve education/training, knowledge sharing and communication within regulatory authorities and with other global regulatory authorities.
- Establish globally harmonized opportunities to meet with regulatory authorities and a rapid system to produce globally harmonized guidance for innovative technologies in accordance with international regulatory organizations, i.e., International Pharmaceutical Regulators Program , ICMRA, WHO, ICH, etc.
- Introduce a globally acceptable pathway and mechanism to "approve" a platform technology (across multiple products).
- Cultivate a global mindset that innovative technologies and continual improvement ostensibly increase quality assurance for products and reduce risks compared with conventional technologies.
- Establish a common plan (and shared IT platform) for collaboration/mutual reliance/recognition of novel innovative technology among global regulatory authorities, so that plans for implementation and quality concerns can be addressed collectively.
- In accordance with a lifecycle management approach, consider a shift in regulatory governance where, in a Mature Quality Management program the Pharmaceutical Quality System serves as the primary source for regulatory assessment/inspection of continual quality improvement and innovative technologies.
- Introduce opportunities for equipment, facilities and software suppliers to engage with regulatory authorities on innovative technologies and approaches.

The ISPE Enabling Pharmaceutical Innovation team will work on the following actions:

- A summary of responses of the objectives of this initiative, the intent, design, and feedback from the survey on barriers to innovation will be submitted for publication to *Pharmaceutical Engineering* magazine. This action will serve to publicize the work of the team more broadly.
- Data and information from the survey supported by in-depth discussion with several respondents who have direct experience developing, adopting, and implementing innovative technologies will serve as the basis for case studies and provide opportunities for potential solutions which could serve as substrate for engagement with regulatory assessors and inspectors globally.
- The ISPE team will engage in promoting the above proposals with multiple regulatory authorities collectively at appropriate forums that focus on the advancement of globally acceptable and enabling regulatory approaches and opportunities to establish pragmatic incentives for industry and regulatory authorities to address specific sources of challenges to innovation and continual improvement. Ideally, approaches should be made to leverage pre-existing regulatory collaborations such as ICMRA, PIC/S, and WHO.
- The ISPE team will work with industry and equipment suppliers to understand the steps to introduce innovative technologies and develop a “points to consider” document of how to present these internally and externally to regulatory authorities.

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Appendix: Enabling Pharmaceutical Innovation Survey Readout

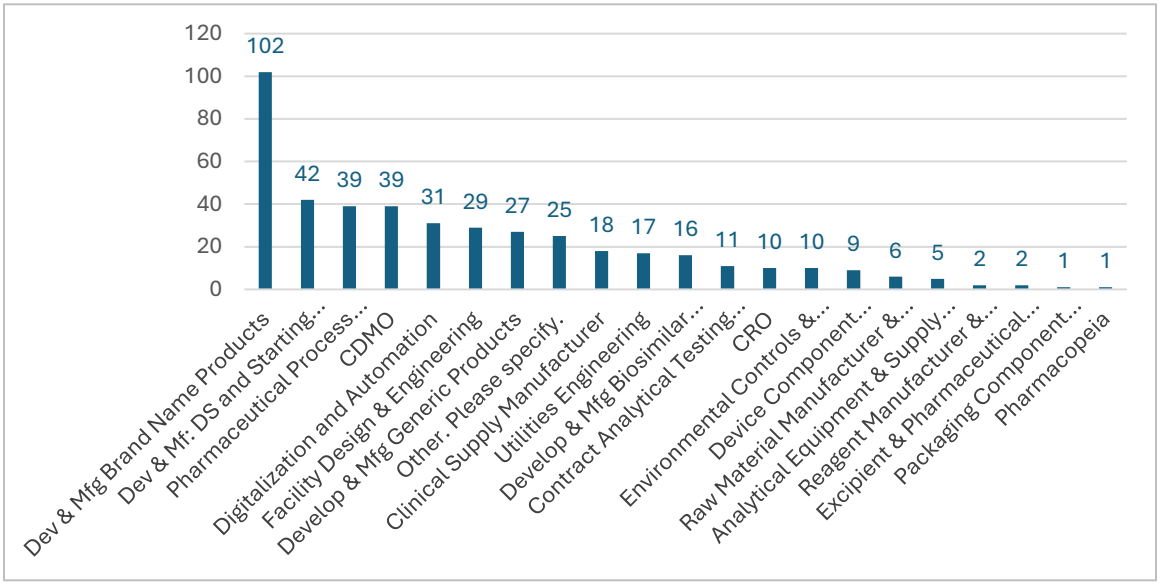
December 12, 2023
The survey had 391 responses.

Survey Part 1: Demographics and Summary Level Innovation Experience

Multiple choice questions

Q1. What role(s) does your company/organization have within the pharmaceutical industry? (multi-select)

Summary: There was broad representation across pharmaceutical manufacturing, suppliers, and service providers. Most responses came from brand name product companies (23%). There was representation from generic companies (6.1%) and biosimilar companies (3.6%).



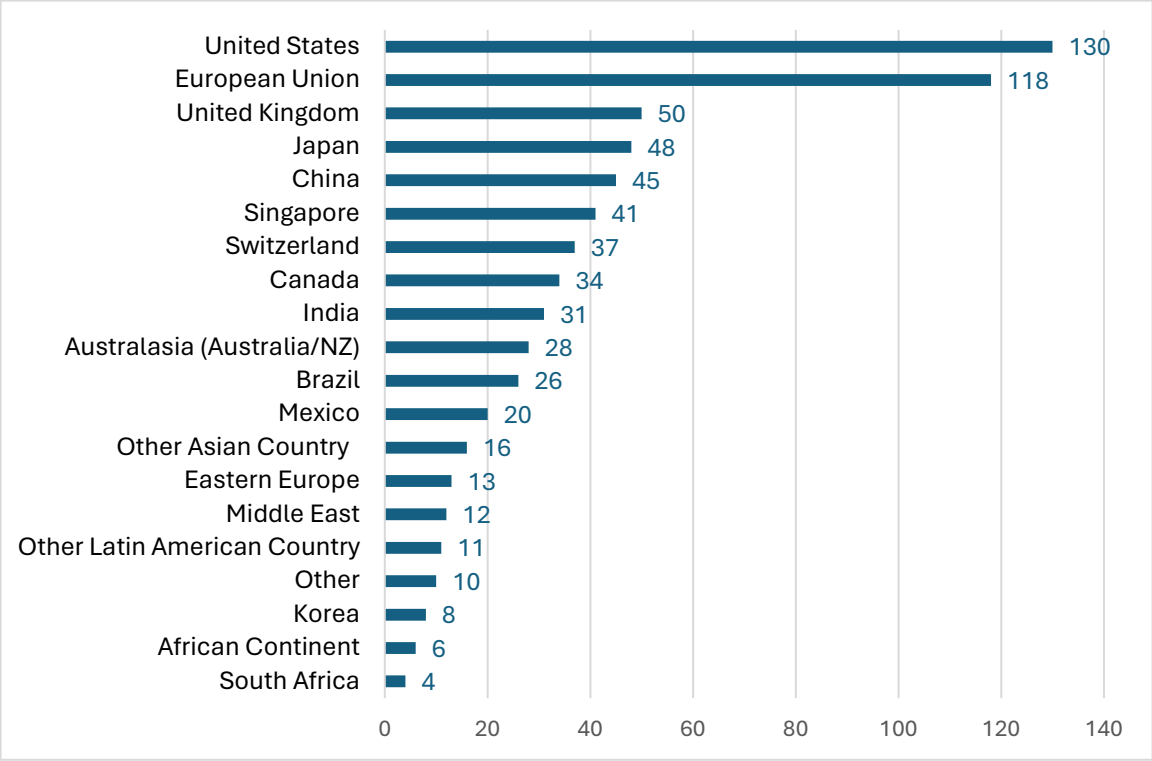
Q1 DATA		
Answer	**%**	**Count**
Develop and Manufacture: Brand Name Products	23.1%	102
Develop and Manufacture: Drug Substances and Starting Materials	9.5%	42
Pharmaceutical Process Equipment and Engineering	8.8%	39
Contract Development and Manufacturing Organization (CDMO)	8.8%	39
Digitalization and Automation, e.g., Artificial Intelligence (AI), Manufacturing Execution System (MES), Enterprise Resource Planning (ERP), Laboratory Information Management System (LIMS), Quality Management System (QMS), etc.	7.0%	31
Facility Design and Engineering	6.6%	29
Develop and Manufacture: Generic Products	6.1%	27

Q1 DATA		
Answer	**%**	**Count**
Other, please specify	5.7%	25
Clinical Supply Manufacturer	4.1%	18
Utilities Engineering	3.9%	17
Develop and Manufacture: Biosimilar Products	3.6%	16
Contract Analytical Testing Laboratory	2.5%	11
Clinical Research Organization (CRO)	2.3%	10
Environmental Controls and Monitoring	2.3%	10
Device Component Manufacturer	2.0%	9
Raw Material Manufacturer and Supplier	1.4%	6
Analytical Equipment and Supply Manufacturer	1.1%	5
Reagent Manufacturer and Supplier	0.5%	2
Excipient and Pharmaceutical Component Manufacturer and Supplier	0.5%	2
Packaging Component Manufacturer	0.2%	1
Pharmacopeia	0.2%	1
Total	**100%**	**442**

Q1. Other, please specify: non-profit association; industry and technology consulting (9; 2.03%); supplier of clinical data software; computer system validation; regulatory affairs; not pharma: blood and tissue; service provider; federal policy development; data management, migration and security; medical device software; validation and GM consultant; contract validation services; drug regulatory authority; facility construction (general contractor); pharma/biotech facility and systems design, procurement, construction and commissioning; auditing and training services; drug product; API; medical device importation.

Q2. In which region(s) does your company have development or manufacturing facilities? (multi-select)

Summary: There was a wide distribution of locations for development and manufacturing facilities, essentially global, with the majority in the US (18.9%) and the EU (17.2%).

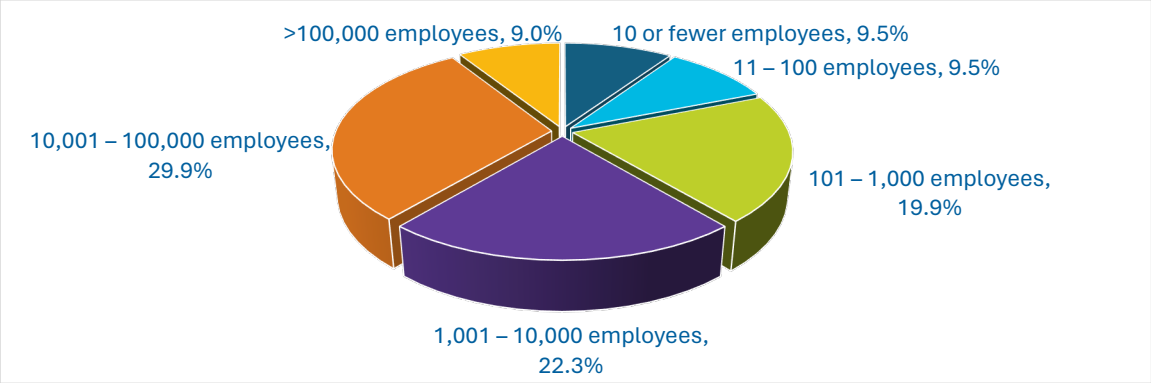


Q2 DATA		
Answer	**%**	**Count**
United States	18.9%	130
European Union	17.2%	118
United Kingdom	7.3%	50
Japan	7.0%	48
China	6.5%	45
Singapore	6.0%	41
Switzerland	5.4%	37
Canada	4.9%	34
India	4.5%	31
Australasia (Australia/NZ)	4.1%	28
Brazil	3.8%	26
Mexico	2.9%	20
Other Asian Country, please specify	2.3%	16
Eastern Europe, please specify	1.9%	13

Q2 DATA		
Answer	**%**	**Count**
Middle East, please specify	1.7%	12
Other Latin American Country, please specify	1.6%	11
Other, please specify	1.5%	10
Korea	1.2%	8
African Continent, please specify	0.9%	6
South Africa	0.6%	4
Total	**100%**	**688**
Q2. Other, please specify: Argentina (4); Armenia; Bangladesh; Brazil; Chile; Colombia (2); Croatia; Czech Republic; Estonia; Georgia; Indonesia (6); Iran; Israel (2); Mexico; client driven sites worldwide; not a manufacturer; none (2); n/a (2); Pakistan (6); Philippines (3); Poland (3); Russian Federation (4); Saudi Arabia (4); Taiwan; Thailand (2); Turkey (2); UAE; UAE/Mubadala; Vietnam; worldwide (2)		

Q3. What is the size of your company/organization?

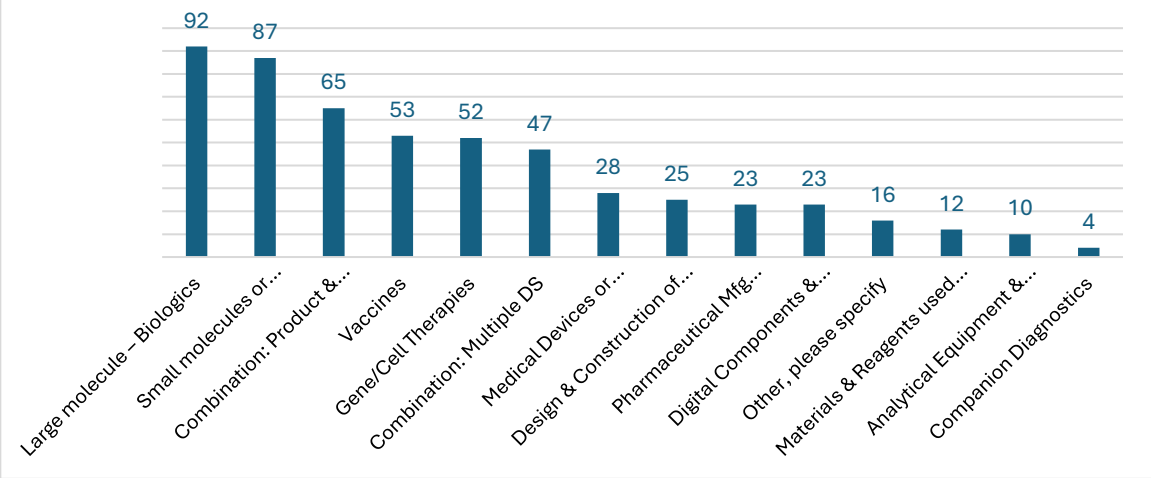
Summary: There was a good balance of company size with a skew towards larger companies (>1000 employees).



Q3 DATA		
Answer	**%**	**Count**
10,001 – 100,000 employees	29.9%	63
1,001 – 10,000 employees	22.3%	47
101 – 1,000 employees	19.9%	42
11 – 100 employees	9.5%	20
10 or fewer employees	9.5%	20
>100,000 employees	9.0%	19
Total	**100%**	**211**

Q4. What types of products does your company/organization manufacture? (multi-select)

Summary: Respondents manufactured a wide range of products and combination products and included vendors of equipment, facilities, and software. Large molecules (17.1%), small molecules (16.2%), combination products (12.1%) and vaccines (9.9%) had the highest responses. This is confirmation of the wide range of products, suppliers, and services represented in the survey.

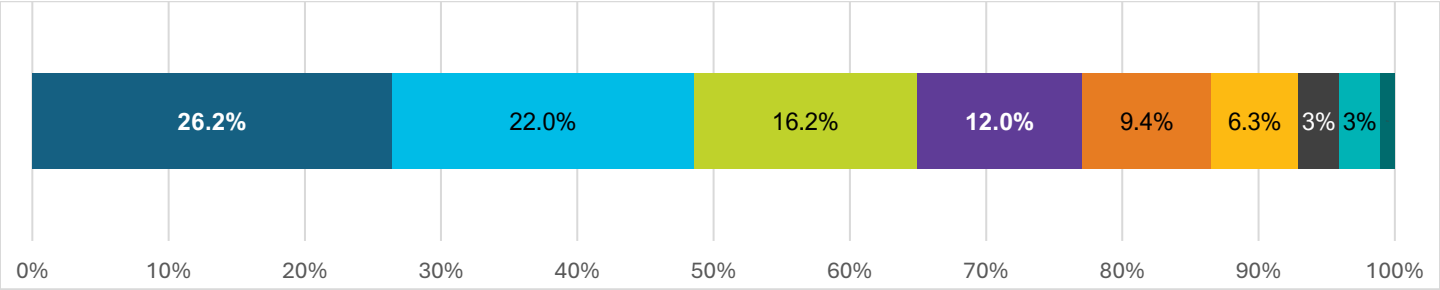


Q4 DATA		
Answer	**%**	**Count**
Large Molecule – biologics, e.g., monoclonal antibodies, Antibody Drug Conjugates	17.1%	92
Small Molecules or synthetics, e.g., oligonucleotides, peptides, etc.	16.2%	87
Combination Products: Product and Device	12.1%	65
Vaccines	9.9%	53
Gene/Cell Therapies	9.7%	52
Combination Products: Multiple Drug Substances	8.8%	47
Medical Devices or Diagnostics	5.2%	28
Design and Construction of Facilities	4.7%	25
Pharmaceutical Manufacturing Equipment	4.3%	23
Digital Components and Software	4.3%	23
Other, please specify	3.0%	16
Materials and Reagents used in Drug Substance and Drug Product Manufacture	2.2%	12
Analytical Equipment and Systems	1.9%	10
Companion Diagnostics	0.7%	4
Q4. Other, please specify: most types of products including technical services and systems; all 21 CFR 210/211 (pharmaceutical manufacturing) companies; CSV service provider and audit support; consulting services; blood and tissue production; water treatment; none; contract services, sterile injectables; process automation integration software; services, no manufacturing; validation consultancy; support of ophthalmics, antibiotics, biologics and solid dosage development and clinical manufacturing; regulation of therapeutic goods; not a manufacturer; consult in support of the above topics.		

Q5. What are the primary drivers for developing and implementing innovative technology? Please rate the following items from most important (1) to least important (9).

Summary: The top three reasons for introducing innovative are Improve Manufacturing Efficiency/Productivity, Improve Quality Assurance and Reduce Manufacturing/Operating Costs. The five reasons ranked at first place are summarized in the first column in the following table. Since ranking assignment does not necessarily follow first place ranking, Total Percent ranked first to fifth values are given in the second column.

Reason	Ranked first (%)	Total Percent ranked first to fifth
Improve Manufacturing Efficiency/Productivity	26.2	94
Improve Quality Assurance	22.0	88
Reduce Manufacturing/Operating Costs	16.2	91
Expand Business Opportunities	12.0	38
Establish an Innovative Technology Platform for Multiple Products	9.4	65



Q5 DATA																		
Option	1		2		3		4		5		6		7		8		9		Total
Improve Manufacturing Efficiency/Productivity	26.2%	50	25.7%	49	22.5%	43	14.7%	28	5.2%	10	4.2%	8	0.5%	1	1.1%	2	0.0%	0	191
Improve Quality Assurance	22.0%	42	21.5%	41	21.5%	41	12.6%	24	10.5%	20	8.9%	17	2.1%	4	1.1%	2	0.0%	0	191
Reduce Manufacturing/ Operating Costs	16.2%	31	24.6%	47	24.6%	47	13.6%	26	12.0%	23	2.6%	5	4.7%	9	1.1%	2	0.5%	1	191
Expand Business Opportunities	12.0%	23	4.7%	9	3.1%	6	8.9%	17	9.4%	18	8.4%	16	9.4%	18	42.4%	81	1.6%	3	191
Establish an Innovative Technology Platform for Multiple Products	9.4%	18	6.3%	12	10.0%	19	20.9%	40	18.3%	35	17.3%	33	8.9%	17	7.9%	15	1.1%	2	191
Meet Specific Regulatory Authority Requests	6.3%	12	7.9%	15	6.3%	12	10.0%	19	8.4%	16	13.6%	26	29.3%	56	16.8%	32	1.6%	3	191
Other, please specify	3.7%	7	0.5%	1	0.5%	1	0.5%	1	0.0%	0	0.5%	1	0.0%	0	1.1%	2	93.2%	178	191
Reduce Risk of Drug Shortage	3.1%	6	3.7%	7	5.8%	11	9.4%	18	11.5%	22	20.4%	39	28.3%	54	17.3%	33	0.5%	1	191
Reduce Environmental Impact	1.1%	2	5.2%	10	5.8%	11	9.4%	18	24.6%	47	24.1%	46	16.8%	32	11.5%	22	1.6%	3	191

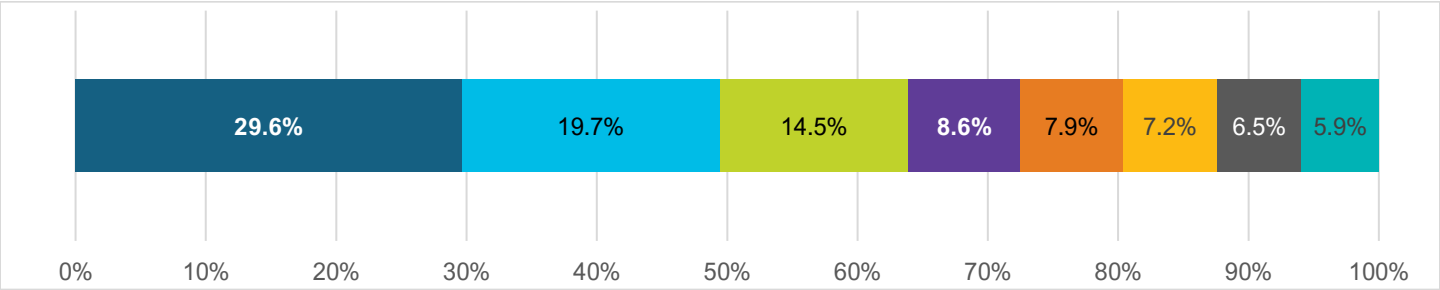
Option	Minimum	Maximum	Mean	Std Deviation	Variance	Count
Improve Quality Assurance	1.0	8.0	3.1	1.7	3.0	191
Reduce Manufacturing/Operating Costs	1.0	9.0	3.2	1.7	2.9	191
Improve Manufacturing Efficiency/Productivity	1.0	8.0	2.7	1.5	2.3	191
Establish an Innovative Technology Platform for Multiple Products	1.0	9.0	4.7	2.0	4.0	191
Reduce Environmental Impact	1.0	9.0	5.6	1.7	2.8	191
Reduce Risk of Drug Shortage	1.0	9.0	5.9	1.8	3.4	191
Meet Specific Regulatory Authority Requests	1.0	9.0	5.6	2.2	4.8	191
Expand Business Opportunities	1.0	9.0	5.8	2.5	6.4	191
Other. Please Specify:	1.0	9.0	8.6	1.7	2.8	191

Q6. Which of the following concerns with regulatory acceptability has prevented your company/organization from proceeding with innovations? Please rate the following items from most important (1) to least important (9).

Summary: The top three concerns with regulatory acceptability were challenges during application review - regulator adherence to conventional expectations that do not apply, lack of globally harmonized regulations and guidance, challenges during application review - regulator understanding of innovative technology.

The five concerns ranked at first place are summarized in the first column in the following table. Since ranking assignment does not necessarily follow first place ranking, Total Percent ranked first to fifth values are given in the second column.

Concern	Ranked first (%)	Total Percent ranked first to fifth
Challenges during application review - Regulator adherence to conventional expectations that do not apply	29.6	90.0
Lack of globally harmonized regulations and guidance	19.7	67.7
Challenges during application review - Regulator understanding of innovative technology	14.5	93.8
Challenges during inspections	8.6	41.4
Lack of implementation of globally harmonized guidelines, i.e., ICH	7.9	57.1



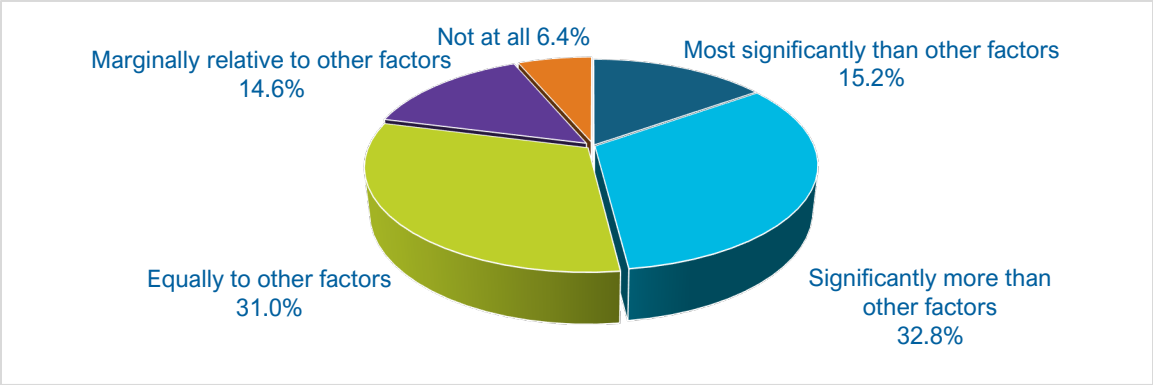
Q6 DATA																
Concern	1		2		3		4		5		6		7		8		Total
Challenges during application review - Regulator adherence to conventional expectations that do not apply	29.6%	45	18.4%	28	22.4%	34	16.5%	25	3.3%	5	5.9%	9	3.3%	5	0.7%	1	152
Lack of globally harmonized regulations and guidance	19.7%	30	21.1%	32	12.5%	19	9.2%	14	5.3%	8	23.0%	35	8.6%	13	0.7%	1	152
Challenges during application review - Regulator understanding of innovative technology	14.5%	22	21.7%	33	19.1%	29	24.3%	37	14.5%	22	3.3%	5	2.0%	3	0.7%	1	152
Challenges during inspections	8.6%	13	2.6%	4	6.6%	10	3.3%	5	20.4%	31	18.4%	28	35.5%	54	4.6%	7	152

Q6 DATA																	
Concern	1		2		3		4		5		6		7		8		Total
Lack of implementation of globally harmonized guidelines, i.e., ICH	7.9%	12	17.8%	27	13.8%	21	7.2%	11	10.5%	16	7.9%	12	30.9%	47	4.0%	6	152
Challenges during application review - Increased regulatory expectations, i.e., data, analytics, etc.	7.2%	11	11.8%	18	21.7%	33	23.0%	35	19.7%	30	13.2%	20	3.3%	5	0.0%	0	152
Other. Please specify:	6.6%	10	2.0%	3	1.3%	2	1.3%	2	0.0%	0	0.7%	1	0.7%	1	87.5%	133	152
Challenges during application review - Delays due to unanticipated queries	5.9%	9	4.6%	7	2.6%	4	15.1%	23	26.3%	40	27.6%	42	15.8%	24	2.0%	3	152

Concern	Minimum	Maximum	Mean	Std Deviation	Variance	Count
Challenges during application review - Delays due to unanticipated queries	1.0	8.0	5.1	1.6	2.7	152
Challenges during application review - Increased regulatory expectations, i.e., data, analytics, etc.	1.0	7.0	3.9	1.5	2.4	152
Challenges during application review - Regulator adherence to conventional expectations that do not apply	1.0	8.0	2.8	1.7	2.9	152
Challenges during application review - Regulator understanding of innovative technology	1.0	8.0	3.2	1.5	2.3	152
Challenges during inspections	1.0	8.0	5.5	1.9	3.7	152
Lack of globally harmonized regulations and guidance	1.0	8.0	3.7	2.1	4.5	152
Lack of implementation of globally harmonized guidelines, i.e., ICH	1.0	8.0	4.6	2.2	5.0	152
Other, please specify	1.0	8.0	7.3	2.0	4.0	152

Q7. To what extent did regulatory challenges influence decisions to develop innovative technology?

Summary**:** Regulatory challenges were reported as a very high challenge influencing decisions to develop innovative technology with 48% answering that these challenges were most significant or significantly greater than other factors. This percentage compares with 31% of answers which were that these regulatory challenges were equal to other factors with a total of 21% indicating that these were marginal or not at factors in influencing decisions to develop innovative technology.

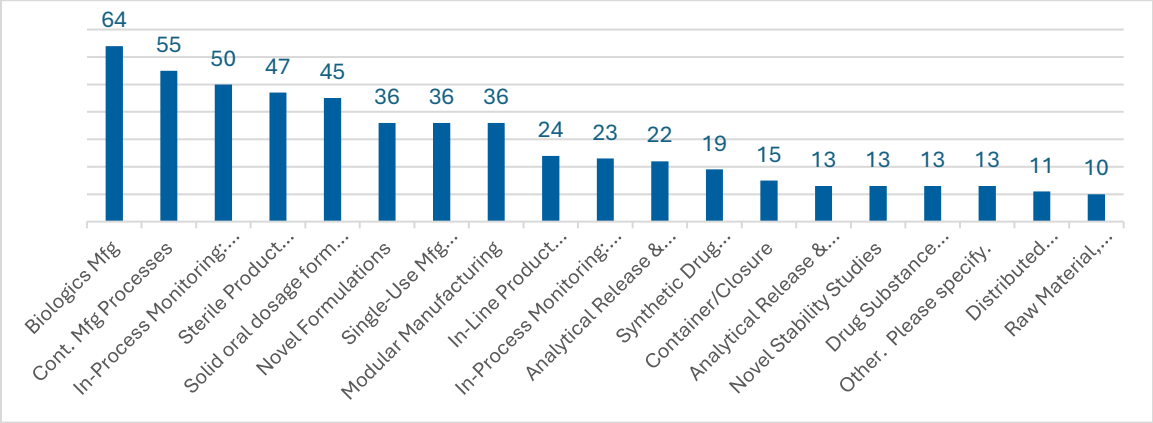


Q7 DATA			
	Answer	**%**	**Count**
	Most significantly than other factors	15.2%	26
	Significantly more than other factors	32.8%	56
	Equally to other factors	31.0%	53
	Marginally relative to other factors	14.6%	25
	Not at all	6.4%	11
	Total	**100%**	**171**

Field	Minimum	Maximum	Mean	Std Deviation	Variance	Count
To what extent did regulatory challenges influence decisions to develop innovative technology?	1.0	5.0	2.7	1.1	1.2	171

Q8. Has your company/organization developed technical innovations for any of the following manufacturing and product control operations? (multi-select)

Summary**:** There was a wide range of innovations reported with innovations with Biologics Manufacturing (11.7%), Continuous Manufacturing Processes (10.1%) and In-Process Monitoring: Process Analytical Technology (9.1%) as the top three.

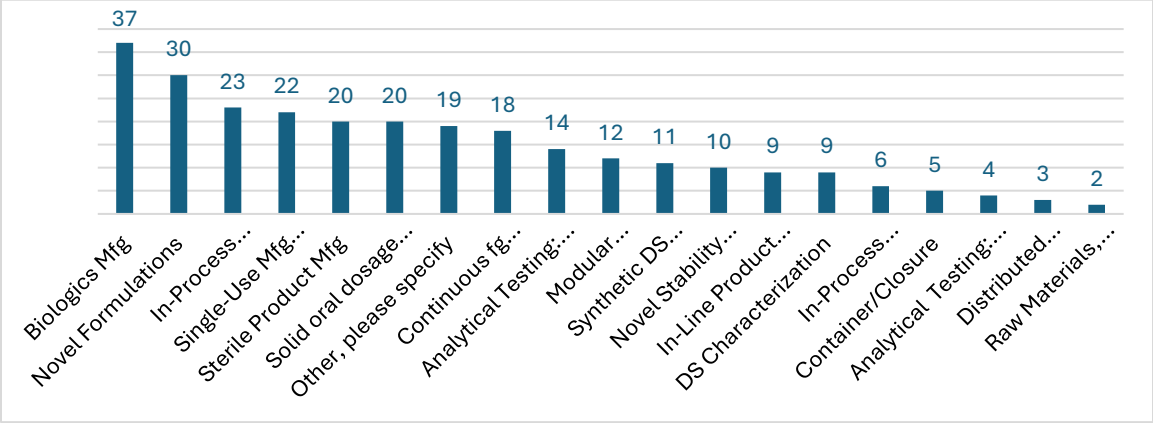


Q8 DATA		
Answer	**%**	**Count**
Biologics Manufacturing	11.7%	64
Continuous Manufacturing Processes	10.1%	55
In-Process Monitoring: Process Analytical Technology	9.2%	50
Sterile Product Manufacturing	8.6%	47
Solid oral dosage form manufacturing	8.3%	45
Novel Formulations	6.6%	36
Single-Use Manufacturing Process Systems	6.6%	36
Modular Manufacturing	6.6%	36
In-Line Product Inspection	4.4%	24
In-Process Monitoring: Adaptive Controls	4.2%	23
Analytical Procedures for Release and Stability Testing: Analytical Equipment	4.0%	22
Synthetic Drug Substance Manufacturing	3.5%	19
Container/Closure	2.8%	15
Analytical Procedures for Release and Stability Testing: Environmental Monitoring	2.4%	13
Novel Stability Studies, i.e., Accelerated Stability Assessment Program, Modelling	2.4%	13
Drug Substance Characterization	2.4%	13
Other, please specify	2.4%	13

Q8 DATA		
Answer	**%**	**Count**
Distributed Manufacturing	2.0%	11
Raw Material, Excipients and Respective Controls	1.8%	10
Total	**100%**	**545**
Q8 – Other, please specify: packaging: electronic product information and traceability; as engineering consultants we optimize existing and new utilities with regard to sustainable practices and meeting Net Zero Commitments; developed sustainable packaging; no code integration of process skids into the digital infrastructure; next generation sequencing, predictive dissolution modeling and PBPK modeling; QbD; product Track and Trace; manufacturing of novel product; Primary Product Quality; code based analysis and reporting tool; none (3x)		

Q9. Which of the innovations identified in question 8 have been submitted in regulatory applications for approval? (multi select)

Summary: Of the innovations identified in Q8, not all have been submitted in regulatory applications for approval since the order ranking for answers to this question are different from Q8. Again, there was a wide range of innovations submitted in applications with Biologics Manufacturing being the highest (13.5%) followed by Novel Formulations (11.0%).

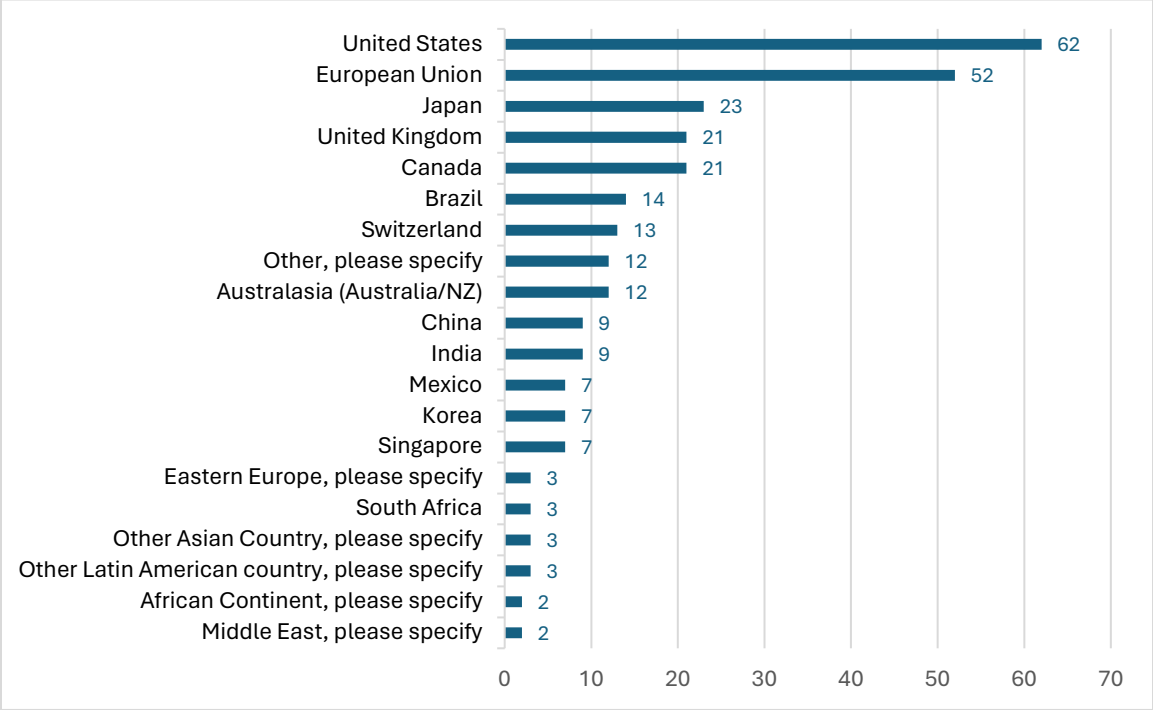


Q9 DATA		
Answer	**%**	**Count**
Biologics Manufacturing	13.5%	37
Novel Formulations	11.0%	30
In-Process Monitoring: Process Analytical Technology	8.4%	23
Single-Use Manufacturing Process Systems	8.0%	22
Sterile Product Manufacturing	7.3%	20
Solid oral dosage form manufacturing	7.3%	20
Other, please specify	6.9%	19
Continuous Manufacturing Processes	6.6%	18
Analytical Procedures for Release and Stability Testing: Analytical Equipment	5.1%	14
Modular Manufacturing	4.4%	12
Synthetic Drug Substance Manufacturing	4.0%	11
Novel Stability Studies, i.e., Accelerated Stability Assessment Program, Modelling	3.7%	10
In-Line Product Inspection	3.3%	9
Drug Substance Characterization	3.3%	9
In-Process Monitoring: Adaptive Controls	2.2%	6
Container/Closure	1.8%	5

Q9 DATA		
Answer	**%**	**Count**
Analytical Procedures for Release and Stability Testing: Environmental Monitoring	1.5%	4
Distributed Manufacturing	1.1%	3
Raw Materials, Excipients and Respective Controls	0.7%	2
Total	**100%**	**274**
Q9. Other, please specify: Next Generation Sequencing for adventitious agents, and dissolution modeling; QbD; support for manufacturing only - no applications submitted; sustainable packaging; we are equipment supplier, we do not directly submit for the approval (2x); none- no approval pathway exists; none as yet; none (6x); not applicable (2x); not submitted.		

Q10. In which regions were regulatory applications submitted for those innovations identified in question 8? (multi-select)

Summary: Innovations that were filed were geographically distributed but focused on the US (21.8%) and EU (18.3%).

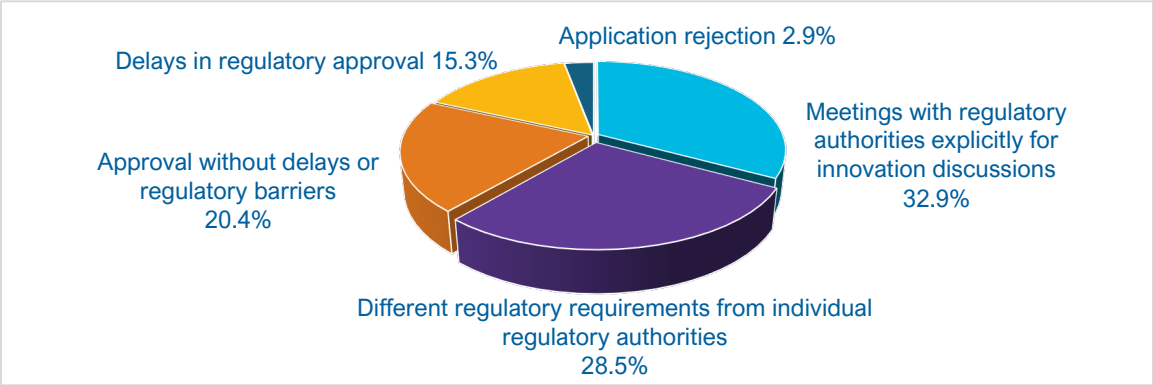


Q10 DATA		
Answer	**%**	**Count**
United States	21.8%	62
European Union	18.3%	52
Japan	8.1%	23
Canada	7.4%	21
United Kingdom	7.4%	21
Brazil	4.9%	14
Switzerland	4.6%	13
Australasia (Australia/NZ)	4.2%	12
Other. Please specify:	4.2%	12
India	3.2%	9
China	3.2%	9
Singapore	2.5%	7
Korea	2.5%	7
Mexico	2.5%	7
Other Latin American Country, please specify	1.1%	3
Other Asian Country, please specify	1.1%	3

Q10 DATA		
Answer	**%**	**Count**
South Africa	1.1%	3
Eastern Europe, please specify	1.1%	3
Middle East, please specify	0.7%	2
African Continent, please specify	0.7%	2
Total	**100%**	**285**
Q10 Other, please specify: Pakistan, Indonesia, Colombia, Ecuador, Costa Rica, North Africa, Philippines, Russian Federation.		

Q11. For those innovations submitted in regulatory applications, which of the following outcomes did you experience? (multi-select)

Summary: Respondents' experiences with the submission of innovative technologies show a range of outcomes, including approvals (20.4%), divergent regulatory expectations from individual regulatory authorities (28.5%), and delays (15.3%). Few rejected applications were reported (2.9%, 4 reported out of 152) indicating that, in general, regulatory authorities appear receptive to innovative technologies albeit with different expectations..

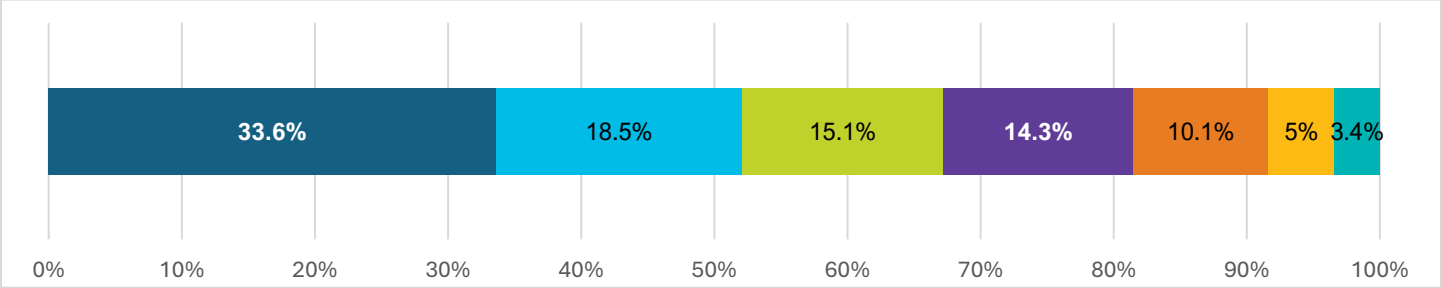


Q11 DATA			
	Answer	**%**	**Count**
	Meetings with regulatory authorities explicitly for innovation discussions	32.9%	45
	Different regulatory requirements from individual regulatory authorities	28.5%	39
	Approval without delays or regulatory barriers	20.4%	28
	Delays in regulatory approval	15.3%	21
	Application rejection	2.9%	4
	Total	**100%**	**137**

Q12. Which of the following critical factors are most important in determining cost/benefit for capital investment in innovative technology? Rate most important (1) to least important (7) for each option that applies.

Summary: Economic factors were reported as the primary drivers of determining cost/benefit for capital investment in innovative technology (Long term revenues and efficiency/productivity) as shown in the following table. Improving assurance of quality was a major factor. The need for global regulatory acceptability was also important.

Option	Ranked first (%)	Total Percent ranked first to fifth
Long Term Revenues	33.6	89.1
Manufacturing Flexibility	18.5	95.0
Global Regulatory Authority Acceptability	15.1	61.3
Efficiency/Productivity/minimizing SKUs	14.3	90.7
Quality Assurance	10.1	95.9



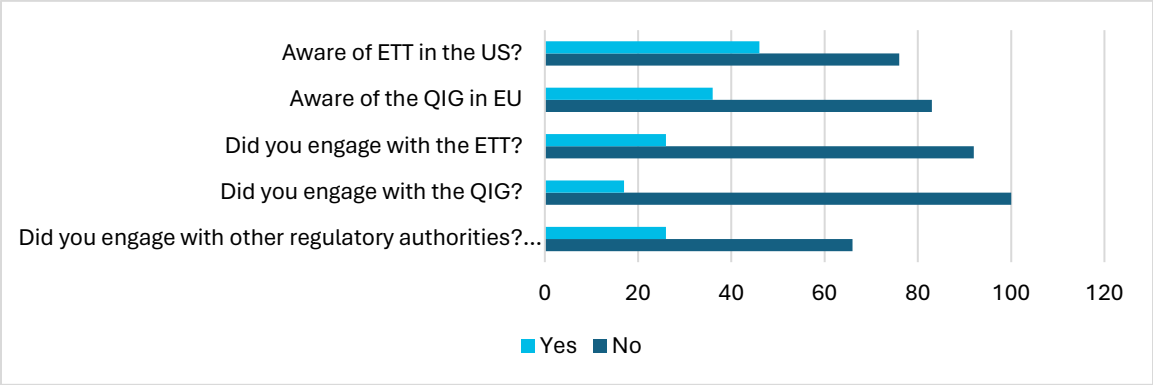
Q12 DATA														
Option	1		2		3		4		5		6		7		Total
Long Term Revenues	33.6%	40	15.1%	18	10.1%	12	17.7%	21	12.6%	15	10.9%	13	0.0%	0	119
Manufacturing Flexibility	18.5%	22	25.2%	30	17.7%	21	22.7%	27	10.9%	13	4.2%	5	0.8%	1	119
Global Regulatory Authority Acceptability	15.1%	18	15.1%	18	11.8%	14	4.2%	5	15.1%	18	37.0%	44	1.7%	2	119
Efficiency/Productivity/minimizing SKUs	14.3%	17	15.1%	18	25.2%	30	27.7%	33	8.4%	10	8.4%	10	0.8%	1	119
Quality Assurance	10.1%	12	20.2%	24	24.4%	29	21.9%	26	19.3%	23	4.2%	5	0.0%	0	119
Patient/Provider Convenience	5.0%	6	8.4%	10	10.1%	12	5.9%	7	33.6%	40	35.3%	42	1.7%	2	119
Other, please specify	3.4%	4	0.8%	1	0.8%	1	0.0%	0	0.0%	0	0.0%	0	95.0%	113	119

Option	Minimum	Maximum	Mean	Std Deviation	Variance	Count
Long Term Revenues	1.0	6.0	2.9	1.8	3.2	119

Option	Minimum	Maximum	Mean	Std Deviation	Variance	Count
Efficiency/Productivity/minimizing SKUs	1.0	7.0	3.3	1.5	2.1	119
Manufacturing Flexibility	1.0	7.0	3.0	1.5	2.2	119
Quality Assurance	1.0	6.0	3.3	1.4	1.9	119
Patient/Provider Convenience	1.0	7.0	4.7	1.5	2.3	119
Global Regulatory Authority Acceptability	1.0	7.0	4.1	2.0	3.9	119
Other, please specify	1.0	7.0	6.7	1.2	1.5	119

Q13. In your plan to develop and implement innovative technologies were you aware of or engage with: (multi-select)

Summary: There was a surprising lack of knowledge of and engagement with health authorities on innovative technology. High percentages of respondents were not aware of the US Emerging Technology Team (ETT) (62.3%) and the EU Quality Innovation Group (QIG) (69.8%) and this is reflected in the low level of engagement with both groups – 22.0% for the ETT and 14.5% for the QIG.



Q13 DATA					
Answer	**Yes**	**Count**	**No**	**Count**	**Total**
Aware of the Emerging Technology Team (ETT) in the US?	37.7%	46	62.3%	76	122
Aware of the Quality Innovation Group (QIG) in EU?	30.3%	36	69.8%	83	119
Did you engage with the ETT?	22.0%	26	78.0%	92	118
Did you engage with the QIG?	14.5%	17	85.5%	100	117
Did you engage with other regulatory authorities?	28.3%	26	71.7%	66	92
Please specify: (no entries)					

Answer	Minimum	Maximum	Mean	Std Deviation	Variance	Count
Emerging Technology Team (ETT) in the US?	1.0	2.0	1.6	0.5	0.2	122
Quality Innovation Group (QIG) in EU?	1.0	2.0	1.7	0.5	0.2	119
Did you engage with the ETT?	1.0	2.0	1.8	0.4	0.2	118
Did you engage with the QIG?	1.0	2.0	1.9	0.4	0.1	117
Did you engage with other regulatory authorities?	1.0	2.0	1.7	0.5	0.2	92

Survey Part 2: Feedback from Specific Examples of Innovation Development Experience

Text entry questions, 250-character limit

For Parts 2 and 3, many comments were received which have been summarized in a cumulative manner to comply with the survey request that responses would be anonymized and not attributable. The ISPE team has access to these comments.

Q14. In your company/organization experience, how receptive are major regulatory authorities to innovative manufacturing?

Summary: Fifty-five respondents gave relevant comments, and they reported a wide range of experiences with regulatory authority acceptability of innovative technologies. Responses indicated variability of experiences by single respondents with different regulatory regions, as well as different experiences between respondents.

Thirty-two respondents made positive comments summarized as “FDA especially with their ETT program, and EMA are very receptive,” however, there were 22 responses that indicated that receptivity, particularly in regions other than US and EU, was lacking. These comments could be summarized as “some regulators prefer to stick with what they know”.

Q15. Is the same true for smaller markets?

Summary: According to respondents (42 relevant responses), regulatory authorities in small markets seem to follow the pattern of regulatory authorities in large markets with a tendency for those in small markets to be more cautious than those in large markets with regard to introduction of innovative technologies.

Q16. In your company/organization experience, how receptive are partner companies (e.g., CRO, CDMO, co-development, co-marketing, etc.) to innovative manufacturing?

Summary: Respondents (59) reported that, in general, many partner companies are receptive to innovative technologies. However, this is not universal, and decisions to proceed with innovative technologies are largely driven by economics and at a high level within an organization.

Q17. In your company/organization experience, are proposed innovative technologies supported by internal governance?

If Yes:

- **Which factors determine proceeding with development and implementation?**
  Summary: As identified in answers to Question 12, economic and other business factors are the major factors which determine proceeding with development and implementation of new innovations.
- **At what levels in the organization are decisions to proceed and implement innovative technologies made?**
  Summary: Although titles and organizations differ between companies, generally decisions to approve and support new innovations are taken at a very senior level.
- **Is there organizational willingness to engage with regulatory authorities to discuss innovations?**
  Summary: A majority of respondents (29/49) to this question reported a willingness to engage with regulatory authorities. Three respondents indicated there was not a willingness to engage with regulatory authorities, which may be related to responses to Question 13 where a relatively low proportion of respondents (20 to 30%) indicated they did not engage with regulators.

If No:

- **Which factors determine discontinuing development and implementation of innovative technologies?**
  Summary: Respondents (28) offered a range of factors which led to discontinuation of innovative projects including business/economic drivers, lack of competence among partners, e.g., CDMOs, CROs, and concomitant appreciation of risk within organizations.

Q18. If you are a supplier or manufacturer of generic products, do your partners/clients embrace innovative technology? Why or why not?

Summary: Generally, respondents from a total of 13 clear responses indicated that generic companies do not embrace new technology due mainly to economic and risk factors. There were some companies and partners to generic companies which indicated that some generic companies embrace new technology when the business case supporting cost reduction is strong.

Q19. Has your company/organization had the opportunity to engage in a dialog to discuss innovative technologies with regulatory authorities and has this improved regulatory acceptability? If so, please provide examples.

Summary: Generally, respondents (22) reported that meetings with a single regulatory authority are positive and appear to reduce concerns. Engaging with FDA's ETT program was reported as being

very positive, with the EMA QIG also mentioned as being helpful. However, specific respondent feedback indicated experiences where there were differences in outcomes from different regulatory authorities and disconnects between regulators reviewing the merits of innovative technologies and regulatory personnel involved in inspections.

Q20. Are meetings with multiple regulatory authorities to secure their agreement a significant obstacle?

Summary: Although some respondents reported that interacting with individual, multiple agencies (13/41 relevant responses) was not a problem, a significant proportion (21/41) did report meeting with individual, multiple regulatory authorities as a challenge, indicating that the possibility of different regulatory expectations/outcomes was a deterrent to the introduction of new technology. In addition, several (3) respondents highlighted the burden associated with preparation and conducting separate and multiple meetings. Relevant comments could be summarized as "there is lack of harmonization and meeting multiple agencies is burdensome."

Q21. Has your company/organization received divergent recommendations from different regulatory authorities regarding approval and implementation of innovative technologies and has this created a significant obstacle to implementing innovative technologies? Please provide examples.

Summary: Similar to Question 20 responses, a significant number of respondents (14 of 38 relevant responses) reported not receiving different recommendations from different regulatory authorities. However, a larger proportion (18 of 38) of respondents reported receiving different regulatory expectations from different regulatory authorities and provided many examples. Divergent regulatory expectations were reported in both assessment and inspection criteria. Examples were not limited to specific issues or technologies but reflected differences in regulatory expectations for innovative formulations and devices, processes, and analytical methods.

Of particular interest was a response that COVID-related medicines did not face regulatory differences, however, for other projects such as new development approaches (quality by design) and less common manufacturing processes, regulatory divergences were observed that challenged implementation.

Q22. Have cGMP inspections from multiple regulatory authorities resulted in increased quality/regulatory requirements, i.e., implementation of excessive or duplicative controls due to a lack of global regulatory harmonization? Please provide examples.

Summary: Similar to Q20 and Q21 responses, a significant number of respondents (14 of 40 relevant responses) reported not receiving different recommendations from different regulatory authorities. However, a larger proportion (20 of 40) of respondents reported receiving different regulatory expectations from different regulatory authorities and provided many examples.

Q23. How would you characterize your experience(s) with respect to developing and implementing innovative technologies?

Summary: There were many positive experiences reported (22 of 50), however, there were also many comments (25 of 50) relating to the cost and time burden and the many frustrations faced.

Q24. How has your company/organization quantified the cost/benefit for developing, introducing, and implementing innovative technologies? Can you provide examples of the estimated total costs associated with specific innovations, particularly those innovations that require customized equipment?

Summary: From the responses, most companies are quantifying the cost/benefit for developing, introducing, and implementing innovative technologies. Perhaps as should have been expected, respondents were reluctant, or it is company policy not to share values for cost/benefit calculations.

Q25. Is innovative technology introduced as a post approval change rather than as part of a new product marketing authorization application?

Summary: A summary of responses shows a balance between regulatory approaches with 8 pre-approval, 15 post-approval and 17 both ways with a total of 40 clear responses.

Q26. In your company/organization experience, approximately how long has it taken to receive global approvals in major markets vs. smaller markets for an innovative technology?

Summary: 21 relevant comments. Approval times were reported as very variable from a few months in major markets to multiple years. Generally, about up to one year in major markets and two to three years for smaller markets. One respondent commented that long global implementation time is a barrier significant hurdle to the adoption of new technologies as separate supply chains need to be maintained until global approvals are achieved/

Q27. Based on your company/organization experience, does your organization have confidence in the cost/benefit to develop and implement innovative technologies?

Summary: 27 of the 45 clear responses showed confidence in the cost/benefit to develop and implement innovative technologies, which is greater than 50%. In addition, eight of the 45 clear responses showed qualification to progressing innovative technology projects. The total of responses indicating confidence or qualified confidence to develop innovative projects was 35 of 45, 78%. Eight of the 45 (18%) reported a lack of confidence to develop innovative technology.

Survey Part 3: Anecdotal Case Studies of Examples of Innovation Development

Text entry, no character limit

Q28. Please provide examples of innovative technologies that your company/organization has developed and prosecuted through regulatory approval and a summary of the of the experience and cost/benefit.

Summary: Examples of innovative technologies that your company/organization has developed and prosecuted through regulatory approval. A number of respondents (19) provided a wide variety of examples for the development of innovative technologies.

- One case study highlighted the benefits of early interaction with FDA, which led to optimized stability programs resulting in significant cost savings.
- In an example of an innovative introduction of equipment and software technology, the respondent was reluctant to make changes due to increased regulatory expectations.
- In an example that incorporated innovative rapid microbiological analytical methods, the respondent highlighted significant challenges with long global regulatory approval timelines.
- Other examples of innovations using Real Time Release Testing for biologics products and modular robotic fillers encountered different regional expectations that have proven to be a significant hurdle, requiring, at times, changes to equipment or methodology for one region that is considered unnecessary in other regions.

Q29. Are there innovative technologies that are cost prohibitive due to regulatory barriers to effectively implement? Please include rationale.

Summary: Respondents (19) mention some cases (7) of innovative technologies that are cost prohibitive due to regulatory barriers to effectively implement. Specific examples most mentioned were related to improved analytical methods such as rapid microbiological test methods and multi-attribute protein characterization methods.

Q30. Would your company/organization be inclined to develop innovative technology for the manufacture and control of generic or biosimilar products? Please include why or why not.

Summary: Respondents were split between those that do develop innovative technology for the manufacture and control of generic or biosimilar products (6 of24 relevant responses) versus. those (5 of 24 relevant responses) that were reluctant. Of those reluctant to invest in innovative technology, three respondents indicated their reluctance was associated with their company business strategy and one highlighted cost barriers.

Q31. What suggestions does your company/organization have to improve the receptivity and effective implementation of innovative technologies by regulatory authorities?

Summary: Respondents (25) provided a large number of suggestions to improve the receptivity and effective implementation of innovative technologies by regulatory authorities, which could be summarized as:

- More education/training, knowledge sharing and communication.
- Establish globally harmonized meeting opportunities and a rapid system to produce globally harmonized guidance for innovative technologies.
- Introduce a mechanism to "approve" a platform technology (across multiple products).
- Have a common plan with collaboration/mutual recognition of novel technology by different regulators. Have a common IT platform such that each regulator can see the plans for implementation and see each other's concerns.
- Greater effort by main health authorities (but also international regulatory organizations like ICMRA, WHO etc.) for harmonization of expectations for new technology.
- Consider a shift of documentation requirements and life cycle management of new technologies in the dossier vs. in the PQS (assessment vs. inspection)
- Introduce opportunities for vendors such as equipment and software suppliers to have discussions with regulators.
- Have a mindset that innovative technologies are proposed which provide higher levels of assurance of quality and less risk than current technologies.

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