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Applying Systems Thinking to Navigate the Global Regulatory Complexity Problem for Post-Approval Changes

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Applying *Systems Thinking* to Navigate the Global Regulatory Complexity Problem for Post-Approval Changes

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"We cannot solve our problems with the same thinking we used when we created them."
~Albert Einstein

1. Introduction

The complex global problem of managing post-approval changes (PACs) and its significant constraint on manufacturers' agility to continuously improve and address supply chain challenges has been known for over two decades. Attempts to solve the problem so far have not been successful, partly because this has been treated as a complicated[1] and not a complex problem[2].

PACs are governed and managed at a national level, even for globally supplied drug products. This leads to many redundant reviews instead of utilising a science and risk-based global review approach. Complex problems, unlike complicated ones, should be addressed by applying *systems thinking*, as outlined later in this paper.

In the pharmaceutical industry, ensuring the safety, efficacy and quality of drugs is paramount. PACs are inevitable, essential and expected by ICH Q10, *Pharmaceutical Quality System* (1), and pharmaceutical regulatory frameworks during a product's commercial life; this is necessary to maintain a state of control and to drive continual improvement. As pharmaceutical companies expand their reach globally, they encounter diverse local or regional regulatory frameworks for the same drug product with varying submission documentation requirements and approval processes for PACs. The global complexity of managing and implementing changes has continued to increase over the past two decades. There is no overarching governance to ensure global harmonisation or standardisation of PAC processes. On the contrary, individual countries continue to take independent steps to ensure supply and avoid drug shortages of global products within their country or region, in isolation of considerations for other countries.

[1] *Complicated* problems can be solved by experts
[2] *Complex* problems have no solutions but can be reduced if managed well collaboratively and collectively by key stakeholders; when a complex problem is approached as a complicated one, with an attempt by individual stakeholders to solve it only for their scope, it often worsens the problem.

Data from over 145,000 PACs across 156 countries reveals the severity of the issue (2); a global PAC rarely receives unanimous global approval within the World Health Organization (WHO)-recommended review timeline of six months (3, 4). This leads to a significant time lag between the acquisition of new knowledge about products and their manufacturing processes, and the implementation of such new knowledge into daily operations, making timely continual improvement near impossible. Addressing this challenge requires a holistic approach that can alleviate the complex problem at a different level of thinking than the one that created it. This article explores how *systems thinking* can alleviate this complex problem and revolutionise the Global PAC Management System. We discuss theoretically why attempts made to date to solve the complex problem by *linear thinking* may have had the opposite effect and made it more challenging. Finally, we elaborate on how the eight approaches recommended by the One Voice of Quality for Post-Approval Changes (1VQ for PAC) Initiative, sponsored by the Chief Quality Officers (CQOs) of the top 25 pharma companies (2) can alleviate the problem by applying *systems thinking* in addition to advancing a global approach to PAC management.

2. What is a System and *Systems Thinking*?

A system is *"a group of interacting interdependent parts that form a complex whole"* (5). In other words, a system is an entity with interrelated and interdependent parts; it is an ecosystem, where every sub-system depends on every other subsystem, either directly or indirectly. Therefore, an awareness and understanding of the boundaries of each sub-system and how it influences the others is of fundamental importance.

The term *systems thinking* has been defined and redefined by many since it was first coined in 1987 by Barry Richmond (6). *Systems thinking* is simply *"the ability or skill to perform problem solving in complex systems"* (7). The concept of *systems thinking* proposes a different way of thinking about interconnected, interdependent, dynamic aspects of complex systems, rather than focusing on individual parts that can be isolated from the whole (5). It can help unravel complex problems by understanding how components within a whole system interact and influence collective behaviours and outcomes. Key concepts of *systems thinking* can be distilled down to four elements for real-world complex systems:

1. **Interconnectedness**: Systems behave as integrated wholes, where elements dynamically impact each other over time. Understanding these linkages is crucial.
2. **Emergence**: Systems exhibit emergent properties that arise from interactions among their parts. These properties cannot be deduced by analysing individual components.
3. **Feedback Loops**: Systems contain reinforcing (positive) and balancing (negative) feedback loops. These loops shape behaviours over time and reveal patterns.
4. **Boundaries and Perspectives**: Systems have fuzzy boundaries, and their behaviour depends on the observer's perspective. Expanding and diverse viewpoints helps uncover hidden dynamics.

By understanding the whole system and its dynamics, stakeholders can collectively identify leverage points for intervention and develop strategies that lead to more effective and sustainable solutions. It

is important to note that complex problems are dynamic, therefore, their solutions must also adapt to changing contexts and unforeseen consequences to be sustainable and empower informed choices.

2.1. Why does *Systems Thinking* Matter for Complex Problems?

John Atkinson, a systems thinker and thought leader, states that (8):

> *"Messy complex problems are just too hard for individuals to comprehend, so we parcel it up into packets of problem we can understand and manage and tell ourselves that we have done a good and right thing."*

Systems thinking challenges this notion and assumption in that:

- the way we run an organisation – be it a regulatory authority, pharmaceutical company, government, legislative or policy-making body, hospital, distribution channel or country – is how it should be run to serve its purpose and be of value to society,
- each stakeholder designing and owning their solutions within their respective organisational accountabilities is an optimal approach and
- each stakeholder's control, or even influence, is limited beyond their own organisation's primary and maybe, secondary boundaries, that interface with another organisation.

It is important for each stakeholder involved in the ecosystem of a complex problem to first look inwards to determine what they could do to contribute towards solving the problem. After this, they can begin to collaborate with all other stakeholders to enable joint application of the resulting solutions.

Organisations manage relationships with other organisations they need to interact with, but this is typically linear and within their individual positional power and hierarchies. However, in a *systems world*, power is dispersed; the relevance of traditional positional authority that certain stakeholders may have over others must be diminished and set aside to connect, collaborate and jointly solve issues for the collective good of society. Current organisational setups, systems and ways of working tend to inherently push back on complex problems and typically address them by applying linear thinking from each stakeholder's viewpoint, which in hindsight often results in superficial, temporary or otherwise suboptimal solutions, and often adds more complexity or bureaucracy to the system as a whole. The global PAC complexity with respect to increasing local or regional requirements is an example of this, and though the objective is to reduce drug shortages at a national level, it doesn't solve the problem at a global level.

Therefore, several system scientists such as Atkinson and Myron Rogers have asserted that complex problems are addressed by asking the key questions below and not by following standard operating procedures (8):

- *"Who are the 'we' who have a collective interest and energy for addressing the problem we face?*

- *What do we individually and collectively know about what is going on in order that we might make more sense of what we are trying to do?*
- *How well do we connect to each other so that we might have the opportunity to decide where to place our efforts?"*

To address these questions, it is critical to have the same level of awareness and a common understanding of the problem and its implications before it can be solved. The ability to work with multiple perspectives, value insights and knowledge offered by each of those perspectives, but not at the exclusion of others, and harness the collective power of the sub-parts of a whole living system to co-create solutions is the fundamental basis of *systems thinking* and *systems leadership* (8), the concept of working beyond organisational boundaries to address issues of mutual concern. As new connections form between stakeholders, new patterns, relationship formats, interaction and decision pathways emerge, and transformative solutions that once could not be conceived become possible. At the same time, this could challenge existing ways of operating and may even lead to the collapse of conventional or traditional ways of working.

To apply *systems thinking*, the following steps should be followed collaboratively across the different stakeholder groups:

1. **Define the Problem**: Clearly articulate the complex problem's scope. Understand its context, stakeholders and interdependencies.
2. **Map the System**: Visualise the system using diagrams, models or simulations. Identify components, stakeholders, relationships and feedback loops.
3. **Identify Patterns**: Explore behaviour-over-time patterns. Look for reinforcing or balancing loops that drive system dynamics.
4. **Intervene Strategically**: Develop interventions based on insights. Address root causes rather than symptoms.
5. **Collaborate**: *Systems thinking* thrives on diverse perspectives. Engage stakeholders across system sub-parts to co-create and jointly implement solutions.
6. **Iterate and Learn**: Continuously adapt and refine the approach. Systems evolve, and so should one's understanding.

3. Applying *Systems Thinking* to the Problem of Global Regulatory Complexity for PAC Management

Systems thinking is intended to drive user-centred processes and solutions. In the case of PAC management, the end user is patients who deserve safe, effective, quality medicines on time, every time, irrespective of country of residence.

Pharmaceutical companies and regulatory authorities (assessors and inspectors) are only two subsystems within the whole, which involves many other organisations, stakeholders and their respective processes. It is acknowledged, as depicted in Figure 1 below, that regulatory frameworks in each country (including those for assessments and inspections) and industry practices are influenced by local or regional healthcare systems, legislation, policies, governmental setups, socio-economic

factors, supply chain considerations, etc., which make this a complex ecosystem. Figure 1 is a high-level simplified representation of the system in any one country relevant to providing products to patients in that country. Every country has a similar system, which exponentially increases the complexity at a global level. The industry stakeholder in most cases is the same company producing the same product for patients worldwide, while the assessors and inspectors are country specific.

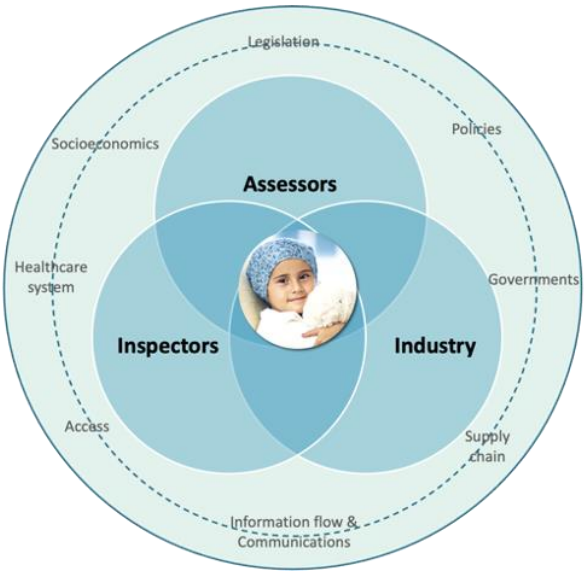

Figure 1 – High-Level Representation of the System (Sub-systems and Stakeholders) Involved in a Country

However, if only two of the sub-systems, namely pharmaceutical industry and the many national or regional regulatory authorities, could collaborate to understand their interconnectedness, interdependencies and feedback loops, the start of *systems thinking* could be applied. From this, these entities could begin to jointly design and implement solutions across both their sub-systems, potentially resulting in a meaningful impact for the pharmaceutical sector in terms of advancing timely innovation and continual improvement.

Figure 2 illustrates the interactions between these two sub-systems. Companies interact with assessors and inspectors from each country or region that the product is marketed in.

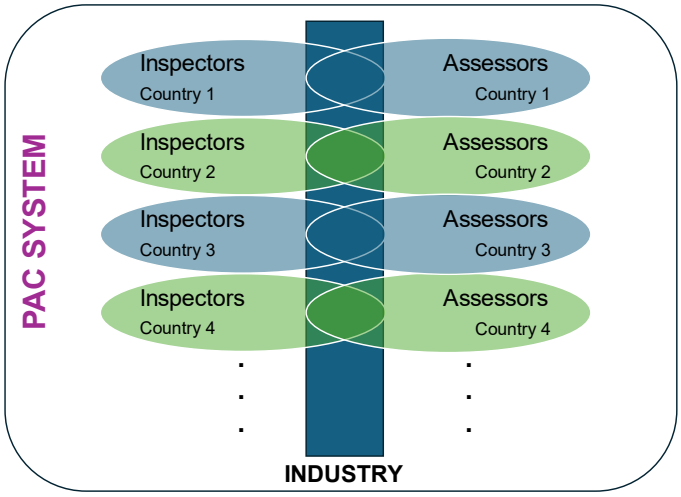

Figure 2 – Interactions between Industry (Companies), Assessors and Inspectors

The general modus operandi in the pharmaceutical sector has remained that regulatory authorities establish expectations and requirements primarily at a national or regional level, collectively as 'guidance' for industry, which must then be implemented by those companies. Decades of emphasising compliance as a means to achieve quality might have limited continual improvement and innovation in the pharmaceutical industry. Beyond complying with the Good Manufacturing Practices (GMPs), the pharmaceutical sector (both industry and regulatory authorities) must adopt mainstream quality management standards and principles (9). This was indeed the intent of the ICH Q10 PQS model, but thus far, the ISO 9001 quality management-based concepts that ICH Q10 has been based on, have not been realised.

Many regulatory authorities have a practice of inviting feedback on draft regulatory guidance before they are finalised and brought into force. Beyond this practice, over the last few years, some regulatory authorities and organisations such as the United States Food and Drug Administration (FDA), Pharmaceutical Inspection Cooperation Scheme (PIC/S) and World Health Organisation (WHO), have started inviting more input from the industry for pilot projects. Such projects to date have related to the implementation of tools and concepts, such as quality maturity assessments, inspection protocols, post-approval change management protocols (PACMPs), etc. A current example of this is the International Coalition of Medicines Regulatory Agencies (ICMRA's) Pharmaceutical Quality Knowledge Management System (PQKMS) Initiative that is conducting pilots for the joint review of PAC submissions by select regulatory authorities (10).

However, there have been very limited, if any, collaborative proposals made by the pharmaceutical industry to regulatory authorities or vice-versa. There is also no guidance for regulators to facilitate harmonisation of data requirements for PAC submissions, harmonisation of reviews across assessors from different countries and overall standardisation of PAC assessment and decision-making.

It is imperative that solutions to address the global regulatory complexity for PACs be developed through active collaborative dialogue and input-gathering, across both pharmaceutical companies and regulatory authorities. Exchange in workshop settings between regulatory authorities and pharmaceutical companies to reach common understanding, followed by co-development, testing,

implementation, iteration and continued adaptation of solutions as the system dynamics and stakeholder behaviours evolve, is an integral component of the systems approach fostered by *systems thinking*. Such exchange also serves a valuable means for pharmaceutical companies to build credibility and trust with regulators. So far, no solutions that have been implemented or are in progress are being approached in this manner.

Yet, *systems thinking* propounds that involved individuals or stakeholders must constantly be aware of and understand the boundaries between their respective sub-systems, and design solutions that are not linear or siloed in addressing only their individual parts, but the whole. It is contrary to the conventional tendency to reinforce organisational boundaries through structures, systems, policies, etc. When applied to the problem of global regulatory complexity in PAC management, *systems thinking* offers several key insights and strategies.

Firstly, *systems thinking* encourages stakeholders to view regulatory compliance as part of a larger ecosystem rather than as isolated requirements. This perspective recognises that regulations are influenced by various factors, including political, economic, social and technological forces. By analysing these factors and their interactions, pharmaceutical companies can anticipate regulatory trends, identify potential barriers, proactively adapt their processes and engage with regulatory authorities to comply with evolving requirements.

Systems thinking also emphasises the importance of collaboration and communication among stakeholders within the pharmaceutical and regulatory ecosystem. In the context of post-approval change management, this means pharmaceutical companies and regulatory authorities fostering open dialogue, building trust-based relationships, sharing best practices, streamlining processes, harmonising standards and co-creating solutions that optimise both sub-systems.

Thirdly, *systems thinking* encourages the adoption of flexible and adaptive regulatory strategies that accommodate the diverse needs and preferences of different regions and consider quality system maturity and robust science and risk-based decision-making by companies. Instead of pursuing a one-size-fits-all approach, pharmaceutical companies and regulatory authorities can tailor each their change management and review and approval processes to align with specific regulatory requirements while maintaining consistency in quality and safety standards. This may involve conducting risk assessments, utilising advanced technology for data analytics and information exchange, utilising an effective PQS or leveraging agile regulatory reliance for timely decision-making on PACs. Regulatory agencies can assess the effectiveness of the company's PQS, including the change management system during inspections as outlined in the PIC/S Recommendation Paper on *How to Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management* (11).

Furthermore, *systems thinking* highlights the importance of continuous learning and improvement. In the dynamic global landscape, there is no single or static solution that guarantees long-term success. Instead, companies and regulatory authorities must embrace a culture of innovation, experimentation and adaptation. By monitoring key performance indicators, regularly soliciting feedback from involved stakeholders and conducting post-implementation reviews, both sub-systems can identify

opportunities for optimisation at a system level and refine their change management and approval processes iteratively.

Lastly, *systems thinking* encourages a holistic approach to risk management that considers not only regulatory compliance but also quality performance and broader implications for patient safety, product quality and business continuity. This requires assessing the potential impact of post-approval changes across the entire value chain, from manufacturing, supply and distribution to global market access. By integrating risk management principles into their decision-making processes, pharmaceutical companies and regulatory authorities can mitigate potential risks, minimise disruptions or drug shortages and ensure timely continual improvement and innovation during the commercial life of a product.

4. How can Ongoing Initiatives Enable *Systems Thinking*?

Various initiatives have been undertaken over the past two decades to solve the problem of the complexity of PACs. More recent initiatives such as ICMRA's *PQKMS* initiative (10) are increasing collaborative work and active engagement of senior leaders among regulatory authorities, similar to the industry *1VQ for PAC Initiative*, which is bringing the industry together to align, standardise and speak with one voice (12). This is a new and valuable emerging theme as coordinated efforts within any sub-system as a first step will drive better results and greater impact. The *1VQ for PAC Initiative* sponsored by the Chief Quality Officers of the largest 25 global pharmaceutical companies in a recently published paper recommended the following eight approaches to alleviate this complex problem (2):

- **Approach 1** (1VQ for PAC): **Manage more low risk PACs in the PQS only** for companies that demonstrate an effective PQS and have good product and process understanding per ICH Q10 Annex 1 (1)
- **Approach 2** (PIC/S): Inspectors **use PIC/S Recommendation Paper**, *How to Evaluate and Demonstrate Effectiveness of the Pharmaceutical Quality System in Relation to Risk-Based Change Management* **to assess effectiveness of a company's Change Management System** (11)
- **Approach 3** (WHO): **Increased reliance** among regulatory agencies following the WHO guidance to reduce redundant assessments of PACs (13)
- **Approach 4** (ICMRA): **Harmonise/standardise data elements** and electronic formats for PACs through ICMRA's PQKMS Initiative (10)
- **Approach 5**: Industry and regulatory authorities jointly **standardise** and bring transparency to the **process** and **data for assessing a PAC**, based on the scientific/technical risk basis for the change
- **Approach 6:** Adoption of the WHO guidance on PAC review **timeline of six months** (3, 4) and the WHO guidance on regulatory reliance by all National Regulatory Authorities (NRAs) (13)
- **Approach 7**: Establishing a consistent approach for how **assessors** should **consider PQS effectiveness** assessment by inspectors, when deciding on PAC reporting levels
- **Approach 8:** Set up metrics and regularly **publish data on PAC review and approval timelines** for each country

These approaches are relevant for both pharmaceutical companies and regulatory authorities (assessors or inspectors) and several are being led by specific industry or regulatory authority groups. They mark a starting point and an excellent basis to start driving *systems thinking*. Relating back to the four key elements of *systems thinking* – interconnectedness, emergence, feedback loops and boundaries and perspectives – the next step for these approaches and the leading stakeholder groups would be to address the following questions raised by Atkinson (8) to drive *systems thinking*:

First, *"Who are the 'we' who have a collective interest and energy for addressing the problem we face?"*

> Considering the two sub-systems, the 'we' with the collective interest and energy for addressing this complex problem would be industry and regulatory authorities (assessors and inspectors) globally. Today these stakeholder groups are actively working on solving the problem as noted above in approaches 1 through 4; however, they are doing so independently within their respective sub-system's scope and boundaries.

Next, *"What do we individually and collectively know about what is going on in order that we might make more sense of what we are trying to do?"*

> Over the past three to five years, there has been a notable increase in the level of awareness and understanding on how complex the problem is at a global scale, the challenges it leads to in routine operations, logistics and supply planning and the delays it causes in continual improvement and innovation during the commercial life of a product (2, 12, 14). This higher level of awareness has activated both the industry and regulatory authorities to individually and collectively acknowledge the problem and initiate activities to attempt to solve it. However, most of these activities have been individual stakeholder-focused thus far; for instance, guidances and expectations for the industry (ICH Q12), solutions intended for companies (1VQ for PAC risk-based approach for PACs), solutions targeted for regulators (e.g., ICMRA's *PQKMS* initiative, regulatory reliance), national approaches, etc. No solutions yet have been co-designed or co-implemented through joint stakeholder collaborations; more needs to be done in this regard. Additionally, there is limited knowledge about this complex problem and its impact on product supply and continuous improvement amongst politicians, policy makers, the scientific press and patient groups.

"How well do we connect to each other so that we might have the opportunity to decide where to place our efforts?"

> While there has been an increase in dialogue at conferences, efforts across the industry and regulatory authority sub-systems have not been well connected yet. During the COVID-19 pandemic, regulatory authorities rapidly put in place various emergency procedures for managing PACs to avoid drug shortages. These included taking a risk-based approach to

> manage more PACs in the PQS only (for a while) and more reliance between countries. The next step towards *systems thinking* would be for the stakeholders to come together and
>
> (1) collectively understand the interconnectedness and feedback loops for their respective solutions,
>
> (2) co-create solutions based on a deeper understanding and appreciation of their interface dynamics and how it shapes practices and behaviours within and among their sub-systems, also building on lessons learned from the pandemic, and
>
> (3) jointly implement the co-created solutions, actively exchange learnings (what worked well, challenges, what could be improved), and continuously adapt to improve.

Below is a listing of how the earlier-mentioned stepwise approach could be taken to apply *systems thinking* to this complex problem for global PAC management:

1. **Define the Problem**: The *1VQ for PAC Initiative* has defined the problem and its complexity well over the last five years, and has also clearly articulated the context, impact, stakeholders and interdependencies (2, 12, 14). The problem, however, still needs to be appreciated by politicians and policy makers who continue taking steps to reduce drug shortages with a linear siloed thinking approach, focusing only on their respective country or region.
2. **Map the System**: Several visuals and graphics have been published to depict the problem. Additional joint multi-stakeholder exchanges in the form of workshops, for instance, would be useful to visualise the system holistically, identify sub-system components, stakeholders, relationships and feedback-feedforward loops. There have been useful examples of the same visuals being used by both industry and regulatory authorities. Developing one set of visuals jointly agreed upon by regulatory authorities and industry would help with mapping and aligning on the boundaries of the system and its sub-systems.
3. **Identify Patterns**: The context of patterns and behaviours for this problem have not been explored fully yet. While the level of awareness and dialogue has certainly increased, an understanding of the overall system dynamics, including reinforcing and balancing loops within the system and resulting behaviour-over-time patterns, is still non-existent. The recently published large PAC dataset showing approval timelines across 156 regulatory authorities indicates that maturity level 3 and 4 countries in general approve PACs faster than maturity level 1 and 2 countries. This should be investigated further to identify 'the long tail' for each PAC approval. A practical way to explore and develop this understanding at a system level would be through simulations and pilots on a variety of actual PAC use cases where industry, assessors and inspectors jointly value stream map the process(es). The objective is to understand the interfaces, connections, decision nodes and behaviours, to ultimately identify patterns. An open, curious mindset to explore and understand would be essential for such an exercise. The *PQKMS* Initiative could be broadened to enable such joint exercises across the industry, assessor and inspector stakeholder communities.
4. **Intervene Strategically**: The resulting learnings and insights should then lead to the co-development of sustainable solutions and interventions at the senior decision-making level

for all stakeholders to address root causes, rather than react only to the symptoms. This could lead to a strategic redesign of the system, including modifications to the sub-systems, their respective processes, decision nodes, communication mechanisms and information flows. An example of this is the use of standard data sharing platforms whereby global submissions can be made by companies and reviewed collaboratively and concurrently by multiple regulatory authorities; the technology is available, but so far, it hasn't been effectively used for this purpose. It is important to emphasise that sovereignty must be ensured for each country for PAC approvals.

5. **Collaborate**: *Systems thinking* brings in and uses diverse perspectives by engaging stakeholders across system sub-parts to co-create and jointly implement solutions. The system design itself should lend towards collaborations that enable faster decision-making, timelier implementation of improvements and are science-based rather than country-based. An example is the concept of agile regulatory reliance through adoption of the already existing WHO guidelines on regulatory reliance (13) and PAC review timeline of six months, where regulatory authorities that cannot review within six months (3, 4) would leverage the review performed by a reference country. Another example is an upcoming workshop between PIC/S and the industry *1VQ for PAC Initiative* to jointly implement for inspectors and companies, based on the PIC/S Recommendation Paper on *How to Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management* (11). Reducing the gap and calibrating more efficiently between companies and inspectors on what an effective change management system should look like would be a direct application of *systems thinking*.
6. **Iterate and Learn**: Complex problems cannot have static solutions since the system dynamic constantly evolves. Therefore, the system design should be amenable to continuous adaptations and refinement of the solutions. This includes the development of new solutions based on the evolution of our understanding. This is currently not the norm for the PAC management global framework. It may be too early to articulate what this might look like, but joint stakeholder exchanges should be initiated to explore how this aspect might be built into the design of the overall system and the respective sub-systems. When improvements are realised, these 'wins' should be broadly communicated, and lessons learned sessions conducted to facilitate further improvements.

5. Conclusion

In conclusion, applying *systems thinking* to the problem of global regulatory complexity in PAC management offers a new and different comprehensive and strategic approach for pharmaceutical companies and regulatory authorities. The approach should be science-based rather than individual country-based. Attempts to alleviate the PAC problem to date have applied a 'one stakeholder at a time' approach, which in practice has not yielded expected results because of the complexity of the problem. If companies and regulators were to co-develop, implement and jointly measure impact of these interconnected solutions within and across their sub-systems, the reduction in number of open PACs at any given point in time for a company, and the global approval timelines for individual PACs, could become useful measures of success for the timely management and implementation of new knowledge gained during the commercial life of a product. It would also advance continual improvement and innovation through effective and timely PAC management, in addition to alleviating

drug shortages caused by aging facilities, equipment, processes and methods that need to be improved. Finally, an aligned effort on *systems thinking* would also be a useful indicator of the level of trust and regulatory flexibility earned by a company from regulatory authorities. To achieve this, open sharing and exchange on current practices, collaborative dialogue on challenges and how to overcome them and ways to optimise for both industry and regulators, will be essential. Without this, all parties involved run the risk of trying to solve the problem at the level it was created using traditional linear, siloed, stakeholder-focused approaches.

By using the steps described in this paper to understand the interconnectedness of industry and regulatory subsystems, industry and regulatory agencies can create the opportunity to

- foster collaboration and communication
- adopt flexible regulatory strategies,
- embrace continuous learning and improvement and
- be open even to possibly redesigning current processes and decision-making nodes,

In turn, both industry and regulatory authorities can navigate this global complexity more effectively and ensure the timely and compliant implementation of PACs. There is unprecedented opportunity for these sub-systems and their stakeholders to come together in applying *systems thinking* to collectively serve the needs of both their individual sub-systems and the interfacing, interconnected and interdependent aspects of other sub-systems with which they co-exist. This may be an opportunity for academia to intervene and help facilitate such a collaboration opportunity.

As the pharmaceutical industry continues to evolve in an increasingly interconnected world, *systems thinking* will be essential for driving innovation, resilience and sustainability for commercial products.

References

[1] ICH (2008) *ICH Q10: Pharmaceutical Quality System*. Available from: https://www.ich.org/page/quality-guidelines.

[2] Vinther, A. *et al.* (2024) Approaches to Design an Efficient, Predictable Global Post-Approval Change Management System that Facilitates Continual Improvement and Drug Product Availability, *Therapeutic Innovation & Regulatory Science*. Available from: https://doi.org/10.1007/s43441-024-00614-9.

[3] WHO (2015) *Guidelines on Procedures and Data Requirements for Changes to Approved Vaccines*, Annex 4, TRS No 993. Available from: https://cdn.who.int/media/docs/default-source/biologicals/vaccine-standardization/annex4_guidelines_changes_to_approved_vaccines_eng.pdf?sfvrsn=9046ee8f_3&download=true [accessed: 5 April 2024].

[4] WHO (2018) *Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products*. Available from: https://cdn.who.int/media/docs/default-source/biologicals/biotherapeutics/annex_3_extract_who_trs_1011_web.pdf?sfvrsn=de2b6a0a_5&download=true [accessed: 5 April 2024].

[5] Montuori, A. (2011) Systems Approach, *Encyclopaedia of Creativity*. San Diego: Academic Press, pp. 414–421. Available from: https://doi.org/10.1016/B978-0-12-375038-9.00212-0.

[6] Arnold, R. and Wade, J. (2015) A Definition of *Systems Thinking*: A Systems Approach, *Procedia Computer Science*, 44, pp.669-678. Available from: https://doi.org/10.1016/j.procs.2015.03.050.

[7] Wikipedia (2021) *Systems theory - Wikipedia*. Available from: https://en.wikipedia.org/wiki/Systems_theory [accessed: 5 April 2024].

[8] Atkinson, J. (2018) *Introducing Systems Leadership – Heart of the Art*. Available from: https://www.heartoftheart.org/?p=306 [accessed: 5 April 2024].

[9] Calnan, N. (2014) Protecting the Patient: Enhancing the Quality of Pharmaceutical Products, *Dublin Institute of Technology*

[10] ICMRA (2021) *Global Pharmaceutical Quality Knowledge Management: Enhancing Regulatory Reliance and Agility | International Coalition of Medicines Regulatory Authorities (ICMRA)*. Available from: http://www.icmra.info/drupal/strategicinitatives/pqkms/statement [accessed: 5 April 2024].

[11] PIC/S (2021) *How to Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management*. Available from: https://picscheme.org/docview/4294 [accessed: 5 April 2024].

[12] Ramnarine, E. *et al.* (2020) Industry One-Voice-of-Quality (1VQ) Solutions: Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS)-through Enhanced Science and Risk-Based Approaches, *PDA Journal of Pharmaceutical Science and Technology*. Medline, 74(4), pp.456–467. Available from: https://doi.org/10.5731/pdajpst.2020.011734.

[13] WHO (2021) *TRS 1033 - Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations*. Available from: TRS 1033 - Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations (who.int) (Accessed: 5 April 2024).

[14] Ramnarine, E. (2021) Solving the Continual Improvement and Innovation Challenge for the Benefit of Patients: How an Effective Pharmaceutical Quality System (PQS) and Risk-Based Approach Could Transform Post-Approval Change (PAC) Management, *Technological University Dublin*. Available from: https://doi.org/10.21427/960f-8s69.