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The Ongoing Journey of the One Voice of Quality for Post-Approval Changes (1VQ for PAC) Initiative

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The Ongoing Journey of the One Voice of Quality for Post-Approval Changes (1VQ for PAC) Initiative

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Abstract

Since 2018, the Chief Quality Officers (CQOs) of the top 25 pharma companies have spoken with one voice of quality on the topic of post-approval changes (*1VQ for PAC Initiative*). The *1VQ for PAC Initiative* has developed practical approaches to significantly reduce the complexity of the global PAC regulatory framework. This current framework poses a risk to the supply of products to patients, as it drastically slows innovation and continual improvement. The CQOs built on an opportunity from the ICH Q10 Guideline to earn regulatory flexibility, allowing management of more PACs in the Pharmaceutical Quality System (PQS) only and have published a definition of an effective PQS. The *1VQ for PAC Initiative* has also published data for more than 145,000 PACs covering 156 countries, illustrating the size of the PAC management problem. The CQOs continue to advocate eight practical solutions, including managing more PACs in the PQS only and implementing agile regulatory reliance practices amongst regulatory agencies.

1. Introduction

The role of Quality (Quality unit or Quality Assurance (QA)) is clearly defined in the legal and regulatory frameworks for the pharmaceutical industry. Quality, which must be organisationally separate from Manufacturing Operations, is responsible for the Pharmaceutical Quality System (PQS) and makes the final decision on all current Good Manufacturing Practice (cGMP) and quality matters for the company. This includes approval of deviation investigation reports, corrective and preventive actions (CAPAs), change requests and the final disposition of drug product batches intended for patients.

The head of the Quality organisation often has the title Chief Quality Officer (CQO). The CQOs of the top 25 pharmaceutical companies (by revenue) decided to come together in 2018 to speak with one voice of quality (1VQ) on the topic of post-approval changes (PACs). The current global regulatory framework for managing PACs is highly complex and it drastically slows down innovation and continual improvement. It is also a risk to the supply of products to patients. The reason is that for a globally marketed product, each PAC requires submission to several (often several dozens) individual national regulatory agencies for prior approval, each with varying reporting requirements and, in many cases,

unpredictable response timelines. In practice, full global approval can take three to five years. This makes inventory planning challenging, and since companies need to operate with several versions of the same product at any given time, product supply becomes complicated.

2. The Objective: 1VQ for PAC

The objective of the *1VQ for PAC Initiative*, since its inception in 2018, has been to develop practical approaches within the scope of the CQO's responsibilities' to significantly reduce the complexity of the global PAC regulatory framework. These approaches are science and risk-based, using the framework laid out in the ICH Quality guidelines. The CQOs decided to build on an opportunity outlined in the ICH Q10 Guideline (1) to earn regulatory flexibility, allowing management more PACs in only the PQS.

This specific opportunity, outlined in ICH Q10 Appendix 1, states that for companies whom *"demonstrate effective PQS and product and process understanding"* there is an opportunity to *"optimise science and risk-based PAC processes to maximise benefits from innovation and continual improvement."* In other words, companies meeting these criteria should be given flexibility to manage more PACs in the PQS only, without requiring regulatory agency prior approval. Figure 1 below shows an example of this. For the company that has not demonstrated an effective PQS, all 16 PACs require prior approval, each with an estimated review and approval timeline of three to five years. For the company that demonstrated an effective PQS, 12 of the 16 PACs (75%) were deemed low risk and managed in the PQS only. Four companies required prior approval. The benefit for the company demonstrating an effective PQS is that the 12 PACs can be implemented immediately.

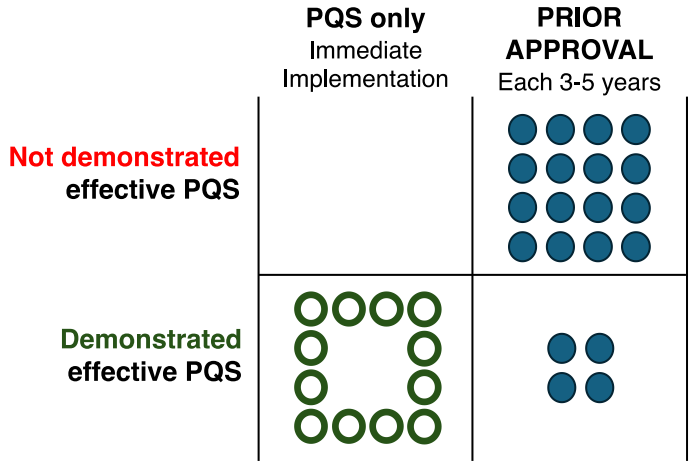

Figure 1 – Example Showing the Benefit of Having an Effective PQS for Managing PACs

The opportunity outlined in ICH Q10 Annex 1 has not been granted to companies yet, and at the start of the *1VQ for PAC Initiative*, there was no accepted definition of an effective PQS. Thus, in 2019 the CQOs published a Concept Paper (2) with the following proposed actions:

"An aligned and standardised industry approach to overcome barriers to proactive continual improvement and innovation, and help reduce drug shortages in the global environment:

1. *Define and demonstrate effective management of post-approval changes (PACs) in the pharmaceutical quality system (PQS) (during review and inspections) so that more changes can be managed in the PQS and be reported via notification pathways (e.g. annual report or changes-being-effected) instead of prior approvals, without negatively impacting risk to patient and drug product efficacy and quality.*
2. *Develop standard risk-based assessment of PACs that incorporates latest product and process knowledge.*
3. *Pilot the proposed solutions for PACs with a limited number of companies. Seek input from regulatory agencies on outcomes."*

The CQOs, as experts and owners of the PQS, published a solutions paper (3) in 2020 that:

> *"Outlines how PACs can be effectively managed in the PQS so that more changes can be managed in the PQS or via notification pathways instead of prior approvals utilising enhanced science and risk-based regulatory strategies aligned with ICH Q10. It identifies specific PQS elements to further develop and define for managing PACs in the PQS, provides points to consider for PACs for each of these elements, and how the effectiveness of PAC management in the PQS can be demonstrated."*

The paper also included *"a standard risk-based assessment of PACs that incorporates latest product and process knowledge at the individual change level."* The 4-step standard risk-based assessment is shown below in Figure 2. The assessment approach is in line with the ICH Q12 Lifecycle Management Guideline (4), published in 2019. Eight practical examples of applying the risk-based approach outlined in the *1VQ for PAC Initiative* 2020 paper were developed and published in 2020 and 2022; look to references (5-12) to see the titles of the eight examples.

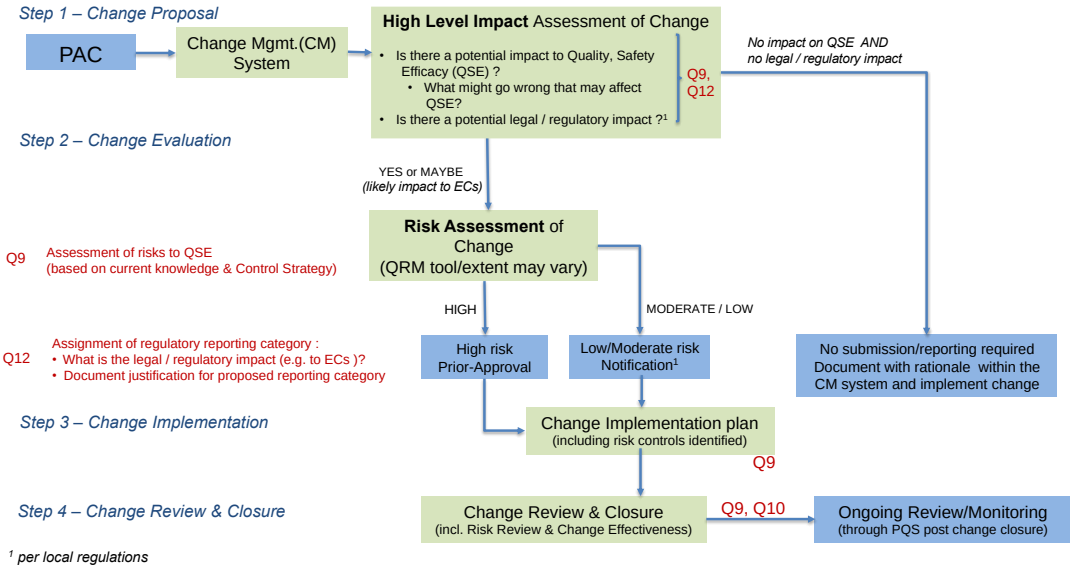

Figure 2 – A 4-step Risk-Based Assessment of Individual PACs

Furthermore, in 2021, the CQOs published a paper outlining how companies during their management review can assess the effectiveness of PQS for managing PACs (13).

3. Raising Awareness of the PAC Challenge for Pharma

Since the beginning of the *1VQ for PAC Initiative*, the CQOs also decided to raise awareness of the complex problem of the existing PAC regulatory framework. This problem has been known for at least two decades when, in 2002, Dr Janet Woodcock in the *FDA Vision for 21st Century Manufacturing* stated the desired state as (14):

> *"a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."*

Figure 3, developed by the authors, has been shared in several forums by industry and regulators to acknowledge the problem. Whereas a national regulatory agency receives one PAC for assessment, a company must manage many submissions for the same PAC, one for each country or region where prior approval is required for the change.

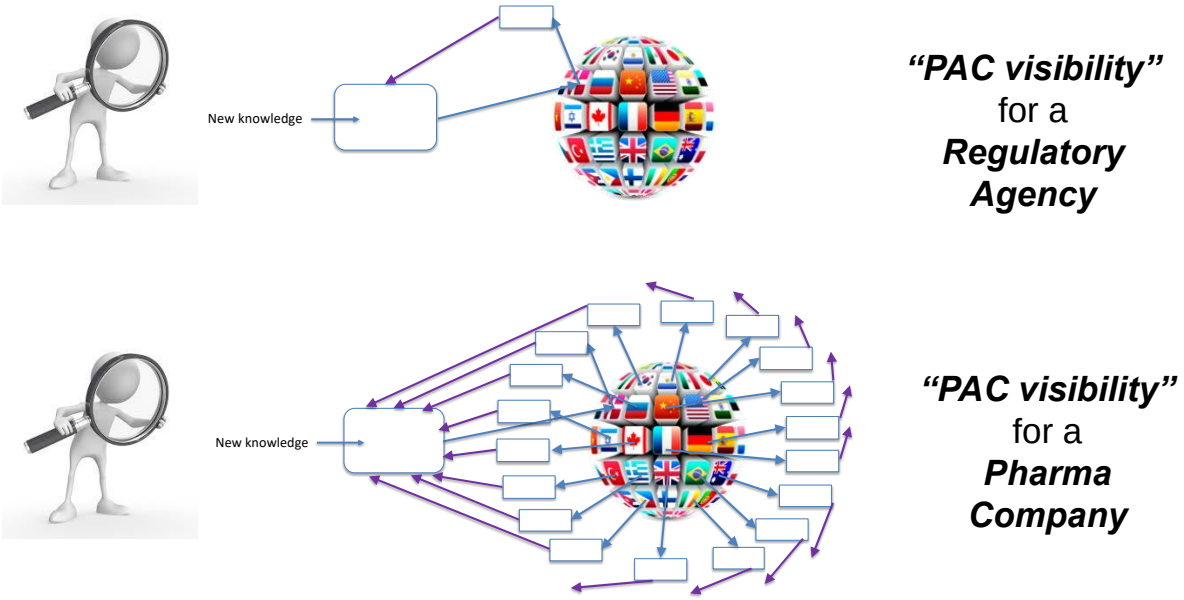

Figure 3 – One PAC seen from Regulatory Agency and Pharma Company Viewpoints

This figure has created awareness of the complex global PAC regulatory framework problem and has stimulated work amongst regulators towards the harmonisation of PAC assessment processes. These two such efforts are the International Coalition of Medicines Regulatory Authorities' (ICMRA) Pharmaceutical Quality Knowledge Management System (PQKMS) initiative (15) and the Pharmaceutical Inspection Cooperation Scheme (PIC/S) Recommendation Paper on how to assess and demonstrate the effectiveness of the Change Management System during inspections (16).

Awareness of the complexity and advocacy for managing more PACs in the PQS only for companies that meet ICH Q10 Annex 1 expectations has been presented at numerous conferences and in submission of comments to regulatory agencies. The latter includes:

- comments submitted to the ICH Q12 Expert Working Group (EWG) regarding draft document versions via the European Federation of Pharmaceutical Industries and Associations (EFPIA),
- comments submitted to the European Commission on the draft EU Pharmaceutical Strategy,

- comments submitted to PIC/S on the draft PIC/S Change Management Recommendation Paper,
- comments submitted to the United States Food and Drug Administration (FDA) on the draft ICH Q12 Implementation guidance and
- Qualified Persons (QPs) representing the *1VQ for PAC Initiative* in the EU structured dialog drug shortage workshops.

Members of the *1VQ for PAC Initiative* continue to speak at conferences about the PAC challenge.

4. Current State: PAC Review and Approval Time

Recently, the CQOs presented and discussed the most comprehensive compilation of PAC data to date in the article, *Approaches to Design an Efficient, Predictable Global Post-Approval Change Management System that Facilitates Continual Improvement and Drug Product Availability* (17). In this article, data analysed from more than 145,000 PACs for 156 countries, collected by 18 global pharma companies over a 3-year period (2019 to 2021), illustrated how severe the problem of global regulatory complexity is. The companies shared data that took less than or equivalent to six months and data greater than six months from submission to regulatory agency approval. This 6-month timeline was chosen because it is the recommended review timeline for major changes in the World Health Organisation (WHO) guidance for vaccines and biotherapeutic products (18, 19). Figure 4 shows the percentage of PACs that took more than six months for approval for each of the 156 countries over the 3-year period.

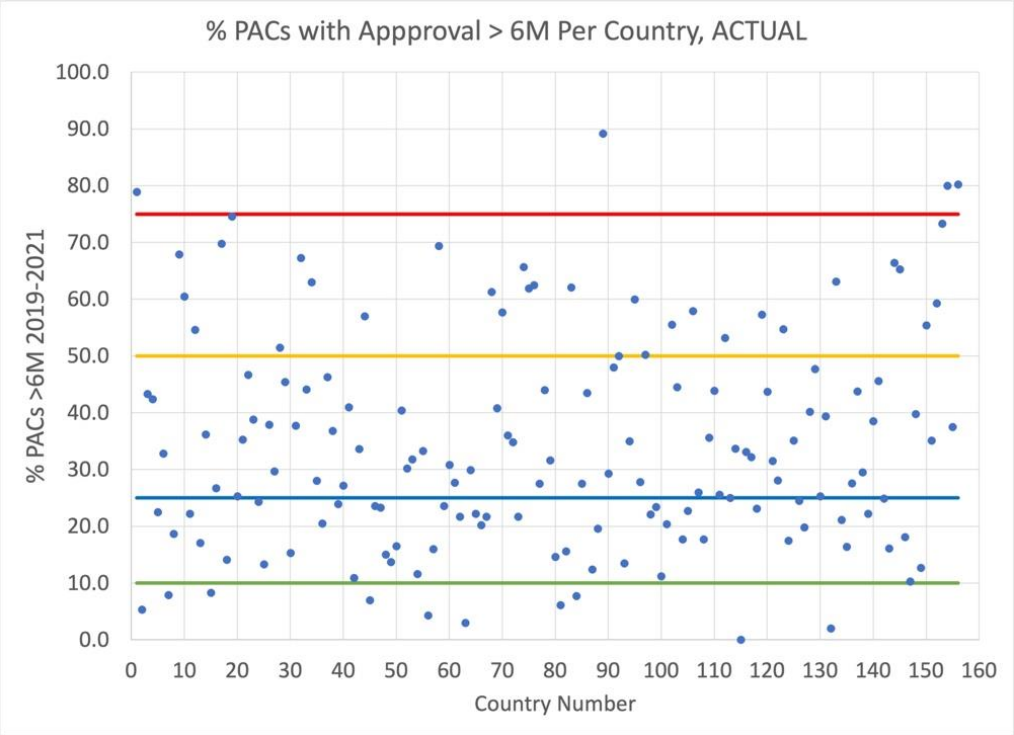

Figure 4 – Percent PACs that took more than 6 Months for Approval per Country

Ten out of the 156 (6%) countries had no more than 10% of the PACs reviewed and approved in more than six months. In 33 (22%) countries, more than half of the PACs took greater than six months for

approval. It is rare that the same PAC is approved globally within six months, as individual National Regulatory Agencies (NRAs) can take anywhere from a few months to years (in some cases, greater than five years) for their review.

The long and often unpredictable review and approval timelines make inventory and supply chain planning very difficult for the manufacturer. The complexity could be reduced tremendously if a company had certainty on review and approval timelines from all agencies where prior approval of a PAC is required. Thus, the *1VQ for PAC Initiative* is also advocating for 'agile regulatory reliance.' WHO has developed a framework and is promoting regulatory reliance, meaning national regulatory agencies may rely on the review done by another national regulatory agency when deciding on approval of a PAC.

Additionally, the *1VQ for PAC Initiative* suggests that if any regulatory agency cannot commit to the WHO recommended 6-month review timeline, they should rely on another national regulatory agency that has already reviewed and made a decision on the same PAC. Figure 5 below illustrates the difference between regulatory reliance and agile regulatory reliance, and its impact on reducing the number of product versions at any given time, thereby reducing the complicated supply chain challenge.

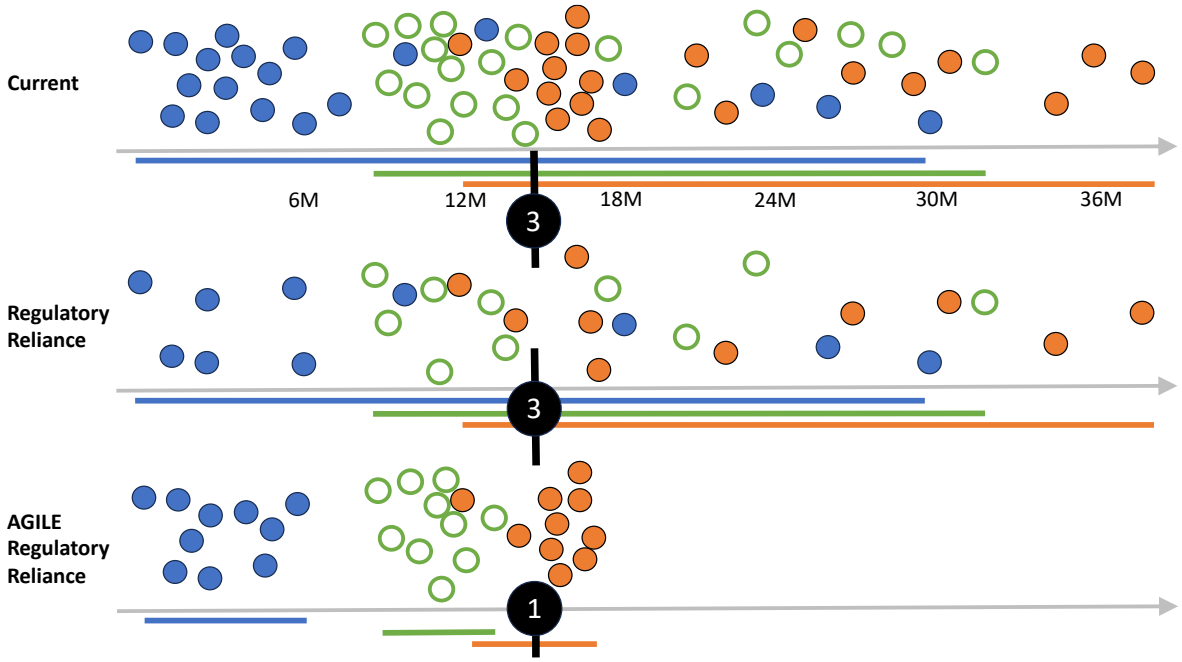

Figure 5 – Example Illustrating the Difference between Regulatory Reliance and Agile Regulatory Reliance

In the top panel of the figure ('Current'), three PACs illustrated in different coloured dots were submitted to 20 national regulatory agencies; the time for approval is on the x-axis. The solid bars below the dots show how long each change was 'open,' i.e., from first to last approval. As an example, the first change was open from 0 to 30 months. At around 15 months, all three PACs were 'open,' which means that the company needed to have inventory of all three product versions represented by the PACs.

The middle panel ('Regulatory Reliance') illustrates that for 50% of the approvals, the national regulatory agencies relied on other agencies for their approval. Thus, there are only ten dots for each example; in other words, ten countries reviewed independently, instead of 20. This limits the resource burden for the company (and for the agencies relying on other agencies). However, it still did not reduce the number of product versions open at any given time. This is an important point to emphasise, as even with regulatory reliance the supply chain challenge did not reduce. For Quality, whom manages the distribution of product to countries around the world, it made no difference between the first two examples with respect to the number of product versions.

The last panel ('Agile Regulatory Reliance') illustrates a scenario where all national regulatory agencies approved the PAC or relied on another regulatory agency to review and render a decision on the PAC within the WHO recommended 6-month timeframe. In this case, it reduced the number of product versions by shortening the overall time each PAC was 'open.' At the 15-month time point only one PAC was 'open.' This example illustrates that only when regulatory reliance is agile, does it truly help reduce the supply chain challenge caused by multiple product versions being needed in parallel.

The *1VQ for PAC Initiative* is thus advocating for agile regulatory reliance to reduce the risk of drug shortages that is exacerbated by the complex global PAC regulatory framework.

5. Eight Approaches to Alleviating the Complex Problem

The term 'complex' has been used for years to describe the global PAC regulatory framework. It is important to distinguish between 'complex' and 'complicated' problems as the approaches to manage each of these fundamentally differ. Complicated problems can be solved by experts. An example is building an airplane which can be done by skilled experts. On the other hand, complex problems have no solutions but can be reduced if managed well collaboratively and collectively by key stakeholders. Examples of complex problems are smoking or poverty. 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. This might be a reason why the complex problem of the global PAC regulatory framework has remained unsolved for over two decades, because it has been approached as a complicated problem. Complex problems must be tackled with a systems approach and requires the involvement of all key stakeholders at senior decision-making levels (20).

The objective of the *1VQ for PAC Initiative* remains to significantly reduce the complexity of the global PAC regulatory framework. In addition to raising awareness of the problem and pursuing the opportunity to manage more PACs in the PQS only (through sound science and risk-based approaches within an effective PQS) as outlined in ICH Q10, the CQOs are now also advocating for the application of agile regulatory reliance where national regulatory agencies cannot meet the WHO recommended 6- month PAC review timeline. This would greatly reduce the challenge of managing multiple versions of the product at the same time for companies.

In the paper, *Approaches to Design an Efficient, Predictable Global Post-Approval Change Management System that Facilitates Continual Improvement and Drug Product Availability* (17), the CQOs recommend the following eight approaches to alleviate the complex problem:

- **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. This is the approach published by the *1VQ for PAC Initiative* aligned with ICH Q10 Annex 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**.
- **Approach 3** (WHO): **Increased reliance** among regulatory agencies following WHO guidance to reduce redundant assessment of PACs.
- **Approach 4** (ICMRA): **Harmonise/standardise data elements** and electronic formats for PACs through ICMRA's Pharmaceutical Quality Knowledge Management System (PQKMS) Initiative.
- **Approach 5**: Industry and regulatory agencies 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 6 months** and the WHO guidance on regulatory reliance by all NRAs.
- **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.

6. Conclusion

In conclusion, the *1VQ for PAC Initiative*, sponsored by CQOs of the top 25 pharmaceutical companies, aims to significantly reduce the complexity of the global PAC regulatory framework. The initiative has raised awareness of the problem and has developed practical, science and risk-based approaches to manage more PACs in the PQS only, as outlined in ICH Q10. The CQOs are also advocating for the application of agile regulatory reliance where national regulatory agencies cannot meet the WHO recommended 6-month PAC review timeline. The initiative recommends eight approaches to help alleviate the complex problem, including managing more low-risk PACs in the PQS only, increasing reliance among regulatory agencies and harmonising or standardising data elements and electronic formats for PACs. These approaches have the potential to greatly reduce the challenge of managing multiple versions of the product at the same time, and to reduce the risk of drug shortages that is exacerbated by the complex global PAC regulatory framework.

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