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Quality Officers Call For New Approaches To Reduce Global Manufacturing Change Complexity

by Bowman Cox

Pharmaceutical quality leadership proposes eight-step “dance” with complex global regulatory system for allowing manufacturing processes to improve more quickly. The data showed many authorities take more than the recommended six months to decide on post-approval changes, with assessments taking almost eight years in some cases.

Chief quality officers of global pharmaceutical companies recently shared data on the problem of global regulatory complexity preventing continual improvement of manufacturing processes, explained why they believe the situation has persisted and outlined eight additional approaches that they believe together offer significant improvement.

Writing 18 February in a Drug Information Association *journal*, Anders Vinther, founder, Quality Business Administration, Emma Ramnarine of *Boehringer Ingelheim GmbH*, and quality leaders with *Sanofi*, CSL Behring, *Bayer AG* and *Astellas Pharma, Inc.* explained how chief quality officers are engaging on the seemingly intractable issue through their One-Voice-of-Quality for Post-Approval Changes initiative.

They cited the analysis of sociologist Roberto Poli, a professor at the University

Key Takeaways

- Two decades of efforts to unleash post-approval manufacturing changes have not helped.
- New approaches recognizing the complex systems nature of the problem are needed.
- Eight approaches, four of them already

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of Trento in Italy, distinguishing between complicated problems, which can be solved, and complex problems, which cannot.

> underway, could go a long way toward reducing the problem to more manageable levels.

Complex systems "cannot be controlled," Poli *wrote* in the Cadmus Journal. "The best one can do is to influence them, learn to 'dance with them,' as [environmental sustainability and complex systems expert] Donella Meadows aptly said."

The Challenge Of Post-Approval Change Complexity

Global pharmaceutical companies need to change manufacturing processes to upgrade aging facilities and equipment, improve compliance with good manufacturing practice requirements, change suppliers, meet new regulatory requirements and take advantage of new technologies, among other things, wrote the authors of the article in DIA's Therapeutic Innovation & Regulatory Science journal.

Many of these changes cannot proceed without the prior approval of multiple national regulatory authorities, which manufacturers must request in submission packages tailored for each of dozens of authorities, and which they typically receive over a period of three to five years.

Manufacturers typically do not request approval simultaneously, in part because some authorities will not consider a change until a reference country has approved it.

Eighteen of the largest pharma companies provided change data for the One-Voice-of-Quality initiative's analysis.

With multiple changes approved by some countries but not others at any given time, "companies must consider how many parallel versions of a product it can manage simultaneously," the DIA article said.

To produce 83 batches of a vaccine one year, one author's firm had to make 55 different versions, each with a different mix of pre- and post-change processes, because of all the manufacturing changes wending their way through the world.

If firms submitted all changes to all authorities simultaneously and those authorities completed

their assessments within six months as the World Health Organization says they should for vaccines and biotherapeutics, it would be much better, the authors wrote.

Need For Global Approach Seen

"Attempts have been made to solve the complex problem for over 20-plus years," the article observed; "yet no substantial progress has been made." (Also see "*The Post-Approval Challenge of Global Regulatory Complexity*" - Pink Sheet, 29 Sep, 2014.)

The common thread among the fixes proposed over the years: they approach it as a complicated problem, not a complex one. In such cases, "individual attempts by a stakeholder, while reasonable and well-intended, can often make the problem worse."

Noting quality management guru William Edwards Deming's recommendation to approach quality systemically, the article suggests moving away from the current state of national regulatory authorities managing post-approval changes on a country or regional basis without global coordination.

It would be more effective, the paper said, for there to be a global system that "is jointly owned, collectively managed, and navigated in partnership by all stakeholders to continually improve and deliver high quality medicines on time every time."

What The Data Showed

The chief quality officers of 18 of the world's largest 25 pharmaceutical companies agreed to provide certain post-approval change data for the study, conceptualized and designed by Vinther and Ramnarine.

Although many national regulatory authorities allow firms to implement some types of post-approval changes if they simultaneously or subsequently inform the authorities, the most significant changes require prior approval.

The chief quality officers of the 18 companies agreed to tally how many prior-approval supplements regulatory authorities granted their firms in 2019, 2020 and 2021, and of those146,550 approvals, how many were granted within six months of submission. All but two of the companies provided country-specific details, anonymized in the report, for their 125,886 change approvals.

Even though the COVID-19 pandemic interfered with a lot of regulatory activities during that period, the total approved and the share requiring no more than six months of review held steady through the three-year period.

Of the 156 countries that approved supplements during the three-year period, only one met the

six-month goal for every approval. Another 10 countries approved 90% of their prior approval supplements within six months.

One company showed how long each approval had taken, along with country averages. Most approvals came within a year, with most of the rest coming in two years, but a significant number stretched into the two-to-five-year range, with some taking almost eight years.

Complex Problem Has Outlasted 'Complicated Problem' Solutions

The article recapped approaches taken since 2002 when Janet Woodcock, who was then the director of the US FDA's Center for Drug Evaluation and Research, established the goal of "a maximally efficient, agile, flexible pharmaceutical sector that reliably produces high quality drugs without extensive regulatory oversight."

The various efforts undertaken over the years to achieve that desired state have failed to attain the promised regulatory flexibility, the article observed, instead resulting in increased documentation and reporting requirements.

Much of the work was conducted jointly by industry and regulatory authorities under the auspices of the International Council on Regulatory Harmonisation, with the development of its Q8 pharmaceutical development, Q9 quality risk management and Q10 pharmaceutical quality system guidelines in 2005-2008, and when the Q8-10 trilogy failed to deliver, the Q12 pharmaceutical lifecycle guideline in 2014.

There were FDA-led initiatives as well, most notably the 2013 quality metric program and the follow-on 2022 quality management maturity initiative.

The COVID-19 pandemic brought renewed attention to the post-approval change issue as a factor in global supply chain vulnerability, spurring a report on the topic from the European Commission.

Meanwhile, the Pharmaceutical Inspection Cooperation Scheme (PIC/S) published recommendations in change management in 2021 and the International Coalition of Medicines Regulatory Authorities published a paper on pharmaceutical quality knowledge management systems that recognized the challenge.

"The common red thread across all these solutions so far," the article concluded, "is that they have treated the global PAC complexity as a complicated problem and not as a complex problem."

Four New Initiatives In Progress

The article identified four initiatives already underway that could help:

- The authors' One-Voice-Of-Quality initiative to assess opportunities for companies to manage post-approval changes in their pharmaceutical quality systems without prior review or notification of regulatory authorities.

- A checklist approach the PIC/S published in 2021 that inspectors and companies can use to evaluate the effectiveness of pharmaceutical quality systems for change management.

- WHO guidance encouraging regulatory authorities to rely on approvals that WHO-listed agencies grant for post-approval changes.

- A harmonized, structured and standardized system that ICMRA is developing to enable simultaneous post-approval change submissions.

Four More Things To Try

The chief quality officers are calling for four additional approaches:

- Industry and regulatory authorities should work together to standardize the post-approval change assessment process.

- National regulatory authorities should adopt WHO recommendations to assess major changes in six months and moderate changes in three months, while relying on WHO regulatory reliance guidance to reduce redundant assessments.

- Authorities should establish a consistent approach for assessors to use in evaluating the effectiveness of corporate pharmaceutical quality systems as it relates to downgrading change reporting levels.

- All stakeholders should establish metrics and report data on country-specific timelines for the review and approval of post-approval changes.

It is possible to drastically reduce the more than two-decade-old problem, the article concluded, but "only when all key stakeholders look beyond their operational boundaries."

The companies that submitted data for the article were: *Amgen, Inc.*, Astellas, *AstraZeneca PLC*, Bayer, *Biogen, Inc.*, Boehringer Ingelheim, *Bristol Myers Squibb Company*, CSL Behring, *Gilead Sciences, Inc.*, *Johnson & Johnson*, Merck Sharp & Dohme Corp, *Novartis AG*, *Novo Nordisk A/S*, *Pfizer Inc.*, *Genentech, Inc.* , Sanofi, *Takeda Pharmaceuticals USA Inc.*, and *Teva Pharmaceuticals USA Inc.*.