RAO Solutions

Why Should Regulatory Professionals Care About Quality By Design?

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Introduction

The intent of this paper is to bring together Quality By Design (QBD) and regulatory processes by discussing two processes: The first process represents the proactive use of QBD and the second represents use of QBD for a legacy issue.

- Proactive use of QBD to effectively manage the quality of submission content.
- Use of QBD to identify and solve a problem with legacy processes (see section below, Remediating a Dispersed Archive).

This paper will provide you with tools to support a "Quality" mindset for identifying and mitigating compliance risks within critical regulatory processes.

"…regulatory processes will (also) significantly benefit from using the QBD model…"

Background on QBD

Quality By Design (QBD) is a concept first outlined by quality expert Joseph M. Juran in his seminal work, *Juran on Quality By Design*, in 1992. Designing for quality and innovation through quality planning

is one of the three universal processes of the Juran Trilogy, in which Juran describes what is required to achieve breakthroughs in new products, services, and processes. Juran showed that most quality crises and problems relate to the manner in which quality was planned, thus he demonstrated that quality must be rigorously planned for as opposed to “inspecting in” quality after the fact.

The Quality By Design Road Map as described by Juran consists of the following steps:

1. Establish Quality Goals
2. Identify stakeholders impacted by the Quality Goals – i.e., the customers
3. Determine the customers’ needs
4. Develop the features of the new design that will meet these needs
5. Develop/redevelop the processes to produce the features
6. Develop process controls to transfer the new designs to operations

This model is not specific to a Quality organization. Simply stated, Juran is telling the reader to identify and understand your Quality Goal(s), ensure early stakeholder involvement and develop clear and measurable processes to ensure stakeholder agreement.

Over the last 10+ years these QBD steps have been adapted as a quality planning approach for the development and manufacture of pharmaceutical products. However, this is not the only place QBD can be applied; regulatory processes will also significantly benefit from using the QBD model. Throughout the rest of this paper, our goal is to illustrate this point. We will begin by examining our first process.

Effectively Manage the Quality of Submission Content

Health Authority submissions are complex and this complexity provides considerable risk to the *quality of the content* if rigorous submission planning is not used. While there are certain requirements that are tactical (e.g. formats or languages) there are also strategic requirements that are often left to the end

of the process and typically to the peril of the regulatory organization. This situation should drive the development of a **shared** *Quality Goal* that could be as simple as:

Maintain Dossier Approvability at All Times During the Product's Life-cycle

Quality planning of this nature is managed through application of risk management tools, as described in the International Conference on Harmonization QBD guideline, ICH Q9, *Quality Risk Management.*[1] These tools enable a common or shared understanding across the submission stakeholder community of what must be addressed within the submission to ensure approval. There are typically two self-evident categories of risk that must be addressed:

> *"Quality planning…is managed through application of **risk management tools**…"*

Key Regulatory Risks

Regulatory risks answer the question,

> "*What events can potentially derail approval if they occur and are not proactively managed?"*

Whether risks are technical or non-technical, identify and manage the risk; understand and establish the impact to approval.

Key Communication Risks

Communication risks answer the question,

> "*What key content can potentially derail approval if not communicated consistently across the entire submission?"*

As with regulatory risks, these risks can be technical or non-technical but if they are not communicated consistently, they can create a significant risk of non-approval.

The identified risks and their respective mitigation plans are continuously managed as the submission content goes through multiple iterations and reviews.

[1]It is noteworthy that ICH Q9 explicitly identifies quality planning of this nature within its scope statement: "This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include…submission/review processes throughout the lifecycle."

Remediating a Dispersed Archive

Applying the QBD model and framework to submission archiving helps in two ways:

1. Let's say you have an existing archiving process that is ineffective or "broken". To fix this process, you need to understand the most ***relevant*** root causes of the issues, and design new processes that correct them.
2. Or, you have a legacy archive process no longer in effect that led to a ***dispersed*** archive. To remediate this situation, you need to understand the most relevant legacy root causes. This guides consolidation, which will enable greater efficiency and sustainability.

These are two very different scenarios met through the same QBD framework. Let's take a look at the second scenario, and we'll walk you through how using QBD helps to effectively solve the problem.

Situation – Dispersed Legacy Archiving

1. Team members are attempting to locate documents in a paper archive where the archiving process has evolved over several years since implementing electronic submissions.
2. There is very high confidence in the inventory of each application.
3. A significant number of paper documents located in off-site storage are not retrievable, and we must systematically develop a plan for finding them.

Applying the QBD Framework

First, establish Quality Goals. In this case the Quality Goals can be captured as:

- >99.5% of all Health Authority documents are available through the archive within 12 months of a QBD project kickoff.
- 99% of local requests can be fulfilled by local regulatory staff within 12 months of a QBD project kickoff.

Second, identify the stakeholder community. In addition to understanding who they are, we also need to understand what process gaps existed with the legacy archive that impact our ability to meet our goals defined above.

Third, based on needs analysis, identify potential causes with process owners/stakeholders and determine any correlation of specific causes contributing to the unmet need. Below are some examples of potential causes and the associated incidence (also known as a Pareto analysis):

- Authors were trained and accountable for using the archiving process; however, some were not sending documents to the archive (90%).
- Authors were not trained or held accountable for using the archiving process (8%).
- Authors sent documents to an off-site storage vendor but were not using the currently approved vendor (2%).
- Files requested for retrieval were not delivered by the off-site storage vendor; however, documents were there (0%).

Before we go any further, just by looking at each incidence already tells us:

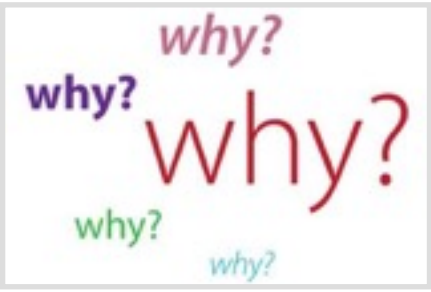
- NOT TO spend time looking at current or previous off-site storage vendors as the incidence was 2% or less.
- NOT TO assume the paper documents aren't available and/or no longer exist due to lack of awareness or training as the incidence is <10%.
- WE SHOULD spend time investigating the *root causes* behind authors being trained or accountable but not archiving documents according to the archiving process. This incidence is 90%. Spending time on this issue will enable us to locate missing files.

*"…we should spend time investigating the **root causes**… asking 'WHY?' repeatedly"*

Root Cause Analysis

At this point, a root cause analysis is applied. Two common techniques are the 5-Whys (asking "Why?" repeatedly until reaching a root cause) and Fault Tree Analysis (a deductive analysis approach for tracing an event to its causes). An evidence-based 5-Whys/Fault Tree Analysis of the leading cause shows us that:

- Authors accumulated documents in their files with the intent of sending them to archiving. The root cause analysis showed that means didn't exist for knowing whether documents were sent or not (80%).
- Authors delegated archiving to administrative staff that neglected to send documents to the archives. The root cause analysis showed that means for the administrative staff to send documents to the archive were inefficient and therefore, not used (20% contribution).



QBD-based approaches to regulatory processes provide other critical benefits to the business:

- *Waste elimination and time savings through reduced rework*
- *Data-driven risk management and mitigation planning*
- *Performance metrics that enable ongoing improvements and preventive actions*
- *Process controls that enable focused and efficient corrective actions*

What does this tell us?

1. Evidence shows that in some cases, the missing paper documents reside with *authors*, or their administrative staff.
2. We need to ask the individual authors for their documents, read the individual documents, and determine where they belong in the archive.

There might be a scenario where some of the missing documents cannot be found. This can be related to causes such as documents being filed incorrectly or the author is no longer with the company. In either scenario, we still benefit from using QBD since we have higher confidence this is a true gap because this outcome is based on data instead of guesswork.

Summary

QBD offers a great value to regulatory processes by simply leveraging the core principles. Furthermore, current pharmaceutical QBD guidelines state that regulatory processes are an opportunity for applying the tools and principles of quality risk management and a fully integrated pharmaceutical quality system (see ICH Q9 and Q10 for further details). The application to regulatory processes advances the concept where we can create end-to-end, QBD-based approaches to the entire drug product value chain and not limit ourselves strictly to product development and manufacturing processes.

Although it has not been intuitive for regulatory professionals to use the QBD model, once you start using a quality approach to regulatory processes, you will quickly realize the benefits. Probably the most critical is the concept of objective and measurable Regulatory Quality Goals, all of which are linked to larger Quality System objectives around product realization. It isn't possible to ensure control over a product's safety and efficacy without also ensuring control over regulatory processes that exist for the purpose of complete product transparency.

In all of these instances of regulatory process improvement, the QBD framework is there to lead the way and ensure true excellence in regulatory process performance.

About the Authors:

Christopher Hanna, PhD, *Principal at Kattner-Thalmann Partners, is a Lean Six Sigma Master Black Belt with more than 20 years of process excellence experience within the Life Science industry. Within regulatory, Chris has brought Quality By Design (QBD) principles to various regulatory processes, including the management of submission content and product lifecycle, as well as RIM data quality.*

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