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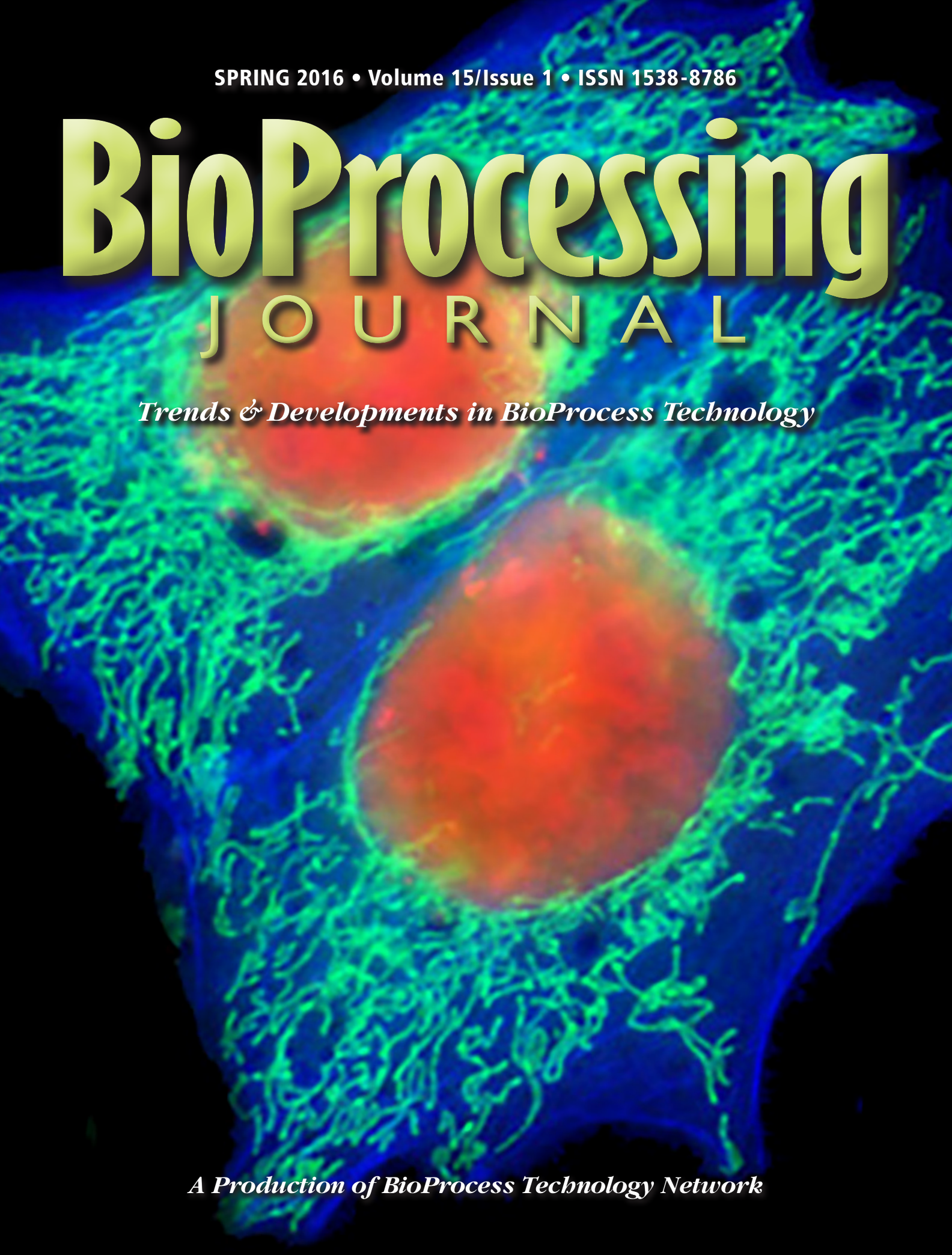
Trends & Developments in BioProcess Technology



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TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

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Regulatory and Monetary Drivers for Real-Time Analytics

By Barry Rosenblatt

Introduction

Implementation of "real-time" analytics (RTA) in processes for biologics is challenging from a technological and timeline perspective. Therefore, there need to be significant drivers from both a regulatory (quality) and a monetary standpoint to justify investment. Understanding how regulatory agencies define real-time analytics and the expectations for implementations (how and when) is a key component to rational decision-making, and dovetailing process improvement and facility design is important in the planning and development process.

Defining Real-Time Analytics

The FDA Guidance on process analytical technology (PAT) describes real-time analytics as:

Nondestructive measurements that contain information related to biological, physical, and chemical attributes of the materials being processed.[1]

The three types of analytics, as per the FDA guidance, can be found in **Table 1**.

TABLE 1. The FDA definitions of analytics.

▶ **AT-LINE:** Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream
▶ **ON-LINE:** Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream
▶ **IN-LINE:** Measurement where the sample is not removed from the process stream and can be invasive or noninvasive

Use of RTAs

RTAs can be used in several ways:

- Defining/developing design space for a new or existing process
- Defining/controlling operating parameters
- In-process checks
- Defining/tracking critical quality attributes (CQAs)

Examining each of these individually, we can see how transitioning from traditional "off-line" analytics to "on-line" or "in-line" analytics can fit into an expedited program, potentially saving time, and as a result, money.

Determining/developing design space is traditionally broken down into three stages and performed as an off-line exercise. In the early development stage, the process is developed with an eye toward defining the "edge of failure" for the parameters used for production and purification of the product. It is usually applied to a "platform" process to save time and is built for speed toward the investigational new drug (IND) filing milestone. During the mid-development stage, the process has been developed and the company is moving toward Phase 2 clinical. During this phase, the process parameters are being explored with an eye toward narrowing those parameters and making the process more robust. This is in anticipation of the late-stage phase in which the process qualification runs are planned for entry into Phase 3 clinical and biological license application (BLA). In this stage, traditionally companies are performing failure mode and effect analysis (FMEA). Statistical experimental tools such as design of experiments (DOEs) are utilized to fully define the design space of the process. In this paradigm, the process may be modified in each stage, requiring comparability and specification revisions between stages (**Figure 1**).

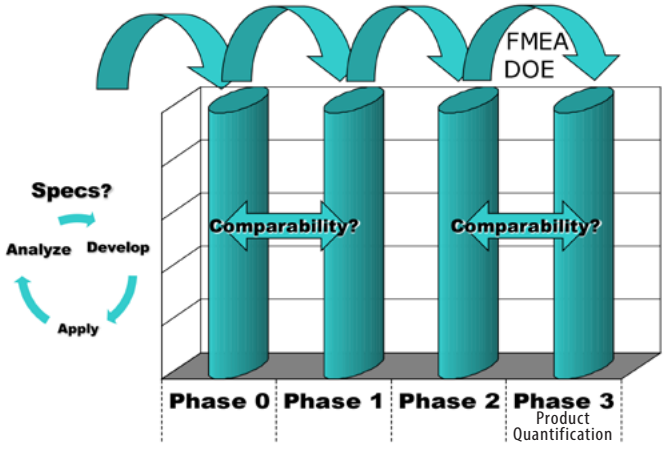

FIGURE 1. Current paradigm of determining/developing design space.

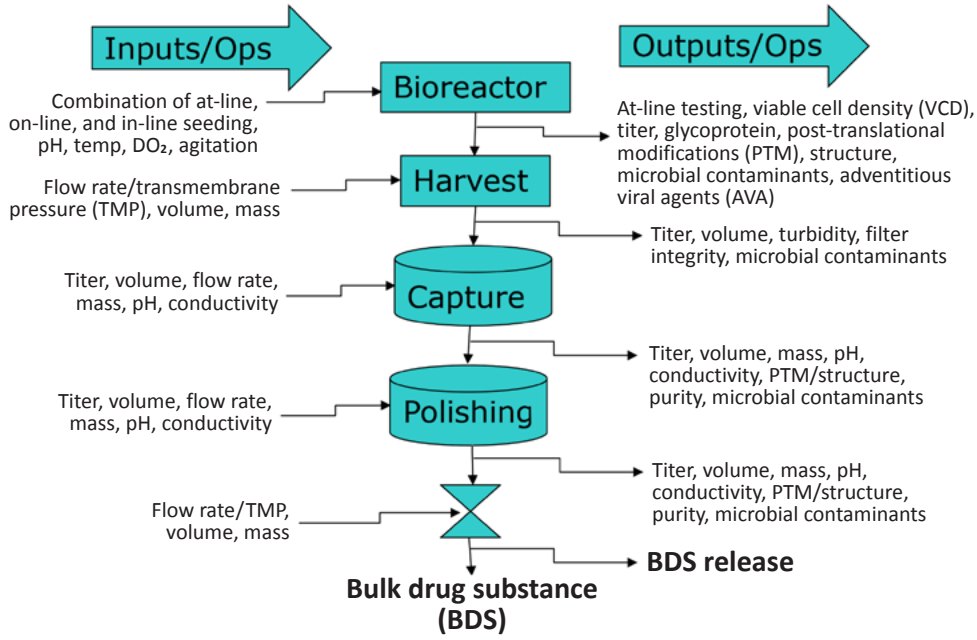

FIGURE 2. An example of the inputs and outputs applied to a typical process.

An example of the inputs and outputs applied to a typical process is shown above. The parameters are usually measured in a mixture of at-line and off-line analytic procedures, with some tests repeated by both the process floor and the QC department (*i.e.*, OD_{280}, pH). Linkage between these measurements and CQAs of the product need to be established to define these as critical process parameters (CPPs), potential critical process parameters (pCCP), or non-critical process parameters (nCPP). The earlier in the development program these linkages can be established, the more robust of a process will be developed[2–4] (**Figure 2**). The use of tools such as Ishikawa (or fishbone) diagrams can be used to help develop these linkages (**Figure 3)**.

Traditionally, many of these linkages are established via scale-down models, requiring qualification of models and demonstration of repeatability at scale. The more real-time data available at scale, the more accurate this type of analysis becomes as it applies to the process as it is being performed. It also shortens the time frame, allowing for more accurate qualification of scaled-down models for process qualification. Thus, the design space for the at-scale process can be established fairly early in the development time frame. Understanding these critical parameters, moreover, allows for a more comprehensive FMEA analysis and more efficient DOE design[6] (**Figure 4**, on the following page).

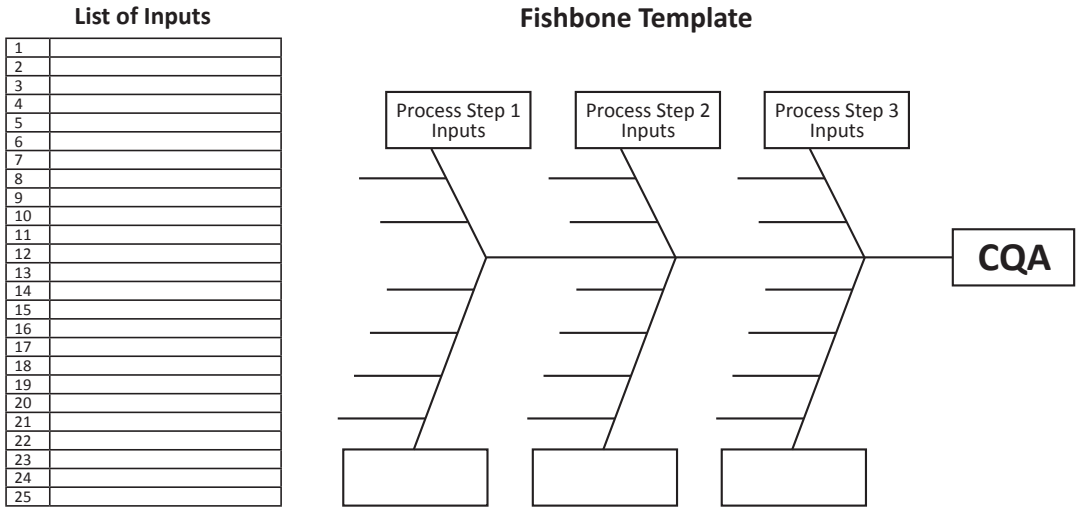

FIGURE 3. An example of the Ishikawa (or fishbone) diagram.
(Refer to "A Mab: A Case Study in Bioprocess Development," CMC Biotech Working Group[5] for an example of the use of this tool.)

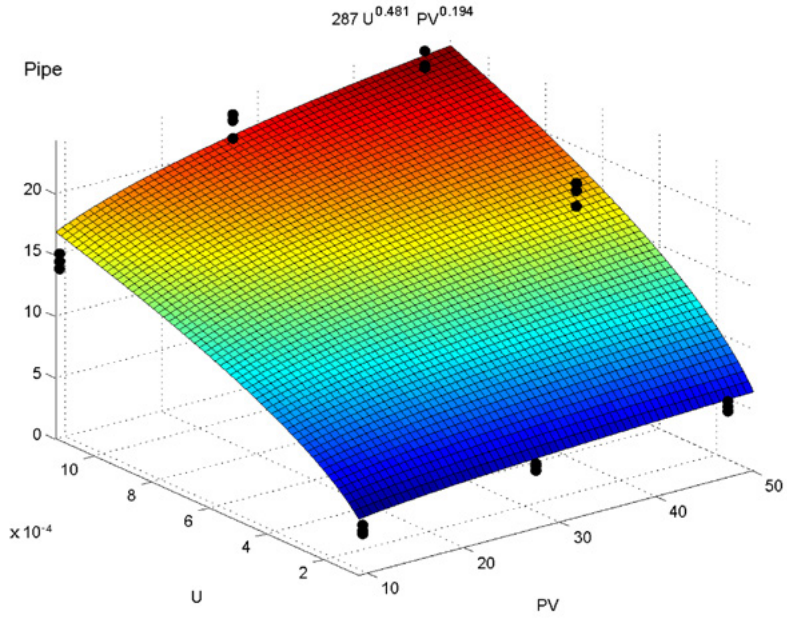

FIGURE 4. An example of a DOE heat mat for the process parameters used in protein A purification of a monoclonal antibody.
(Adapted from: "A Mab: A Case Study in Bioprocess Development," CMC Biotech Working Group[5])

Another aspect of the utilization of these tools in early to mid-development is the application of "quality by design" (QbD) to biologic processes. QbD is "*… the desired state of pharmaceutical manufacturing and regulation" (and) may be characterized as follows:*

- *Product quality and performance are ensured through the design of effective and efficient manufacturing processes*
- *Product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product performance*
- *Continuous real-time quality assurance"*[1]

In the QbD paradigm, design space is established in early development, including establishing the linkage between CPP and CQA of the product, and early DOE treatment of process parameters. Mid-to-late-development is reserved for "continuous" process improvements while moving within the established design space.[7] Ideally, a fully developed process using QbD would eliminate the need for testing the bulk drug substance, or at least allow for real-time release of the product as the quality of the product is continuously monitored during the process. This is due to the linkage of the CPPs to the CQAs of the product (**Figure 5**).

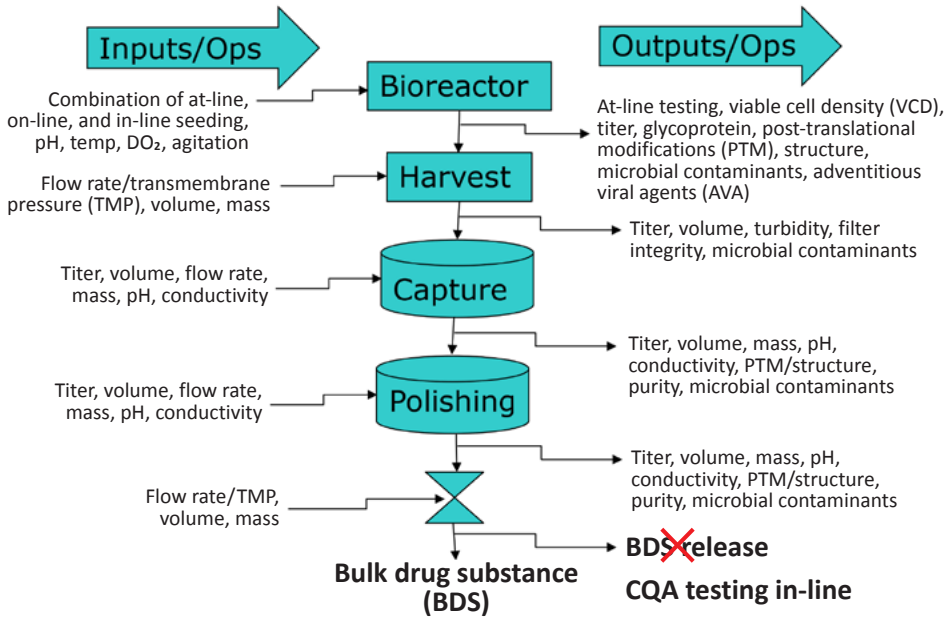

FIGURE 5. Using the QbD paradigm for real-time release of the product.

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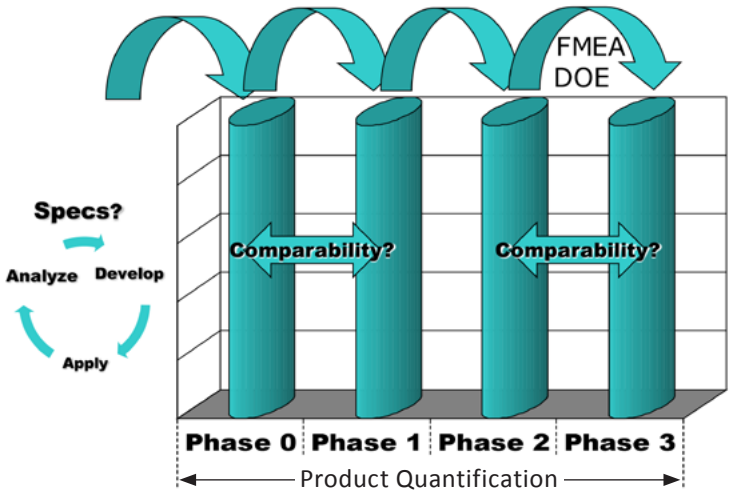

FIGURE 6. QbD paradigm.

Under the QbD paradigm, the process is defined in the earliest stages of development, including a FMEA analysis and DOE of all process parameters. So the paradigm is shifted from **Figure 1** to **Figure 6**.

Monetary Drivers

Implementation of RTA to a process, especially in the early stages of development, can be a costly process as it may require new equipment and development hours for a product that has not been in clinical trials. So, what are the monetary drivers that make implementation of RTA a good return on investment?

For companies utilizing platform processes, implementation of RTA would allow for a better definition of the platform, providing for quicker and wider applications. Better definition of processes should also result in fewer lost lots due to operational variations that will have been defined as part of the design space.

The use of RTA can also result in shorter processing times as the shop floor will spend less time waiting for a test result. Ultimately, using RTA can possibly lead to real-time release of product, shortening the time to clinic or commercialization.

RTA can also allow for implementation of continuous or semi-continuous processing, driving down production costs (*e.g.*, labor, turn-around times) by allowing for greater plant utilization.

Finally, the utilization of RTA simplifies implementation of QbD principles, allowing for continuous process improvement while driving down cost of goods and loaded production costs.

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About the Author

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Dr. Rosenblatt is a subject matter expert on the chemistry and manufacturing control (CMC) of biotherapeutics. For more than 25 years, he has developed, transferred, and validated purification processes for multiple new molecular entities through all stages of drug development, including licensure.

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