Reducing Tech-Transfer Risk

Collaborative Data Access, Trending, Reporting, and Analytics Span Process Development and Manufacturing

Justin O. Neway

When it comes to reducing technology transfer risk, the "secret sauce" is really process understanding. The "desired state" for manufacturing is a design based on a mechanistic understanding that provides real-time quality assurance (rather than expecting quality to be tested in). The Food and Drug Administration (FDA) is promoting risk-based regulation, so the greater the extent to which you can support your process understanding based on good science, the more constructive your relationship with the agency will be.

Connecting analytics to on-demand data access helps to create that desired state based on good science and process understanding. Successful teamwork between process development and manufacturing groups depends on real-time data access and investigational analysis — benefiting from technology that is readily available today.

PRODUCT FOCUS: ALL BIOPHARMACEUTICALS

PROCESS FOCUS: PROCESS DEVELOPMENT (PRECLINICAL)

WHO SHOULD READ: PROCESS DEVELOPMENT AND MANUFACTURING, IT, QA/QC AND DEVELOPMENT LABS

KEYWORDS: PRECLNICAL STUDIES, CRITIAL PROCESS PARAMETERS, PROCESS UNDERSTANDING, CMC, BLA/PLA, DATA ACCESS AND MANAGEMENT, TECH TRANSFER

LEVEL: BASIC

THE ORIGINS OF PROCESS UNDERSTANDING

In bioprocesses, a certain level of understanding about a product and its therapeutic characteristics comes from early animal studies and discovery work preceding them. Once testing advances to later stages, you need to make more material to satisfy demand; therefore, you need a more productive process. At the same time, if a molecule's efficacy and safety profile look promising, you also want to begin developing a commercial process during those early studies.

When you begin exposing a molecule to humans, regulatory requirements become more stringent. Your opportunities to explore the outer limits of critical process parameters are limited unless your company has enough resources to pursue process development in parallel with clinical supply. Very few companies, especially younger ones, can do this. But if you believe that your process will progress to commercial production, then it should quickly start to look like the eventual commercial process — economically and in terms of process robustness — particularly as you move into late-stage clinical trials.

In later stage trials, you face a significant challenge known as the chemistry manufacturing and controls (CMC) section of the biologics license application (BLA). This document

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records the science in support of FDA approval for commercial operations. So process understanding really starts in process development. If you can invest in process understanding in parallel with process development and clinical supply, you end up with a CMC section that gains more rapid approval and that supports future postapproval production changes based on solid science. If your communications with the FDA have been supported by data all along, you help build a constructive relationship. Companies have more opportunity to make changes today than they did 10 years ago based on the evolution of FDA policies.

Interestingly enough, economic stringency often doesn't play a significant role — particularly for biotech products — until a product is very mature in manufacturing. A company typically will go to market with a drug for which no comparable therapeutic is readily available. But as products mature, eventually companies face competition from other molecules. Particularly as patents expire, manufacturers look

more closely at production costs. So even if process economics aren't considered a big factor during process development, they will become important for late-stage commercial manufacturing.

Shared Responsibilities and Requirements

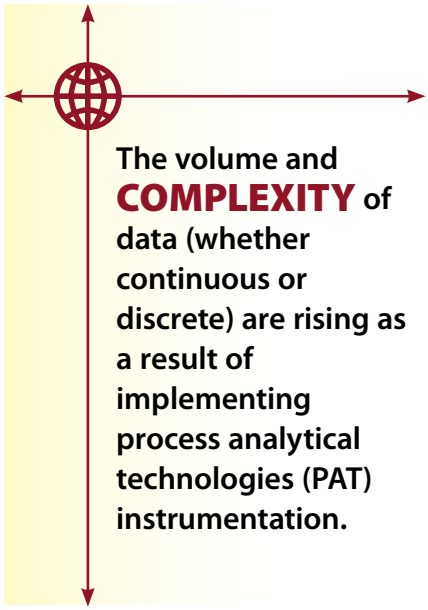
Ideally process development and manufacturing should enjoy a collaboration based on solid science and process understanding derived during process development. Their goals include

- Ensuring a stable supply of materials for clinical trials
- Shortening the time to value for start-up of commercial manufacturing (either through in-house operations or contract manufacturing organizations, CMOs)
- Preparing and supporting the CMC section of the biologics license application/product license application (BLA/PLA)
- Getting faster approval of future process changes based on defining a design space early on using sound science.

All groups want to avoid reinventing the wheel no matter what their individual goals may be. Process development and manufacturing teams have a set of requirements for accomplishing such a technical collaboration.

Real-Time Data Access: The first requirement is interactive, real-time access to all accumulated data on-demand in a combined format. This enables you to complete investigations in minutes instead of weeks. The use of the term *investigations* in this context means exploring cause-and-effect relationships, which is different from just describing what is going on — what you might see on a "dashboard." You need to be able to quickly explore causes and effects, regardless of scale. Analytical capabilities should be descriptive (what happened?) as well as investigational (why did it happen?).

Process development and manufacturing groups should work to improve productivity and compliance in ways that go beyond logistical and organizational issues. It's clear that a batch can fail because a wrong ingredient was used, but a batch also can fail if the chemistry and physics aren't under control. Such cause-and-effect relationships need to be understood.



Therefore, access to information should include all types of data, including paper-based data, to make meaningful investigational analysis possible. Nonprogrammers and nonstatisticians should collaborate to complete tasks and achieve their goals.

Technology Solutions to Data Challenges

Today's technology gives us connectivity and plenty of data to explore, but those data reside in many different places and in various formats. Relationships between data in different data stores are usually not very coherent. The volume and complexity of data (whether continuous or discrete) are rising as a result of implementing process analytical technologies (PAT) instrumentation. Data you first collect steer you in a preliminary direction. It's very rare to say, "Yes, I've got it!" after the first time around. To get the right answer, you need to be able to get back to additional data that support a planned deviation or validate changes to operating procedures. Iterative access to data needs to be simple and quick. You also have to account for batch genealogies when you need to compare batches to one another.

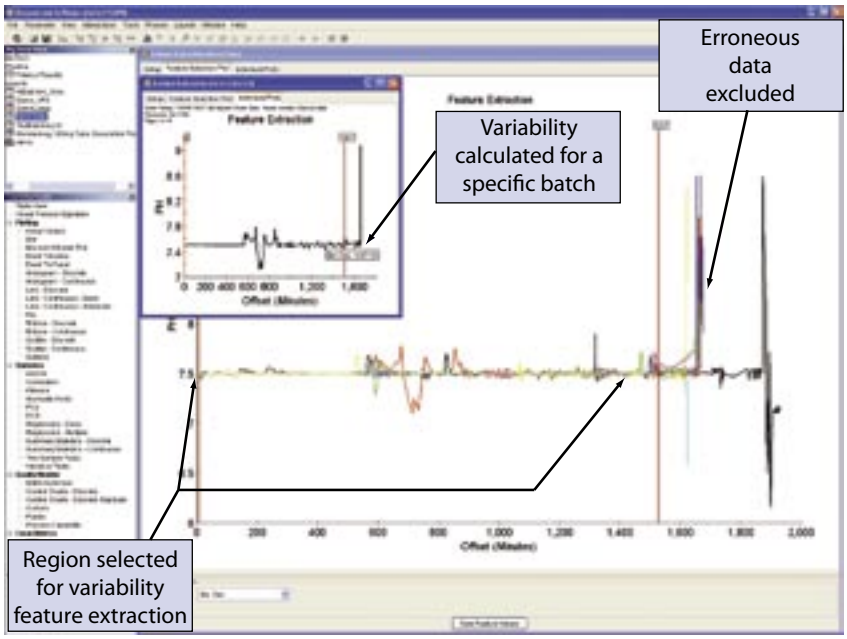
A consortium of companies that faced this familiar on-demand data access problem helped develop a preferred way to use software to access process data. They use a process flow layout simpler to Windows Explorer, using organizational nodes for process steps such as fermentation, recovery, purification, and chromatography. (See www.aegiscorp.com/product for examples.)

Quality data are usually associated with an end product, but they are often taken from in-process samples as well. People find it easiest to access information in terms of where it was collected in a process. So how do they map to particular points in a process that may use operating systems such as laboratory information management systems (LIMS), manufacturing execution systems (MES), or even paper records? Ideally, they "click" on those data through a standards-based interface rather than an application specific to those data stores.

But you still need to map information in a way that provides access and accounts for its location, its format, its batch genealogy, and its type (continuous, replicate, or discrete) in an "analysis group" that preserves its batch relationship to other data elements. Then you can work with data from an analytics point-of-view or from a descriptive point-of-view, or export them to other applications for more sophisticated analyses. You can also do this through an SAP NetWeaver (www.sap.com/netweaver), IBM Websphere (www.ibm.com/software/netsphere), or Fusion Software integration layer (www.fusionsoftware.net) if that's a standard installed at your company.

If you've used a **data warehouse,** you may have collected data, but you still need to get information in process rather than IT terms. New data sources can be added directly through a server or through a data warehouse. Mapping technology allows continuous, discrete, and replicate data to live together harmoniously in an analytical environment.

Figure 1: An example using analytics software to determine a critical process parameter



For paper records, you need a means for regular collection of valuable data. Hypertext markup language (HTML) interfaces enable users to create electronic forms that look like the paper forms. You can make double entries with computer checking and human intervention to approve data in compliance good with manufacturing practice (GMP). Even in these electronic times, paper records still exist, and you need a consistent, Part 11-compliant way to readily access data.

In summary, a company works with a number of data sources, one of which may be a warehouse, and a number of users — who can be anywhere in the world because they are connected by a network. A subset of users enter data from paper forms, and all those data are made available in an environment that provides point-and-click analytics such as trending, Q sum and root-cause analysis, and process capability for setting specifications.

Levering Continuous Data: One example of analytics software (Figure 1) assumes you want to test the notion that in a holding step, the variability in a pH level is correlated to a critical quality attribute. In other words, you need to prove that variability in this step is a critical process parameter. Using this analytical program, you can exclude irrelevant data by clicking on the screen to define the start and stop points. Software extracts the variability from the profile to test the hypothesis and discover whether pH variability is a contributor to the critical quality attribute you've identified.

Connecting Process Development to Manufacturing

Prepilot, pilot, and commercial-scale operations need to be connected for data-intensive collaboration. In prepilot stages, such as small-scale fermentations, you are defining a recipe and beginning to repeat runs to explore its critical process parameters. At this stage, data-specific stores for the work done in process development can be accessed through process views at all scales of operations. You can connect all views so that they can speak to each other. Users at different geographic locations can gain access to data from all previous batches regardless of the operating scale. Accessing data on-demand through a hierarchy lets you retrieve all instances to compare batches and analyze trends, learning from previous work.

Technology-enabling data-intensive collaboration ultimately has several benefits, which are particularly important for bioprocesses. They enable you to

- Review previous runs and understand multiple causes
- Access data from multiple sources, including paper records, so you can look at continuous and discrete data together
- Condition continuous data and plot it in real time
- Extract and quantify features from continuous data on-screen
- Analyze continuous data profiles for interactions
- Take care of process splits and recombinations automatically
- Share reports and results across multiple sites and geographies, pushing them automatically if needed
- Simplify periodic reports because you can quickly get access to the required data — reducing the time needed to hours instead of weeks
- Characterize and compare chromatography profiles.

Ultimately, the goal of reducing tech transfer risks is achieved through collaborative process understanding. The combination of on-demand data access, trending, reporting, and analytics that span process development and manufacturing allows you to achieve process understanding. The sooner you do it — in process development rather than at the manufacturing stage — the lower the risk and the shorter the time to value.

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