RAW MATERIALS MANAGEMENT

Technology advancements improving transparency and global collaboration
What we strive for is a condition where we collaboratively build raw material, process knowledge, and control strategies, and thereby improve product quality and process performance.”

**Nigel Darby, Senior Advisor, GE Healthcare**

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Advancement together: Working across company lines to overcome raw material variability

An introduction

When nearly 150 industry experts gathered in San Ramon, CA, for the second annual Raw Materials Variation and Control Symposium, the spirit was open and collaborative. Attendees of the symposium, hosted by GE Healthcare Life Sciences, shared the same industry mission — ensuring a consistent supply of safe and effective drugs to patients who need them.

The hope was to advance a collective approach to the challenges faced in raw material sourcing and management by revealing the transformative power and speed-to-market benefits today’s technologies offer to the raw materials supply chain. At GE, we are committed to understanding our customers’ needs in order to address their challenges and are eager to help you prepare for a new future in healthcare.

That is why, in this e-book, you will find insight and advice from top experts as they answer questions critical to our mission, such as:

• Is the biopharmaceutical supply chain fit for purpose given our industry’s growth?
• Can we still use it to serve the millions of patients who depend on us?
• How will advancements in big data and real-time predictive analytics impact the raw materials space?
• How can we use technology across the supply chain to better understand sources of variation in raw materials and increase process and raw material control?

These answers and more are leading the technological evolution of the biopharmaceutical landscape.

With the pressures to innovate and keep costs down, it would be naïve to deny that collaboration has its limits in our increasingly competitive environment. At GE, though, we are committed to pushing those limits and creating new boundaries, and we hope you are, too. As we experienced at the symposium, advancement together is not only possible through collaboration and openness but also a reality worth pursuing.

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• A qualitative method to improve process understanding and control while confirming media suitability and consistency
• Operation with a simple sensor that is fully automated, rugged, and capable of direct, offline contingency
• Low upfront cost and LTCO
• Repeatable, reproducible detection of major solid components and potential abnormalities that is specific to each medium

While several technologies were considered, such as a more sensitive pH reader, refractometers, and turbidity, Biogen eventually decided upon refractive index (RI). RI, which measures how light propagates through a specified medium and is used in the food and chemical industries to measure the consistency of formulations. It is designed for tank-mounted and stream applications using both flush and immersion sensors with a wide range of probe diameters. RI offers a high degree of sensitivity with the ability to detect the refractive index shift from individual component additions like salts, amino acids, and base media as each one is added, allowing trending of complex hydrations over multiple batches. Figure 1 shows examples of target media that exhibited repeatable and reproducible profiles using inline RI.

Figure 2 shows a comparison between an inline RI profile and an inline conductivity profile after 15 different component additions, showing that RI is more sensitive for detecting individual components. The driver for this change is not just gaining a better image of what dissolution looks like. With titers increasing, cells are now in high density environments and need more nutrients, so feeds have become much more concentrated, creating potential issues with what can and cannot pass through sterile filters during hydration. With a more detailed profile, Biogen could identify potential issues before a batch is added to the production process, when more time and money have been invested.

Comparison between supplier materials

The team also used RI to compare raw materials between different suppliers. While all of the suppliers were using pin mill technology to make their materials, they are produced at different sites using different settings, different flow rates, etc., and particle size can have an impact dissolution rate. If the particles are too small, the media can take longer to go into the solution. If they are too big, the volume ratio is different, again affecting the length of time it takes for dissolution. In its analysis of multiple suppliers of the same material, Biogen found that the particle size distribution of the material from Supplier 1 was different than that of Suppliers 2 and 3. (Supplier 1 material appeared to have larger particle size.) Figure 3 shows this comparison.
When they noticed this difference, they were then able to link that to the attributes of those raw materials and determine that Supplier 1’s material RI value stabilized approximately 1 to 2 minutes earlier than the other supplier materials. In the end though, the final RI value was comparable (Fig 4), indicating that media samples reached a similar final dissolution state.

As information such as this is collected from suppliers, it creates an opportunity to pull together raw material data from various sources in one organization that would otherwise operate in silos. It can then be put into a platform that can be accessed across a network, offering a flexible, visual representation of genealogy on demand from any starting point.

Identifying the genealogy of raw materials

Genealogy and processing data from a supplier can be used to understand the differences in raw material and link the inputs with that raw material data to process outputs. The challenge, though, is developing a common syntax across all systems. For example, if one database labels a raw material “CDM-6” but in another database it is labeled Media-6, a database integrator will not be able to recognize it is the same material. To address this, Biogen has begun to take steps to create an integrated system where that information can be collected and controlled more effectively with standardized labeling syntax.

First, Biogen has started to collect information from their suppliers to link to their local database and then using logic in data analytics software to identify supplier lots and even sub-supplier lots. This allows them to tie information together to trace raw material performance and use the platform and analytics to identify any trends. So far, the team has built a library of about 1,400 raw material samples and their attributes in order to understand what the normal range of variations is for a given raw material. When a process is being developed, they can then use samples that represent the high and low ends of that range for a variety of attributes, run them in a process as it is being developed, and determine if the process can handle that range of variation. If not, either the process needs to be adjusted to accommodate the normal range of raw material variation or, if this is not possible, a custom specification range for that critical raw material attribute needs to be agreed to with the supplier(s).

This technology has already been leveraged at Biogen’s site in Research Triangle Park in an investigation related to product quality. The team suspected the problem was a potential raw material issue, but after reviewing the raw material lot trend data and investigating further, they were able to determine an operational deviation resulted in extra material to be added to the batch. Without a proactive and integrated raw material characterization system, the approach to a resolution would have been to send raw material lots out for analysis, likely taking weeks to complete instead of days. The goal for this system is to get to a continuous state where Biogen can predict the process performance of any given raw material ahead of its use in development.

In the end, manufacturing consistency is a function of both process and raw material variation control and transparency of data from supply chain partners. Not only do Biogen’s efforts to understand control sources of variation from materials mitigate adverse effects on its manufacturing process, but they also become a valuable tool in ensuring a consistent supply of safe and effective drugs to their patients.

### ABOUT THE AUTHOR

David Kolwyck is currently the Director of the Global Materials Science team at Biogen where his team has technical responsibility for defining critical material attributes, supplier technical assessments and operational improvement projects related to raw materials used in Biogen’s global drug substance manufacturing network. He has been involved in the manufacture, characterization and development of pharmaceutical raw materials for more than 14 yrs as both a supplier and end-user. Prior to Biogen, he was at Amgen as the technical lead for upstream Raw Materials used in their biologics manufacturing network. As a supply chain partner, he held a variety of technical and commercial roles at JRH and Sigma Aldrich, specific to the manufacturing of cell culture media and chemicals intended for use in pharmaceutical manufacturing. David holds a B. Sci. from Truman State University, M. Sci. from University of Iowa and a M.B.A. from Washington University.
Amgen’s digital transformation: Linking raw material data from suppliers to patients

Cenk Undey, Executive Director, Amgen

In drug development and manufacturing, variability in raw materials presents high risks to the success of our processes and our products. When raw material variability issues arise, manufacturers and suppliers must address them immediately by analyzing data and determining the root cause. Sometimes these issues can be fixed quickly, and other times they can be more serious, creating a significant setback to your development and manufacturing timelines. This is why understanding, monitoring, and controlling raw material variability across the biopharmaceutical value chain from raw material suppliers to patients is critical. However, doing so depends on how a company’s raw material data is collected, shared, and analyzed.

At Amgen, a Supplier Relationship Excellence (SRE) program was designed to open the lines of communication with suppliers and create a feedback loop where data can be shared to better understand operational performance. In doing so, Amgen has advanced several digital and predictive technologies across the value chain that have contributed to the success of SRE and the exchange of electronic data (eData) with suppliers. This includes establishing smart contracts, developing data exchange standards, using predictive models to anticipate issues or identify improvement opportunities, and leveraging artificial intelligence tools and technologies.

While the bio/pharma industry has historically lagged when it comes to digital technologies, adopting a digital transformation such as this for the collection and analysis of raw material data, along with other critical data throughout the value chain, could modernize drug development and potentially revolutionize patient care.

Standardization of raw material eData exchange

At Amgen, it is estimated that 500 million continuous data points are generated per product from manufacturing equipment used in therapeutic protein production. In research and development, one of the robotics-based drug candidate screenings generates an additional 200,000 data points per day. Much of this data comes from raw materials, as many raw material components are used at each stage of the development process. Traditionally, this information is stored and exchanged using Excel® spreadsheets, proprietary databases that are hard to access, or other paper-based systems. When a raw material issue arises, process developers use this information to look for possible trends that might help identify where the problem exists, which is very time consuming.

Rather than continue to operate in a reactionary way to raw material variability issues, Amgen Operations decided to create an in-house, validated information system, called Raw Material Information System (RMIS), where we could document and store raw material data. While RMIS allowed for a more organized way of collecting raw material data, our team wanted to explore ways we could use the system to increase supply chain visibility and anticipate/reduce variability issues. If we could achieve that, it would set up a quick mechanism for feedback between us and our suppliers that could facilitate troubleshooting and offer continuous improvement opportunities. One major challenge of this system, however, is that there was no standard file format for data that would allow a seamless data exchange between suppliers and users.

To address this, our team worked with one of our suppliers to develop a data file format based on scientific data exchange technologies, which we eventually presented at an annual Pharmaceutical Process Analytics Roundtable (PPAR) meeting. PPAR includes 30 representatives from across the industry interested in the current state and future direction of process analytical technology (PAT). The PPAR group encouraged our team to initiate an industry-wide effort to create eData exchange standards that would allow for the systematic study of raw material variability. The result was a group that consisted of 12 major pharma and biopharma companies and nine suppliers, who discussed the current plan and identified areas for improvement. The format was then documented in an article that also explained how it operates. We later submitted it to the American Society of Testing and Materials (now known as ASTM International), and in less than two years, it became a published standard that can be used as a reference guide for eData exchange. With this standard in place (ASTM E3077), it provides a common data structure and ease of accessibility of all other related processes and product information. In the end, facilitating the exchange of data across an entire supply chain allows a more complete understanding between the supplier and manufacturer about the impact of raw material variance and what it means to the process or product performance.

Identify, track, and control variation (ITCV) and multivariate analysis

ITCV (Fig 1) is a framework used by Amgen that applies statistical process control to detect trends in data over time, using either one variable at a time or multivariate analysis (i.e., analyzing many variables simultaneously), and to identify possible areas of variability. If any issues are identified, they are escalated to the supplier, so the supplier can take actions to mitigate the risk, if possible. The action(s) could be at the supplier, at Amgen, or at both. For example, our team used ITCV to measure 52 variables across 42 lots of different raw material against in-house performance data. While doing so, we noticed two statistically distinct clusters of data. When comparing them...
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Across the 52 variable measurements to see which variable was causing the separation of data, we found the clustering was related to a difference in the raw material coming from a plant in one geographic location versus another. Although the systematic differences between the two sites did not have a significant impact on Amgen’s operational performance, it demonstrates the ability of the system to detect potential variability issues in their infancy. Figure 2 shows the path of our analysis and how we came to our final conclusion.

Another example of how ITCV helps us understand, reduce, and increase control of raw material variation is related to an issue discovered with a legacy product at one of our commercial manufacturing sites. A raw material was posing high variability and risks to our manufacturing performance. To mitigate that, we were historically running bench-scale experimental models using raw material samples to mimic actual commercial operation. Each sample would be run through a bench-scale model in the process development lab to determine how much, if any, risk it poses. The turnaround time for sampling, running experiments, and analyzing these materials is 80 hours. After years of amassing raw material data, our team ultimately established a sizeable database of raw material information. We were then able to build a predictive multivariate model that uses data readily available from certificates of analysis and prior to drug substance manufacturing to provide accurate expected performance results from the pertinent step in less than an hour. With the click of a button, the model provides the same information gathered during a lengthy laboratory analysis. This gave our team more time to work on more important process improvement efforts.

Mobile handheld technologies to capture data and enable rapid analyses

To reduce the amount of time it takes for lot release of raw materials, some companies are using handheld Raman and NIR spectroscopy technology, which uses Raman laser or near-infrared light, respectively, for rapid multi-component analysis. Our team realized that while this on-site identification of raw material is occurring, the handheld device is simultaneously gathering valuable data that could be useful for mathematical modeling and statistical trending about raw material variability. If this information is collected early in the life cycle of drug development, it creates an opportunity to produce a library of raw material variability. In addition, we also began to think, “How can we enrich this data, so we can use it for performance management and addressing variability issues?” To be predictive in a proactive way, or as the team at Amgen calls it, “proactive,” we began to use the data from the handhelds for computational modeling to study how a raw material might impact process and product performance.

Computational modeling

While we made strides toward monitoring and controlling raw material variability via data-driven and empirical modeling techniques, those techniques are limited to the ranges of the variables measured. We then started thinking about how we could expand our work in leveraging first principles of computational models into explaining raw material impact into our processes. Much of the current modeling techniques have roots in engineering, biology, chemistry, physics, and fluid mechanics. However, advances in computational power and scientific understanding are enabling more modeling of biopharmaceutical process development and manufacturing. The key is to form a mathematical model that will mimic the process, equipment, and raw materials and identify anything that might contribute to performance variability. If and when those signals are found, we can determine if there are any levels in our process design and control that might compensate for the disturbance. It is early for these advanced models to be effective in understanding raw material variability. However, we believe there is a significant potential to explore wider parameter ranges in silico.

Fig 2: Weak signal of a raw material variability shows differences between two sites of the same supplier. Amgen performance data does not highlight an operational difference between the raw materials from another site.
Watson Explorer Content Analytics

To achieve even further insight, Amgen has been leveraging advanced artificial intelligence tools, such as Watson Natural Language Processing (NLP). This system is capable of searching massive amounts of data very quickly. At Amgen, we have connected over 21 different source systems to Watson with close to 5 million records (and increasing every day; Fig 3). Watson is capable of reading into these documents and providing sentiments and correlations that are non-numerical (i.e., analyzing text).

Recently, during an inspection at one of our manufacturing facilities, the regulatory inspector requested documentation justifying our decision to check for a raw material used as an excipient in the manufacturing process. We were able to use the Watson system to search for that specific excipient. Within 10 minutes, 42 documents containing the two query items were made available to the inspection support team. What would have previously taken hours to accomplish was done in minutes.

This system not only allows us to understand raw material variability but also creates feedback loops from patient experiences. Any information from patients that is made available in our complaints databases is connected to the Watson system, so it can perform text analytics on those freeform sentences. It then reads the information and applies natural language understanding to return related results. We can then trace this information and determine if we see any trends that might call our attention to an issue in, for example, a specific region. Not only does this offer many benefits to the business of drug development and manufacturing, but also, most importantly, to the patients it serves.

While Amgen continues to seek ways to better understand raw material variability, it is important we share our lessons and experiences. By collaborating openly across the industry, we can minimize and control raw material risk and better manage our supply chain for the purpose of delivering the safest and most effective drugs possible.

Next steps

The future trend will be to leverage the aforementioned data exchange ASTM standard and increase investments in data infrastructure at suppliers and manufacturers to drive towards more seamless data integration. Through the use of eCoA and potentially direct connections to supplier manufacturing sites, it will be possible to have near real-time automated detection when a raw material results in variability in process and/or product performance.

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References

The past and future of managing raw material and process risks in biomanufacturing

Nigel Darby, Senior Advisor, GE Healthcare

For many years, the biopharmaceutical industry has been predominately occupied by antibodies, which has strengthened our knowledge and expertise about how to successfully bring them to market. Now, pipelines are filling with innovative and potentially groundbreaking molecules tackling many unmet medical needs. As the complexity of these molecules increases, so do their development processes and the unique challenges that accompany them. The inherent vulnerability of these increasingly difficult processes makes them susceptible to even the slightest change, renewing anxiety over the long-standing issue of managing raw material variation and process risks.

With biologics predicted to contribute to 52 percent of the top 100 product sales by 2022¹, we must ask ourselves: Is the biopharmaceutical supply chain fit for purpose given the growth of our industry, and can we still use it to serve the millions of patients who depend on us? Answering these questions requires a look back at how far we have come in raw material supply management and what still needs to be accomplished to ensure the delivery of safe and effective drugs.

A supply chain under scrutiny

Supply chain visibility has always been an important topic of discussion in drug manufacturing, as any changes can lead to patient safety issues and extended plant shutdowns. And because too much or too little capacity can lead to unfavorable manufacturing economics, there is little slack in the overall supply chain, whether it is in terms of capacity or raw materials. As an industry, there have been many challenges when it comes to having enough capacity to meet demand and enough quality raw materials to supply patients with safe and effective drugs.

When issues do occur, they sometimes result in scandals that call into question whether biopharmaceutical manufacturers can effectively protect and manage the pipeline of drug supply funneling into the industry and prompt a renewed focus on control measures. For example, when nearly 80 people were killed as a result of contaminated heparin in 2008², it triggered the refinement of supply chain controls and analytical assays to make sure that raw materials and their origin could be authenticated. The adulteration of infant formula and other food materials with melamine the same year also triggered a reevaluation of the supply chain to better understand how it was corrupted. These scandals raise difficult questions about the supply industry, raise doubts about whether the growth rate of the biopharmaceutical industry has outstripped the capabilities of the supply chain, and also increase regulatory scrutiny. Industry regulators encourage pharma companies to keep raw material quality in focus by making sure we have a supply chain appropriate for treating millions of patients.

The key to maintaining control is to create enough visibility so that we have the best chance of understanding the risks within our supply chains and can pave a clearer path toward constant improvement. One of the most critical challenges we face in this endeavor is raw material supply and raw material variation. If we can get these factors under a sufficient level of control, process development becomes much more straightforward, and as a result, we can achieve more robust processes.

Doing so requires us to address three key areas within our supply chains:

1. **Transparency** – We must create visibility into supply chains so that people have the best chance of understanding the risks within those supply chains. There is a balance between too much transparency and too little. One customer may receive a change control notification (CCN) and see it as a very low risk while another customer may see it as a very high risk. How does a supplier assess the likely impact of changes when every customer has different expectations?

2. **Consistency** – Small changes in raw materials, even though they remain within specification, can have a dramatic impact on manufacturing yield. Given the high price at which biopharmaceuticals sell, the economic consequences of this can be millions of dollars lost. By improving raw material consistency, you can better control process variability. So how can we enhance the reproducibility of our products?

3. **Risk** – Because of the types of products the biopharmaceutical industry works with, you may have only a single source for your raw material. If that supplier shuts down or runs out of material, you are faced with the possibility that you do not have the raw materials you need to produce your product, leading to delays and/or drug shortages. If you add a second source, you could potentially be creating more raw material variability. How can we balance and mitigate these risks in raw material supply?

It is when we begin to consider these questions that some of our biggest challenges — and potential successes — begin to present themselves.

² FDA Recall: Heparin, FDA News (2008)
A continuum of challenges and successes

The journey to secure a robust process necessitates a complex series of interacting choices about raw materials and their security of supply. Today we see a continuum of risk in manufacturing processes. At one end are high-risk processes that were often developed using first-generation methods and much less knowledge than we have now. Those processes often include raw materials that are not ideal for biomanufacturing, such as serum, where the material is so variable you need to batch test every lot to ensure it works. At the other end is the promised land, where processes are developed through a thorough mapping of process space using raw materials from a diversified supply chain with multiple manufacturing lines, where the origins of variability are well understood and controlled.

Most processes today fall somewhere in the middle. Raw material variability and its effect on process outcome is reasonably understood, though our inability to completely control it means that, on some occasions, processes may fail at significant cost. Moving past this midpoint requires partnerships with trusted suppliers who can deliver a high level of consistency and a two-way exchange of data. It is particularly important for suppliers to get insight into exactly how raw materials impact processes, as this allows them to focus on the most important factors that contribute to process success. It also necessitates a toolkit that allows you to deliver process robustness and a significant degree of control over how variability with your supplier contributes to variations in your manufacturing process.

Raw material supply

Achieving greater continuity and security with raw material supply requires several key elements currently in practice in the industry:

- Creates transparency in your supply chain, so you can see its vulnerabilities (including where key raw material suppliers converge) and assess risk.
- Uses analytical techniques to understand the key characteristics of a raw material and, ultimately, how they contribute to process quality.
- Turns characterization data into tactical management of how you can/should source raw materials.
- Secures and stabilizes inventory levels and costs to mitigate the risk of sudden disruptions; also establishes mutually beneficial terms for a healthy partnership and continuously improving quality measures, communication, and transparency.
- Achieves a greater level of security, albeit sometimes at the cost of more raw material variation.

While many suppliers are increasingly focused on controlling raw material risk and securing supply, supply chain controls, safety stocks, and business continuity plans only go so far. What can the industry do to make ourselves resilient to raw material variability?

Raw material variability

Suppliers are increasingly applying Quality by Design (QbD) to create a smart process design that minimizes the impact of raw material variability. In particular, some major suppliers have used QbD to produce better, more predictable single-use film, which is a reflection of the industry’s willingness to learn from some of its most challenging experiences. More consistent and predictable film properties are seen as key to increasing single-use technology adoption. However, while QbD is a valuable tool, you must obtain a substantial amount of knowledge about the raw materials going into your processes for QbD to be effective (Fig 2).

For example, while exploring the development process for chromatography resins based on agarose, a team at GE Healthcare Life Sciences spent a considerable amount of time and money understanding the physical and chemical properties of agarose and how it worked in the manufacturing process. While it may have seemed like an exorbitant investment at the time, it resulted in vital knowledge that helped GE understand how the properties of agarose, combined with other chemicals, contributed to the quality of the end product. In particular, it allowed the team to tune the way those raw materials were used to produce an end product with varying desirable properties in terms of chromatographic performance. This investment in raw material science is fundamental to the development of a strong product base, which is beneficial when dealing with subsequent manufacturing challenges. The knowledge collected offered GE the confidence to institute a second source of agarose without concerns that the change would impact the functional properties of its customers’ products or the manufacturing process employed. Without the investment in raw material understanding and analytical capability, such a change would have been inconceivable just a few years ago.

So how can suppliers make it easier for process developers to gain a better understanding of raw material variation and what tools they can provide to do so? Process development often focuses more on exploring processes rather than raw material attributes and will often use a limited number of raw material batches with limited variability. Suppliers can help by providing samples of raw materials that cover the breadth of the specification space, allowing the full impact of raw material variation to be evaluated. As suppliers accumulate experience and develop greater insights, they can then also focus process development efforts.
Some raw material variations can be relatively benign, while others can have devastating impact. Suppliers’ judgements on these matters based on historic experience can be valuable in prioritizing what raw material characteristics process development teams focus on. As more batches of raw material are used over time, long-term trending based on supplier/customer partnerships offer considerable benefits, ultimately allowing processes to be modeled more accurately and raw material impacts to be understood in great depth. Control strategies based on the outcomes of this work can ensure processes not only remain stable, but also gain in efficiency.

Process robustness to variability
Figuring out how to build greater confidence in raw material control requires open communication between manufacturers about how a supplier’s products are impacting the quality of individual steps within a process. Most importantly though, as we look toward the future, raw material data must be moved into electronic form, so it is easily accessible in comprehensive, user-friendly databases. Achieving this allows us to understand the true impact of raw material variation on process outcome and quality and allows a depth of investigation that is impossible today with data scattered between many different systems with both customers and suppliers. While there are tremendous challenges in executing this, due to the sensitivities around data sharing and transparency, doing so would streamline all aspects of the process and have tremendous economic and quality benefits.

In the end, the challenges with raw material and raw material variability are not going to get better as long as the relationship between manufacturers and suppliers remains purely transactional. Both sides must collaborate and work toward a common goal with aligned incentives to control the effects raw materials have on the overall success of serving our patients.

References

ABOUT THE AUTHOR
Dr. Nigel Darby has held several executive positions at GE. He most recently served as Vice President of Bioprocess for GE Healthcare Life Sciences from 2008 to 2016. At present, he is Advisor to the CEO of Life Sciences. Nigel has substantial experience from both the medical industry and academia. For example, he has held executive positions at AstraZeneca and spent 16 years in academic research in medicine and molecular biology.

Industry 4.0: Digitally tackling productivity and growth challenges
Dirk Voelkel, Chief Technology Officer, Innovation and Analytics, GE Healthcare

Today, 3 billion people worldwide are connected to the consumer internet via digital technologies, which has drastically changed how we live, work, and communicate. By 2020, it is expected that 30 billion machines will be connected to the internet, transforming the way we can use data and analytics to drive efficiency, accelerate productivity, and attain operational excellence. As this evolution occurs, the biopharma industry is also experiencing dramatic changes. Increasingly complex molecules, biosimilar competition, and personalized medicine are just a few of the latest trends driving new ideas and strategies about how we can efficiently bring high-quality products to the market (Fig 1). The convergence of the tangible physical world (machines, actuators, sensors) and the digital world (connectivity, algorithms, data analytics) opens up opportunities to access valuable insights about our development processes and manufacturing cycles for these drugs, as well as an ability to support real-time decision making.

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This process creates specific challenges that make cell therapy manufacturing especially difficult, as cell and gene therapy companies must achieve a zero failure rate during the manufacturing process. Should one of these bioreactors fail overnight, for example, when no one is able to notice and there is no alarm or remote access capability, the batch fails, preventing a patient from receiving their vital treatment.

By connecting various cell processing devices and digitizing data gathered from its instruments, GE was able to develop a solution for a partner in Toronto manufacturing cell therapies. The solution required a tight collaboration between Life Sciences Digital, GE Digital, and GE’s bioprocess service and automation queues, which helped create a physical and digital connection between the operational and informational systems. Using APM, GE retrieved critical data during a cell therapy manufacturing process in order to generate a real-time monitoring dashboard. This dashboard is able to track the process health of multiple cell therapy manufacturing lines, so operators receive an alert when something goes wrong, such as a temperature control fail, and avoid the costly and disastrous situation of lost batches.

Creating a digital twin for ultrafiltration

The evolution of Industry 4.0 has taught us that the possibilities of what we can achieve with machines become much more feasible when they are digitally enabled, especially in biopharma where we could use artificial intelligence to create simulations of our manufacturing processes. Such a “digital twin” is created when the physical, biological, and chemical properties of an asset or process are transferred to a digital format to enable a complete statistical analysis of product quality. The resulting “transfer functions” connect the asset or process quality output variables to the process and raw material variables at each level of the value stream.

For the biopharma industry, raw material variability is one of the biggest risks we face when it comes to ensuring asset or process quality. This is because the available data usually comes from supplier-provided certificates of analysis of individual raw materials based on tiny samples. Yet, these samples might not adequately characterize the specific portions of the raw material lots being consumed by the process. If we can successfully collect, analyze, and digitize representative samples of the raw materials being consumed by the process, we can feed this information to the process’ digital twin to analyze the effect of the raw material variability on the process output variables. This, in turn, will allow us to gain greater control over process outcomes.

In one case study, a GE Healthcare Life Sciences customer wants to maximize the yield of a specific protein molecule in their bioprocess, which requires a deeper understanding of how this molecule passes through GE ultrafiltration membranes. The GE team is using designed experiments at the process level and multivariate analysis at the raw material level to build a digital twin of the filter manufacturing process. The digital twin can then be used to learn how to set up the manufacturing process to produce filters capable of optimizing the yield of the customer’s specific molecule.

Brilliant manufacturing

While it is not always easy understanding and accounting for material variation, discerning sources of process and product variation is critical for reliable manufacturing and supply. It is also a focus of regulatory bodies, as they intensify surveillance and increase requirements for traceability. If we heighten supply chain visibility, we can proactively detect and mitigate supply risks. One solution is to connect digital data platforms between suppliers and manufacturers for seamless data access.

At GE’s Cell Culture Center of Excellence in Logan, Utah, this journey has already begun with what GE calls its “brilliant factory” (Fig 2). A GE brilliant factory merges lean manufacturing and advanced manufacturing with advanced software and IT infrastructure to enhance productivity and enable continuous improvement. It is built on a common systems strategy leveraging GE’s cloud-based software development ecosystem, to enable digital analytics in production processes.

This ecosystem will enable GE to collect data from its suppliers and input specific information into the data platform. This platform can then be shared with customers, who also add related information. Data sharing will allow GE and its customers to look at data simultaneously rather than having to provide it manually. Ultimately, the vision is to become fully digitized with optimized processors and real-time release, where it is not just the factory itself connected but also the ecosystem around it.

The digital solutions created by GE illustrate the capabilities of Industry 4.0 and what we can accomplish with them in the new era of bioprocessing. By applying remote monitoring solutions, advanced modeling, and optimization of manufacturing processes, Industry 4.0 can offer improved process reliability and product quality through the unlimited possibilities of connecting machines and data.

Dr. Dirk Voelkel, Chief Technology Officer, Innovation and Analytics Life Sciences joined GE Healthcare Life Sciences in July 2012. In his role he manages the R&D and technology portfolio of GE Healthcare Life Sciences and Life Sciences innovation activities. Previously, Dr. Voelkel headed the Research and Technology department in Roche Diagnostics Diabetes Care Mannheim, developing new technologies to address the needs of diabetic patients worldwide. In prior roles he was a technology scout in the San Francisco bay area and a project leader in R&D, developing systems for glucose monitoring. Before joining industry, Dr. Voelkel was a researcher at the Max-Planck-Institut for Fluid Dynamics in Göttingen, Germany and Sandia National Laboratories, Livermore, CA. He received a doctorate and diploma for Physics from the University of Göttingen. Dr. Voelkel holds 8 patents.

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Raw material variability control: Where do we go from here?

Cory Card, Principal Scientist, GE Healthcare

Managing raw material variation and process risks is critical to ensuring a high level of quality and consistency in drug development and manufacturing. Supply chain partners across the industry must work together to understand the issue of raw material variation and the impact it can have on the safety and efficacy of therapeutic products. A conjoined effort of all stakeholders is needed to identify best practices and apply them in their daily roles to mitigate potential risks.

In May 2018, GE Healthcare Life Sciences hosted the second annual Raw Materials Variation and Control Symposium as one way to bring experts from across the industry together to discuss how they are addressing raw material variability issues in their companies and what they are doing to overcome them. Life Science Connect recently sat down with Cory Card, Principal Scientist at GE, to talk about not just what ideas were shared at the symposium, but, most importantly, where we need to go from here.

Q It is evident from this year’s conference that progress has been made to improve the quality of raw materials as well as gain more control over variation. In your opinion, where are you seeing the most progress?

A I believe the greatest progress has been a better understanding by the industry of the current quality of raw materials used in cell culture, specifically with regard to impurities that are significant sources of variation in the production of biotherapeutics. A number of cell culture media manufacturers and drug substance manufacturers are characterizing these impurities and their impact on cell culture processes and products. As a result, there are healthy conversations taking place across the supply chain that are developing a greater awareness about the challenges we all face and, even more importantly, how we can collaborate to mitigate risks. For example, the BioPhorum Operations Group (BPOG) has published several resources, including a white paper titled “Patient-Centric Requirements for the Supply of Raw Materials into Biopharmaceutical Manufacturing” and a standardized raw material technical questionnaire for suppliers. BPOG is also working to understand variability in test results among various laboratories and across companies within the industry. In addition, an ASTM International standard has been developed to enable electronic data exchange. These are all excellent steps in developing the alignment needed to influence positive changes in the quality of raw materials.

Q What else do you think needs to be done across the supply chain to influence even more change?

A Well, we have a lot of work to do. Many of the changes we need are going to take a united effort in order to really have a positive impact on this issue. The cell culture market is relatively small compared to other markets competing for the same raw materials, which potentially have lower sensitivity to impurities or other aspects of quality. Even if the suppliers of these raw materials are striving to meet the quality standards required for cell culture, they may have little choice in where or how the materials originate or are harvested. There are added costs if additional processing is the only answer to improve the quality of the materials. In general, we need to collaborate throughout the supply chain to identify and implement best practices of sourcing, collecting, deriving, processing, and testing these materials.

Q The ASTM E3077 standard offers a way to standardize digital electronic information sharing across the industry, which is critical when it comes to controlling raw material variation. Where are we with its use across the industry? What, if any, are the current challenges of, or roadblocks to, implementing it?

A There have been some great cases of implementation of the ASTM E3077 standard among some drug substance manufacturers, cell culture media suppliers, and raw material suppliers. However, I feel broader adoption is needed. In my experience, the main reason for a lack of adoption by some companies is that they do not understand it yet or do not have simple tools to implement it. Instructions and converters are available, though, to define and simplify the creation of these files. It is important to keep in mind that this standard allows digital transfer of data in a very flexible way. Data that is traditionally printed and included on hard copy Certificates of Analysis, for instance, can be shared electronically. Therefore, it is much more easily implemented into a database or material/information management system.

Q What concerns are you aware of when it comes to establishing a standardized system for data sharing, and what value do you see in that collaboration?

A When we speak of data sharing, it is often met immediately with hesitation and concern. This reaction typically stems from a lack of clarity around what kind of data is expected to be shared. Concerns over loss of intellectual property or other data typically held private are common. Yet, the data to be shared electronically could be limited to data that is already shared in a nondigital format, (e.g., a Certificate of Analysis). When such data can be shared in a digital format, it reduces manual transcription of the data, preventing typographical and other errors. Sharing data digitally also facilitates integration into a database or data management system, such as a laboratory information management system (LIMS). This can help simplify quality control and other efforts, as well as make electronic lot genealogical information more accessible.
Q In general, how can the industry work together better, specifically with suppliers, to proactively identify raw material issues? Are there any specific resources that would help achieve this goal?

A I have been involved in many discussions with raw material suppliers in an attempt to clearly convey the current challenges with quality and what impact it has on our products and processes, and especially on the quality of drug substances. Initially, these discussions can be difficult, as we often do not get to talk to the appropriate audience. It is also a challenge if those we are speaking to do not understand the technical aspects of raw materials, their use, as well as the capabilities of the suppliers to monitor and control variation. I think forums, such as the Raw Materials Variation and Control Symposium, are a great way to increase awareness and understanding, align resources, and drive the creation of standards that will be important in addressing raw material challenges. However, many supply chain stakeholders are not yet participating in these discussions, and are thus unaware of these challenges. It is important to reach out through supply chain networks to spread more awareness about raw material variation and control and to foster greater collaboration and communication throughout the industry.

ABOUT THE AUTHOR

Cory Card has dedicated more than 24 years to cell culture development and biotechnology. He has spent the last 19 years supporting GE Healthcare Life Sciences’ Cell Culture business and currently serves as a Principal Scientist. His roles during the past 18 years include leading research and development efforts as a scientist, team leader, and director of research, product, and process development. He received his MS in Virology from Utah State University with a primary focus on factors influencing pathogenicity of the influenza virus.