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Biopharma's Big Breakout

This guide offers insight from some of the industry's top players and opinion leaders as well as a few deep dives into technologies

BY STEVEN E. KUEHN, EDITOR IN CHIEF

WELCOME TO *Pharmaceutical Manufacturing*'s Biopharmaceutical Technical Resource Guide. Once again, we've worked diligently to provide our readers with a true magazine, that is, a publication containing the works of many authors, photographs and art, often focused on a particular topic. In this case we're focusing on biopharmaceuticals and delivering insight from some of the industry's top players and opinion leaders as well as a few deep dives into technologies sure to support quality and operational efficiency. What's thrilling, though, is how exciting the Biopharma industry has become. The last couple of years have been an extremely dynamic period for the category as it breaks from its past and embraces its future as the new face of Big Pharma.

A scan of the features within should help confirm my thesis, as should the strategies and tactics myriad biopharmaceutical companies are employing right now to bring their molecules to market. Amgen's recent announcement outlining the company's growth strategy and its capital spending plans offers a case in point.

Robert A. Bradway, Amgen's chairman and CEO opened his quarterly results conference call by noting the company will maintain its focus on drug discovery and development developing branded biosimilars, developing improved biologic drug delivery systems, and the next-generation manufacturing of high quality biologics in support of global expansion. "With four potential product launches in 2015 and a strong pipeline of innovative and biosimilar molecules, we are well positioned to deliver breakthrough medicines for patients and drive long-term growth," said Bradway.

Bradway affirmed Amgen's operational strategy is on track to produce commercial products from its next-generation biomanufacturing facility in Singapore beginning in 2017. According to Amgen, "Next-generation biomanufacturing will enable dramatically increased bulk production capabilities versus conventional alternatives at one-quarter of the capital costs, one-third of the operating expense, and twice the speed." Not too shabby and certainly highlighting the gains to be had deploying cGMP and QbD-based process. Amgen estimates these new capabilities will result in an estimated cost reduction of 60 percent or more per gram of protein.

On page 17, Bioplan Associates' Eric S. Langer discusses the risks and rewards associated with biosimilars. Speaking of reward, Scott Foraker, vice president and general manager, biosimilars, at Amgen, explained how biosimilars represent a compelling growth opportunity with the potential to deliver more than $3 billion in annual revenues. In addition to its six current monoclonal antibody programs, Amgen has initiated three additional programs noting that Amgen's biosimilar infliximab and rituximab have advanced to the "clinical ready" phase. Amgen's first biosimilar is expected to launch in 2017, followed by four others through 2019.

That's quite a strategy and a break out one at that — but at the heart of it is the investment and attention to operations and process excellence, and that's a winning strategy the whole industry should recognize.

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BIOPHARMA'S GROWING MOMENTUM

Gaining both mass and velocity, Biopharma is an industry on the move

By Steven E. Kuehn, Editor-in-Chief

FEW INDUSTRIES, that is, the ones that actually make something, seem to have attained the luster and momentum than Biopharma has over the last decade or so. The category has really gone upscale since the days when vaccine manufacture had more of an agricultural feel to it rather than the high-science, high-tech aura that makes it shine today, a luster attracting billions in recent capital investment, while producing dramatic gains in successful therapeutic care and patient outcomes across several important categories.

Pharmaceutical enterprises associated with biotechnologies are widely acknowledged to be engines of economic prosperity and a driver of high-paying jobs. The number of states fielding biotechnology-based economic development bureaus, agencies and initiatives is growing as well, with folks working ever harder to bring the industry to their communities.

According to Biotechnology Industry Organization (BIO), the bioscience industry is one of the most innovative and important economic drivers in the United States, accounting for more than 1.6 million jobs and an additional 5 million due to the economic multiplier effect. A significant number of those "biotechnology" jobs are associated with pharmaceutical development. The U.S. Chamber of Commerce also notes that more than 810,000 people work in the biopharmaceutical industry and that the industry supports another 3.4 million jobs across the U.S. economy.

Each year Bioplan Associates Inc. publishes the comprehensive font of biopharmaceutical market intelligence. In its 11th annual "Report and Survey of Biopharmaceutical Manufacturing Capacity and Production," author Eric S. Langer frames the value and scope of the market, which Bioplan Associates pegs at about $190 billion. "This includes all biopharmaceuticals, i.e., biotechnology-derived pharmaceuticals, including classic biologics, such as vaccines and blood/plasma products," says Langer.

Not surprisingly, recombinant proteins/antibodies have passed a milestone, "now constituting >50% of biopharmaceutical revenue/sales and with sales now crossing the ≥$100 billion/year threshold," notes Langer. Among these products, says the report, monoclonal antibodies (mAbs) account for the largest portion, or about $50 billion in sales. "The biopharmaceutical market now constitutes ≥15%, approaching 20%, of the world's total pharmaceutical market, which is now essentially at $1 trillion/year," explains Langer, with growth projected overall to be "approximately twice that experienced by non-biopharmaceutical products, e.g., small molecule-based drugs."

Bioplan Associates' research says we can assume that future growth in biopharma sales will likely continue at an approximate 15 percent rate.

The advent of biosimilars will certainly have an accumulating impact on the market as well, once regulators settle on policies that they feel will address consumer safety concerns. Langer covers this important topic more thoroughly in "Risks and Rewards in the U.S. Biosimilars Pipeline," on page 17. But to summarize, Langer notes in the study that contractions due to biosimilars and cost controls in the U.S. and other major markets will be more than compensated for by organic growth in the market.

In its March 2014 Securities and Exchange Commission filing, Quintiles, self-described and widely acknowledged as the world's largest provider of biopharmaceutical development services and commercial outsourcing services, estimates total biopharmaceutical spending on drug development was approximately $93 billion in 2013, noting that it expects its Product Development services group will see a CAGR of 6-8 percent through 2016 "as a result of increased research and development, or R&D, spending by biopharmaceutical companies and the increased outsourcing of this spending as compared to 2012."

BIG SPENDERS

Quintiles estimated that R&D spending was approximately $137 billion in 2013 and is likely to grow to ~ $145 billion by 2016, "with development accounting for approximately 68% of total expenditures. R&D spending trends are impacted as a result of several factors, including major biopharmaceutical companies' efforts to replenish revenues lost from the so-called "patent cliff" of recent years, increased access to capital by the small and midcap biotechnology industry, and recent increases in pharmaceutical approvals by regulatory authorities."

In 2013, notes Quintiles' filing, approximately 4,060 drugs were in the Phase I-III pipeline, an increase of 19 percent since 2008. In 2013, 27 New Molecular Entities (NMEs) were approved by the U.S. Food and Drug Administration, the highest number of approvals since the late 1990s.

GROWING POPULATION

Bioplan Associates' report finds that as of February 2014 there were more than 460 biopharmaceutical products approved in either the U.S. and/or European markets (primarily, the European Union), including >180 recombinant proteins and >40 monoclonal antibodies. In the U.S., there were >385 biopharmaceuticals approved, including >145 recombinant products and 30 recombinant monoclonal antibody products. There were >355 biopharmaceuticals approved in Europe, including >150 recombinant proteins, including 28 recombinant monoclonal antibody products. Nearly 50 products are either pending at FDA or have applications expected to be filed in the coming months.

Here, Patheon technicians are transferring a batch at its award-winning plant in Brisbane, Australia.

It should be obvious to any industry observer that given the market growth projections, revenue potential, R&D spending trends, as well as the pace of approvals, plenty of production capacity is going to be required to make biopharmaceuticals widely available to health care providers and consumers. Things get interesting here because most agree that for biopharmaceuticals it's the process that's the product.

According to the latest PharmSource Trend Report, Bio/Pharma CapEx Trends: Sponsor Spending on In-House Capacity Trounces Outsourcing, bio/pharma companies invested some $118 billion in facilities and equipment from 2010 to 2013, an amount at least 10 times greater than what CMOs have invested in their own capacity over the same period. PharmSource posits that investment in captive manufacturing capacity by bio/pharma companies is an indicator of the industry's intentions with respect

Investment in biopharmaceutical processing capacity is being led by companies who understand process excellence is everything. Baxter embraces this philosophy at its LA facility shown here.

to outsourcing, and that based on recent capital expenditure trends, bio/pharma companies would rather make than buy capacity.

Offering a deeper perspective, PharmSource's president, Jim Miller, notes "Bio/pharma companies have spent nearly $120 billion on capital investments in the past 4 years, 10-15 times what has been spent by CMOs. The choice by bio/pharmaceutical companies to invest in captive capacity reflects strategic considerations and the fact that their cash flow enables them to readily afford manufacturing investments," he says. Global and generic bio/pharma companies, in particular, have invested heavily in new capacity, especially for biopharmaceuticals and in emerging markets. While CMOs are unlikely to overcome global bio/pharma's preference to own assets, they will nevertheless continue to play a vital role in the supply chain, says PharmSource.

While the industry seems to be driving increased CapEx investment for commercial production capacity in-house, Quintiles' market research seems to indicate that many companies are choosing to farm out the finer aspects of drug development and clinical trial administration. Quintiles estimates that clinical development spending outsourced to CROs in Phases I-IV in 2013 was approximately $19 billion and will grow to approximately $23 billion by 2016. "We expect outsourced clinical development to CROs to grow 6-8 percent annually during this period." Of this annual growth, says Quintiles, up to 2 percent will be derived from increased R&D expenditures, with the remainder coming from increased outsourcing penetration."

Managing complexity was identified as well with Quintiles noting that advancing standards of care in many therapeutic areas, the emergence of new types of therapies, (e.g. biologics and genetically targeted therapies), gene and stem cell therapies, and other treatment modalities will lead to more complex development and regulatory pathways. Quintiles cites personalized medicine: "We believe that companion diagnostics, genomics and biomarker expertise will become a more critical part of the development process as biopharmaceutical companies require more customized clinical trials and seek to develop treatments that are more tailored to an individual's genetic profile or a disease's profile." Of course, Quintiles believes they are particularly well-suited to this task for its customers.

Bioplan Associates' research and experience confirm that CMOs serve multiple functions in the development and manufacture of new protein therapeutics. "The most important of these comes from the fact that many of the most innovative and breakthrough therapies originate in small, discovery-based companies," says Langer. "These are often start-ups, with limited staff and facilities. Their scarce resources must be focused on research, their core area of expertise and value creation. Investing in extensive development programs and especially cGMP manufacturing facilities are a major distraction and drain of resources from their proper focus on discovery and proof of concept." For these types of start-ups and small firms, explains Langer, CMOs provide the "D," in R & D, as well as operationally excellent manufacturing. "In my experience over 30 years in the biopharmaceutical industry, with the past 18 years in CMO organizations, I have seen the emergence of biopharmaceutical virtual companies," which Langer refers to as "Two Guys and a Protein." At Gallus BioPharmaceuticals, he notes, "We have enabled many such companies by developing efficient and scalable bioprocessing procedures to produce first-in-human (FIH) therapeutics for the clinic."

PROCESS INNOVATION LEADERSHIP

For those attending the International Society of Pharmaceutical Engineers (ISPE) Annual Meeting this past October, it was quite apparent that manufacturing innovation and process excellence leadership was being led by the global biopharmaceutical industry. Of the seven nominees for ISPE's prestigious "Facility of the Year Awards," six were dedicated to biopharmaceutical production.

Category Winner for Operational Excellence and overall winner, Pfizer Ireland Pharmaceuticals NSI capacity expansion at its Grange Castle biopharmaceutical manufacturing plant undertook a challenging project to add additional capacity by repurposing existing manufacturing space to add a new vaccine suite plus a multiproduct small to medium scale drug substance bioprocess suite. According to ISPE, Pfizer needed to demolish existing facilities and construct new, without interfering with existing operations. The project team, says ISPE, "had a high interest in making sure that these new manufacturing suites included latest technologies (EBR, PAT and Disposable Bag), but also a Lean Management Strategy that was utilized throughout the project."

Chosen for transparency and flexibility, the Equipment Innovation category winner Boehringer Ingelheim's Aseptic Area 5 and Combi Line project (Aseptic biopharmaceutical manufacturing center in Biberach, Germany) did not win because of a single innovation, but for the combination of multiple innovations, says ISPE. "The use of transparency … was evidenced by the innovative use of glass clean room walls, air returns, and technical space, which allow visitors … to easily observe the ongoing operation[s] Flexibility … was pervasive throughout this project. The U-shape line design allowed flexible usage of individual processing units while maximizing operational time of the area during decontamination of separate isolators on the line."

From its inception, the Roche Analytical Laboratory "B250 – Q2K" built in Kaiseraugst, Switzerland, was conceived with a focus on Sustainability. As Sustainability category winner, the overall facility design followed the Roche Corporate Architectural guidelines ensuring a focus on facility lifecycle and timeless elegance. According to Roche and ISPE, the new facility includes labs with open ceilings and integrated support for technical installations. "A novel combination of glass elements and blinds were developed, enabling maximum natural daylight. Some of the energy-saving features include: heat recovery from an existing data center, solar roof panels to produce warm water, and a green roof to conserve water and create a friendly habitat."

Grifols Therapeutics Inc. won the Project Execution category for their North Fractionation Facility, located in Clayton, North Carolina. According to ISPE, the $340 million project is a 150,000 SF expansion on their existing campus for Human Blood Fractionation. "The project enabled Grifols to update their bioscience process to more current standards through the use of closed processing in order to minimize human interaction and maximized the use of supplier-enabled innovation through a new disk stack centrifuge design and development of an automated bottle opener," says ISPE. "The facility also incorporated a high level of automation to reduce human interaction (to two steps) and decrease process variability."

> OF THE SEVEN NOMINEES FOR ISPE'S PRESTIGIOUS "FACILITY OF THE YEAR AWARDS," SIX WERE DEDICATED TO BIOPHARMACEUTICAL PRODUCTION.

Process Innovation category winner Patheon Pharma Services (formerly DSM Biologics) Facility of the Future in Brisbane, Australia, incorporates innovative technology in both the upstream and downstream areas of the facility. "As a first use at commercial scale, [it] is novel both in those individual process areas and most especially in combination for an end-to-end biopharmaceutical production," says ISPE. For example, Patheon's patented XD technology incorporates technology similar to perfusion technology, but operating at higher cell densities (200 million cells/ml), very high titres (20 g/l) and retains the product inside the bioreactor during perfusion. Their downstream RHOBUST technology incorporates next-generation expanded bed chromatography in a novel configuration that allows the full commercialization of the tecchnique.

Lastly, Honorable Mention honors were earned by WuXi AppTec Biopharmaceutical Co. for its cGMP Bulk Cell Culture Production Facility in the Marshan Area of Wuxi City, PR of China. ISPE says it was recognized because it incorporates two parallel upstream cell culture bioreactor lines with flexible working volumes of 50 to 2,000 liters and one downstream purification production line.

Indeed, the biopharmaceutical arm of the pharmaceutical industry has slowly and steadily built up ahead of steam and like a locomotive at speed it has gained a momentum that will be hard to slow down, let alone stop — something that is unlikely as it moves to lead the industry and improve the lives of millions.

ADVANCED ANALYTICS IMPROVE BIOPHARMA OPERATIONS

Companies that use advanced analytics to improve operations have the potential to transform the biopharmaceutical manufacturing industry

By Eric Auschitzky, Alberto Santagostino and
Ralf Otto, operations practice, McKinsey & Company

SUCCESS IN biopharma has historically depended more on research and product innovation than just about anything else. Both will remain critical in the future, but operational performance will become increasingly important as competitive and cost pressures mount. To achieve operational excellence, biopharma manufacturers must develop capabilities in advanced analytics.

McKinsey's experience working with top biopharma manufacturers shows there is a significant opportunity to improve biopharma operations. Many manufacturers are overwhelmed by the complexity of their operations, and complexity often causes significant process variability.

Consider, for example, the production of biopharmaceuticals. Manufacturing biopharmaceuticals requires sophisticated operations due to the use of live, genetically engineered cells as well as a highly technical manufacturing process with multiple steps. As a result, manufacturers often monitor hundreds of upstream and downstream parameters to ensure the quality and purity of the ingredients as well as of the substances being made.

Two batches of a particular substance, produced using an identical process, can still exhibit a titer and yield variation between 50 and 100 percent. This huge, unexplained variability can negatively affect productivity and quality as well as increase regulatory scrutiny.

ELABORATE STATISTICS AND OTHER TOOLS

Advanced analytics is the application of elaborate statistics and mathematical tools to business data in order to assess and improve business practices (see Figure 1). We see global manufacturers in a range of industries and geographies using these tools to improve their yield, thereby underscoring the opportunity for biopharma.

Manufacturers, for example, have an abundance of real-time, shop-floor data and historical process data. They are beginning to take deeper dives into

this data, aggregating previously isolated datasets and using complex statistical tools to identify patterns and relationships among discrete process steps and inputs. They are using the resulting insights to optimize the factors that have the greatest effect on yield.

Robust datasets support predictive modeling of yield levels — which is a significant differentiator (see the sidebar "Predictive modeling using neural networks"). If the process and environment dataset is exhaustive enough (the dataset is broad enough), statistical significance is high enough (the dataset is deep enough), and the noise level is low enough (the dataset is clean enough), then advanced mathematical tools such as artificial neural networks can be designed for this purpose.

A REALISTIC TARGET

Process variability is often misperceived as intrinsic to biopharma processes. "We use live cells, which makes our processes highly variable" is a common refrain. Despite the strength of this myth, it has been repeatedly demonstrated that advanced analytics can significantly improve processes and decision making for biopharma manufacturers. Regardless of high process complexity, companies using these tools are reducing variability in product quality while also lowering costs and increasing sales.

Here's a case in point. One top-five vaccine maker used advanced analytics to significantly increase its yield in vaccine production while incurring no additional capital expenditures. The company segmented its entire process into clusters of closely related production activities; for each cluster, it took far-flung data about process steps and the materials used and gathered them in a central database.

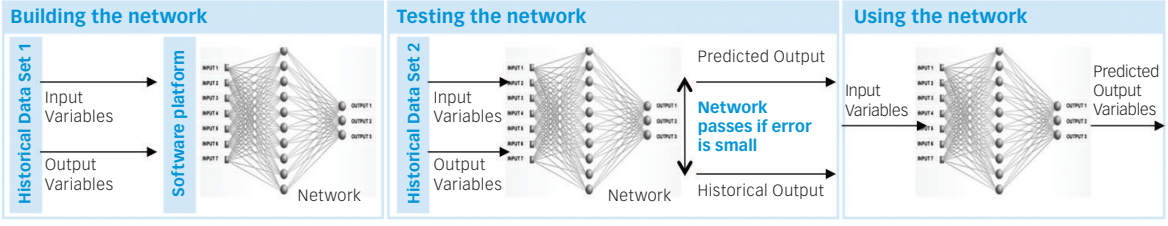
One team "on the ground" ran workshops and focus groups with local experts to draw an initial issue tree hypothesizing which parameters had the greatest influence on performance. A second advanced analytics team then tested that hypothesis using the company's centralized and cleansed data.

In parallel, the advanced analytics team applied various forms of statistical analysis to determine interdependencies among the different process parameters (upstream and downstream) as well as their impact on yield. The team on the ground explored the details of the process (e.g., physics, chemistry, biotechnology) to validate the outcomes of the advanced analytics (in other words, to explain the "why"). This step proved critical in helping the initiative avoid wrong conclusions.

Through iterative loops between the two teams, nine parameters were identified as the most influential. Time to inoculate cells and conductivity measures associated with one of the chromatography steps were proven to be particularly important. Targeted process changes to better control for these nine parameters produced quick results. The manufacturer was able to increase its vaccine yield by more than 50 percent — worth between $5 million and $10 million in yearly savings for a single substance, one of hundreds it produces globally.

PREDICTIVE MODELING USING NEURAL NETWORKS

An artificial neural network (ANN) is a mathematical model or computational model that is inspired by the structure and/or functional aspects of biological neural networks. In most cases an ANN is an adaptive system that changes its structure based on external or internal information that flows through the network during the learning phase. Modern neural networks are non-linear statistical data modeling tools. They are usually used to model complex relationships between inputs and outputs or to find patterns in data.



When to use

Mathematical relationship between inputs and outputs variables
- Cannot be established or is unknown
- Can be established but is complex and time consuming to model because:
  - Highly non linear
  - Too many variables

Problems that can't be solved

- Identifying drivers of system performance e.g. variables that impact the yield/quality/throughput the most
- Predictive modeling of
  - Throughput
  - Yield/Quality
  - Planning/scheduling

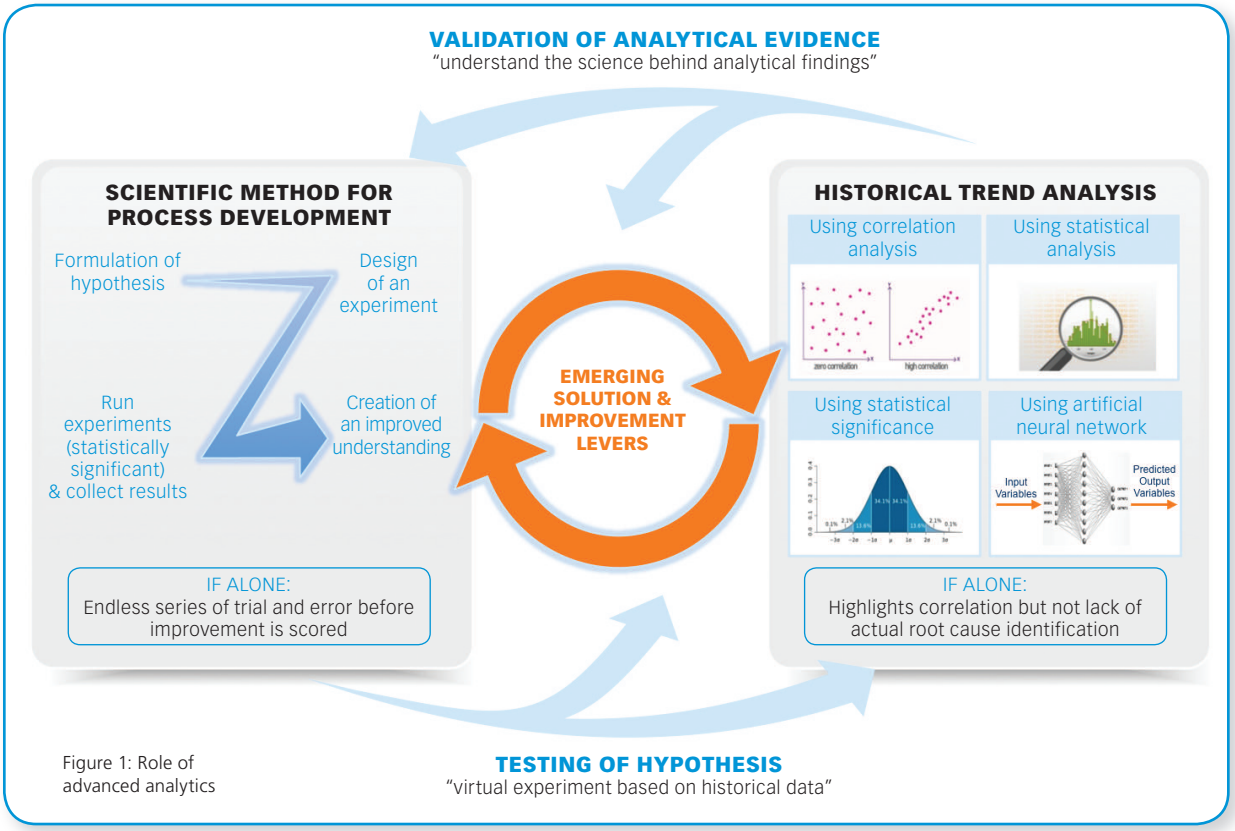


Figure 1: Role of advanced analytics

To achieve a similar boost, most biopharma companies still need to lay the foundation for a strong analytical capability. They currently lack the systems and capabilities to identify the addressable causes of variability in manufacturing. For example, they collect vast troves of historical process data — but typically use it only for tracking purposes, not as a basis for improving operations. Moreover, the collected data is not comprehensive and is stored in multiple databases that are not compatible with one another.

Beyond these data limitations, many biopharma companies lack the skills and tools necessary to develop actionable insights from the data they have. Even if some statistical analysis of processes and tentative correlation of parameters are occurring, the tools used are typically not up to the task at hand. ANOVA, single-variable correlation or other Six Sigma tools are not sophisticated enough to handle the multidimensional and highly complex manufacturing processes of biopharma.

With gaps in the data, skills and tools required for advanced analytics, biopharma companies often have an incomplete understanding of their performance. Furthermore, they may not be able to fully seize the opportunities that they do identify.

Biopharma companies that do build proper advanced analytics capabilities could forge an advantage in manufacturing that will differentiate them from their competitors. To help companies understand that analytics journey, we outline a standard and granular approach here.

1. Create the conditions for analysis.
Gauge the potential for improvement by using historical data to estimate the size of the gaps between average and best-case performance. To start, aggregate data from every available source across the organization into a single, exhaustive database. Map the organization's operations from end to end to account for every aspect of each production process. It is critical to ensure that the data is high quality and that enough data is collected to generate relevant insights. Then segment the data into clusters (e.g., fermentation) of closely related activities that can be analyzed as coherent units. For each cluster, list every process parameter and material characteristic.

2. Analyze data and develop insights.
Once a threshold of data is gathered and segmented, use a variety of advanced statistical tools to identify improvement opportunities and spot trends (see Figure 2).

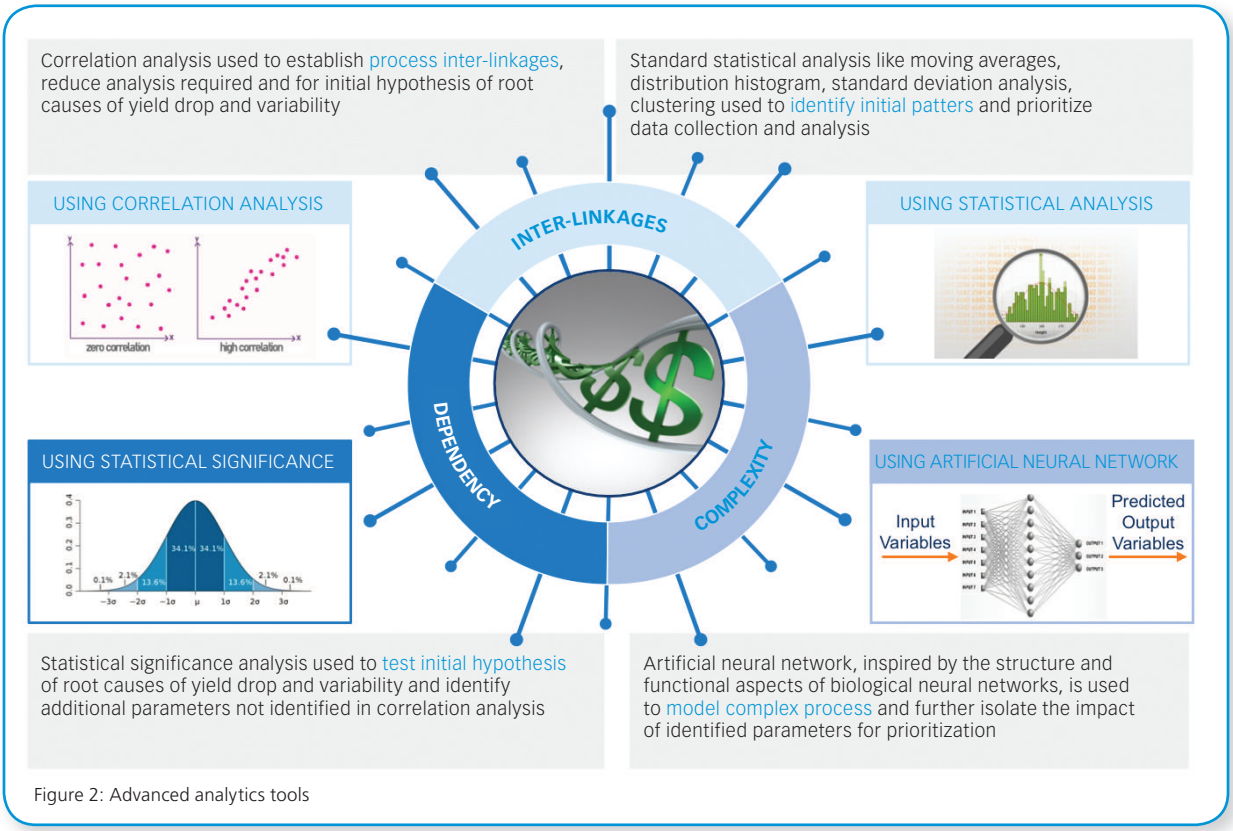


Figure 2: Advanced analytics tools

Correlation analysis can be used to identify relationships and linkages among process parameters. Standard statistical analyses — including moving averages, distribution histograms, standard deviation, and clustering analyses — can be used to identify patterns and prioritize data that has the most predictive power. Statistical significance analysis can be used to test initial hypotheses about the root cause of titer and yield variability and identify relationships among parameters that were not surfaced by correlation analysis. And artificial neural network analysis, which seeks to emulate the structure and functional aspects of biological neural networks, can be used to model complex processes and determine with greater precision how particular parameters affect productivity.

Accelerate progress by conducting workshops with biopharma experts to investigate the trends, correlations, and other phenomena identified. This will foster a deeper understanding of the underlying biopharma parameters along the value stream.

3. Build an action plan

In many cases, opportunities will be identified that are worth pursuing. Rank these opportunities based on potential impact and the effort required to implement. Then prioritize opportunities with the highest impact that are easy to implement. Develop clear initiatives to capture these priority opportunities. These initiatives should include provisions for training and coaching employees at all levels in the organization to ensure they develop the necessary capabilities and mindsets. Also include provisions for monitoring performance to ensure that the initiatives are implemented properly and on time, and provide mechanisms to help teams correct course when they encounter challenges. It is critical to assign clear lines of accountability for every aspect of each initiative.

Executing in waves is recommended. Consider this approach to allow teams to learn on the fly and refine their approaches as they roll initiatives out in full.

Here is a second case in point. A biopharma firm that used this approach increased its yield by 30 percent by stabilizing cell growth. This improvement, triggered by insights gained from analytics, derived largely from improvements in cell storage and adopting more effective standards for discarding expired media used to grow cells.

Manufacturers that use advanced analytics to improve their operations have the potential to transform the industry, establishing new standards for efficiency while reducing costs and increasing sales. The resources they free up can then be poured back into research/product development, fueling their growth far into the future.

RISKS AND REWARDS IN THE U.S. BIOSIMILARS PIPELINE

Too many products, price pressures and other things that "Go Bump in the Night" will challenge those pursuing this potentially lucrative market segment

By Eric S. Langer, Bioplan Associates

MANY COMPANIES will soon be marketing a variety of competing biosimilar products for the U.S. and other major markets. Yet specific guidance from U.S. regulatory authorities is lagging, and this is creating disruptive pressures. Congress has recently pushed the FDA to release guidance documents on biosimilar drug approvals. A group of senators wrote to HHS in August about the implementation of the "Biologics Price Competition and Innovation Act" (BPCIA), enacted in 2010 to push the FDA for a framework to review and approve biosimilars. Although the FDA just recently accepted the first biosimilar application for review (Sandoz), it has not released specific guidance. This delay has heightened concerns about just exactly how biosimilars will affect patients, insurers, the drug companies and even suppliers.

Research in biosimilars and the industry for more than 25 years indicates among the roughly 4,500 biopharmaceutical candidate products in the pipeline, around 20 percent of those products — about 900 — are follow-on biopharmaceuticals, mostly biosimilars (>500), but also biobetters. In the course of Bioplan Associates' studies, analysis shows only a percentage of these will make it to the market.

PRICING MODELS POORLY DEFINED

Along with the attrition rates for biosimilars candidates, factors such as prices and discounts for biosimilars (relative to long-established reference products), remain poorly defined. These questions may well determine success or failure of biosimilar products in the United States. Biosimilars competition will include multiple biosimilars that sooner or later will be competing for each major biosimilars reference product target, and with other products for the same indication. But how many biosimilar players and products will there be in the U.S.? Will there be too many products competing for sales in relatively small markets or disease categories?

To better understand the issues at hand, what follows focuses on genuine biosimilars, those approved through a formal biosimilars regulatory mechanism involving rigorous analytical and clinical testing to prove biosimilarity. The discussion does not include the perhaps 200 biogenerics, (by regulated country standards), now available or being approved in lesser-regulated international commerce (1).

EU MARKET EXPERIENCE

The current market for biosimilars remains rather small and under-developed, with the U.S. not yet involved. To date nearly all biosimilars market development has occurred in Europe, with smaller biosimilar markets developing in Australia, Japan and other highly developed, highly regulated countries. The global market for biosimilars is only about $500 million, on the order of 1/10th the market of just a single major targeted reference blockbuster (≥$1 billion/year) product. With over a dozen biosimilar products approved in the EU, the average market for each biosimilar is trivial by most standards. Despite biosimilars being approved in the EU since 2006, most European countries have moved slowly in adopting biosimilars. Overall, in EU and other countries, biosimilars are priced at about 25-30 percent discount relative to their reference products.

But it is still early in the game. There are currently nearly 40 blockbuster (>$1 billion/year sales) recombinant protein reference products, with 60 generating sales over $.5 billion, prime targets for biosimilars development. Most of these reference products have patents expiring starting in a year or two, a time when a flood of applications can be expected (discussed below).

EU EXPERIENCE NOT RELEVANT

For a number of reasons, many involving politics and some countries' centrally managed healthcare systems, the EU experience with biosimilars market development can not be readily extrapolated to the U.S. Uptake and adoption of biosimilars in the EU has been slow, with Germany the only country with biosimilars capturing significant market share from innovator reference products. This is partly due to the reason that government regulations establish quotas for physicians, requiring them to prescribe biosimilars. European market development has been slowed by the diffuse nature of this market, e.g., with 28 different countries being members of the EU. EU biosimilar approvals still have to be adopted by each member state, along with guidelines implemented for use and insurance coverage; all this complicated by many European countries controlling prices and having socialized health care systems. In these contexts, the EU experience in biosimilars market development is not relevant to U.S. market development, where the market is much more open and competitive.

NUMBERS OF BIOSIMILARS IN DEVELOPMENT BY PHASE OF DEVELOPMENT

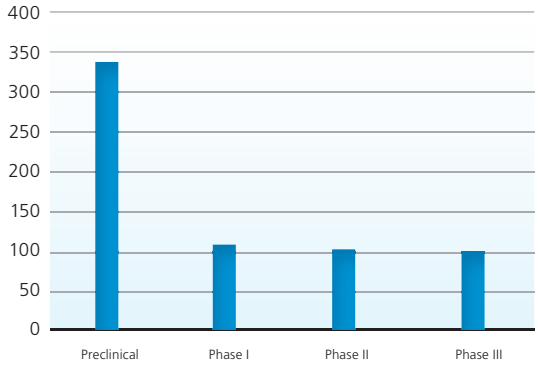


figure 1

IN THE PIPELINE

The biosimilars development pipeline is relatively large. BioPlan databases track over 650 candidate biosimilars in development; plus another 450 biobetters in development (2). Biobetters are products, like biosimilars,

BIOSIMILARS IN DEVELOPMENT

Product	# Biosimilars
monoclonal antibodies (mAbs)	223
mAbs for cancer indications	136
EPO/epoetin alfa products	84
interferon alfa products	66
Neupogen	56
insulin and analogs	47
Rituxan	44
Herceptin	37
Enbrel	27
interferon beta products	26
Humira	24
Avastin	22
Neulasta	20
Remicade	13
Aranesp	7
Lantus	7
Lucentis	3

Source: BioPlan Databases

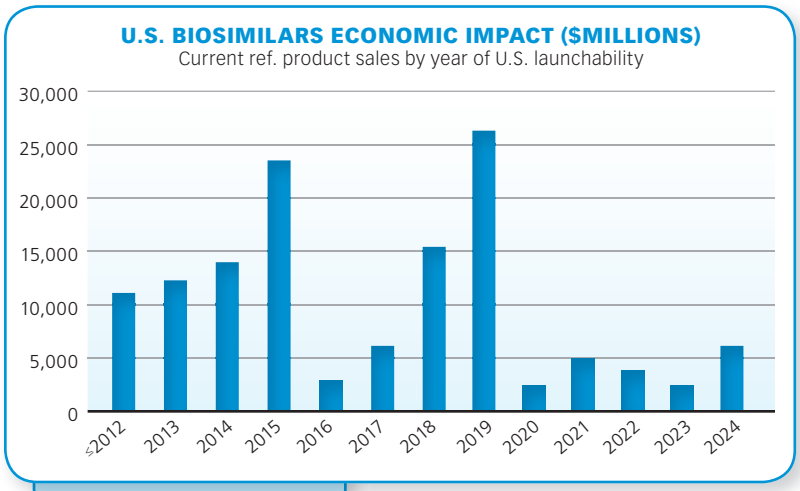


figure 2

incorporating much the same active agent as a reference product but with significant modifications such that it is regulated and considered a new innovative product. The current status of biosimilars in the pipeline (those not yet approved anywhere) is shown in Figure 1.

As is normal with pharmaceutical pipelines, most products are in the earliest stages of development, with most yet to enter clinical trials. Essentially, all of these products are targeting the U.S and other major markets. Over 300 companies worldwide are already involved (in various aspects, e.g., development, marketing agreements). Most of the companies involved in biosimilars are either large international (bio) pharmaceutical companies or small new and foreign-based entrants. Classic venture capital-funded and other mid-sized biotechnology-type companies are generally not involved in biosimilars, with these companies targeting new, innovative products. Small company biosimilar developers can be expected to license product marketing to larger established marketers. So at least in terms of marketing, current major players will dominate the U.S. biosimilars scene, at least marketing, in the early years.

ALTERNATIVE EVOLUTION

The U.S. market will evolve differently than the current biosimilars market in Europe. Biosimilars, like generic drugs and other follow-ons, will be priced at a discount relative to their reference product. Uptake of biosimilars will be rapid, with insurance companies and other payers essentially forcing patients' use of cheaper biosimilars, much as they do with generic drugs.

The U.S. market is attractive because the U.S. will become the largest market for biosimilars, likely surpassing current European and worldwide biosimilars sales as the first few products capture market share. Compared to Europe, the U.S. market is more open, free-market, with more aggressive competition and rapid market uptake likely for any substantially discounted biopharmaceuticals. FDA still needs to implement a number of guidelines and regulations concerning biosimilars approvals. This is causing many companies to go slow in their biosimilars development, particularly including holding off on starting clinical trials directed to U.S. approvals, until FDA makes its own plans clearer.

The likely timeline for the economic impact of biosimilars introduction into the U.S. market is shown in Figure 2. The bar chart shows the cumulative 2013 worldwide sales of reference products vs. their expected year of launch in the U.S. (expected reference product patent expiration). Collectively, the data shows that reference products with about $100 billion in current worldwide sales will soon be subject to biosimilar competition in the U.S. market. A wave of significant U.S. market filings and launches can be expected to start next year with another peak in filings and launches (patent expirations) by the end of the decade.

Table 1 shows the number of biosimilars in development for some of the major reference products and product classes. Essentially, all of these products will be targeting the U.S. market. Even if just a portion of candidate products make it to the market, there will be significant competition among biosimilars.

TOO MANY TO BE PROFITABLE?

Once FDA provides appropriate guidances, biosimilar approvals will progress in an orderly fashion, although patent disputes will likely occur with every product, following the pattern with generic drugs. With blockbuster reference product manufacturers making up to tens of millions of dollars in profits, sometimes simply stalling biosimilar market entry for a single day could be well worth pursuing.

How many biosimilars for any particular reference product will enter the U.S. market? Most analysts extrapolate EU market evolution to the U.S., citing it likely that only a few, 2-4 biosimilars at most, will enter the market for each major reference product. We believe there will be more competition in the U.S. market. Already many large international companies, including major biotechnology players (Amgen and Biogen-Idec, for example), most

Big Pharma and large generic drug companies, as well as many foreign companies are developing biosimilar portfolios targeted primarily for the U.S. market. These companies expect to be long-term players in the U.S. and world biosimilars market, with most planning to have a portfolio of biosimilars and/or include add these to their present portfolios. For many new, including foreign biosimilar developers, biosimilars will be their entry into the U.S. and world biopharmaceutical markets, and they are determined not to miss this opportunity.

FIERCE COMPETITION AHEAD

We expect more biosimilars entering the U.S. market for each major reference product. If Big Pharma, established biopharmaceutical and generic companies, new U.S. entrants and overseas firms all develop a biosimilar for each major reference product to the U.S., it will create a very tight biosimilars marketplace. Also, there will be biobetters of the established innovator and other products for the same indications will all be competing against each other in the marketplace. Competition could be fierce.

How much will biosimilars cost, i.e., be discounted relative to their reference products? Most, based on European experience, presume that U.S. prices will be similarly discounted by up to 30 percent. However, the U.S. market is a larger, more unified, faster-moving, open and competitive. Economics will drive rapid adoption of biosimilars in the U.S. with insurance companies and other payers going for the cost savings biosimilars will provide. Already, a major player, Samsung Bioepsis, a joint venture of Biogen-Idec and Samsung (development and manufacture) and Merck & Co. (marketing), has announced its intension to launch its biosimilars in the U.S. at 50 percent discount. We project that this will become the standard biosimilar discount in the U.S. Note this is much less than the common ~90 percent discount for many generic drugs. With so much competition, biosimilar companies will have no choice but to efficiently manufacture and market their products.

Will there be price wars? Perhaps. A number of biosimilar developers appear intent on getting their products into the U.S. market, including many international players choosing to mark their entry into the world biopharmaceutical markets, via the biosimilars channel. Many companies, including those well established in the U.S. market, may be more concerned with gaining approvals, market share and building their portfolios, than with maximizing profits from a few early biosimilars. Such companies might try to "buy" their way to market share, and become the spoilers prompting price-war battles.

Biosimilars in the U.S. will also require broader marketing efforts. Unlike most generic drugs, biosimilars will not be prescribed like generic drugs, that is, either legally or in practice routinely interchanged and filled with generics. Even if FDA adopts generic rather than unique names for biosimilars (which seems unlikely), the nature of the serious diseases these products treat (not to mention the high cost associated with such products) will require biosimilars to be marketed much the same way as innovator products, including highlighting the quality of trials and results.

PROFIT POTENTIAL

Will biosimilars be profitable in the U.S.? Yes, they will be, with markets collectively worth tens of billions of dollars soon becoming available. But markets for most products will be small, compared to their reference products. For example, Abbvie's Humira is on track for annual sales of about $10 billion/year. Capturing just five percent of this market, $500 million/year, is certainly an attractive and profitable endeavor. Even attaining just 10 percent of a $1 billion market (e.g., having one of 10 competing biosimilars, selling $100 million/year) would be financially attractive, particularly for companies with a portfolio of biosimilars or other complementary products targeting the same indications.

THE U.S. MARKET FOR BIOSIMILARS WILL BE INITIALLY CHAOTIC, WITH MANY PRODUCTS AND PLAYERS

A large number of biosimilars, most targeting the U.S. market, are in various stages of development. The U.S. market for biosimilars will be initially chaotic, with many products and players, including many new to biopharmaceuticals and the U.S. market. There will be many biosimilars for each reference product, with prices generally discounted up to 50 percent. Those companies that efficiently develop, gain approvals, manufacture and market their biosimilars will be profitable. Biosimilar sales and profits will be much smaller than with innovative products, but those in for the long haul, those that best adapt to likely chaotic U.S. market conditions, will be among the winners.

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GENENTECH'S DAWN PATROLS CRITICAL ASSETS ACROSS CAMPUS

Biotech giant's Data Acquisition Wireless Network provides unprecedented infrastructure transparency for transient lab equipment

By Aaron Lee, DAQ Product Manager, Yokogawa

AS WIRELESS technologies expand farther into industrial automation and process manufacturing, organizations across the world are adopting and implementing wireless solutions to provide unique identifiers, along with the ability to transfer data over a network without requiring human-to-human or human-to-machine interaction.

As the heart of its U.S. R&D center of excellence, San Francisco is a special place for biotech giant Genentech. Employing about 10,000 people, Genentech's campus occupies a large area, encompassing 60 buildings within a two-mile radius. To support overall operational excellence, the site contains a dedicated facility-monitoring system that allows equipment owners to view live process values and monitor equipment for performance and alarm conditions via a common, accessible and unified system. Data collected by the system is also sent to a historian to preserve data generated by the many assets across campus.

Using this capability, Genentech's operators monitor

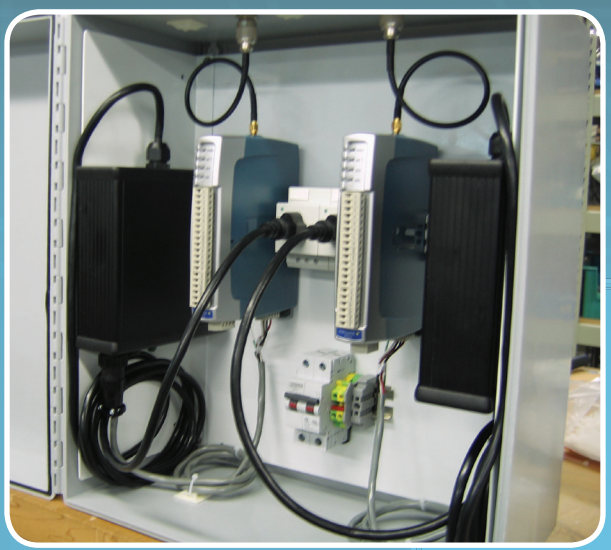


Figure 1: As part of the DAWN infrastructure deployment, wireless repeaters like this one were installed at strategic points around the campus.

INDUSTRIAL WIRELESS NETWORKING: MATCHING THE TOOL TO THE JOB

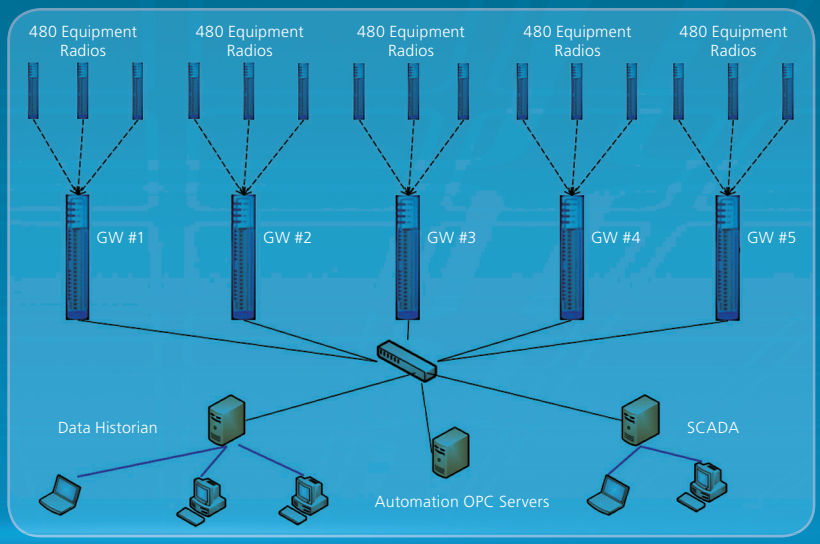
Use of wireless networks in industrial environments has grown a great deal in the last five to 10 years along with developments of networking technology to make such applications more effective and economical. While sending data via radio is not new, earlier deployments were typically single point-to-point installations and weren't very efficient or reliable.

New wireless networking technologies have been developed that are designed to move information bi-directionally from a large number of field devices to a central control system in a way that provides a similar kind of data transfer as wired networks.

These days it's hard to find a place where there are no wireless Ethernet (Wi-Fi) networks, and many of the same techniques have been applied for ZigBee, ISA100.11a, WirelessHART, and many more. These networking strategies developed to fulfill some specific user case that called for a group of operational requirements. Usually those are defined in reference to: determinism (minimizing latency), bandwidth (amount of data), distance, power consumption, and reliability

Mesh networking turns every node in a network into a combination of receiver and transmitter. At some points a node is receiving, listening to the traffic on the network. Other times it is transmitting, sending along data collected from its sensors. In an ideal situation, when a node has a packet of data to send to the gateway, it will go there directly.

However, a given node might not be able to contact a gateway for various reasons. In that case, it sends its data to a nearby node that has a better connection, and that node relays the information. The concept of self-organization gives the network the capability to establish these connections automatically. The network can also adjust the way it communicates when circumstances change and existing connections no longer work.



Wireless nodes on the network work together to organize communications and make adjustments on the fly as circumstances change.

The downside of mesh networking is that it can introduce latency when a given bit of information has to travel from node to node to reach the gateway. That time may be a matter of a few seconds or less, but in some applications this can present a problem. Effective network management can minimize latency across all data transmissions, and some signals can be assigned higher priority than others.

With the Yokogawa DAWN wireless system, each radio can include up to 13 I/O configured in various combinations. Each radio's internal controller interacts with each I/O point and transmits information back to the gateway. While as many up to 2,400 radios can be used, none generate particularly large amounts of information.

Most industrial wireless networks cover distances of a kilometer or less, although radio signals may have to pass through walls and around large steel structures. Using more powerful radios and efficient antennas can overcome those obstacles, but increase power consumption.

For some networking approaches, power consumption is a major issue. Field devices that have to operate for many years with no power source other than an internal battery no bigger than one used in a flashlight, have to be carefully optimized to conserve power.

In the application at Genentech, this has not been a factor given that each node is attached to a freezer or other unit that has to be supplied with mains power to run its compressor. Nonetheless, each individual node can be outfitted with a battery that allows it to continue to sending an alarm message if power to the unit is lost.

For the DAWN system, Genentech and Yokogawa created a configuration suited to the needs typical of pharmaceutical and biotechnology research and manufacturing. The same sort of operational needs apply in many other types of applications in process and discrete manufacturing.

Figure 2: Each individual ultra-low freezer has a group of devices installed, including a wireless module, antenna and power supply that works together to collect data from an array of sensors and sends it back to the central monitoring and control system through the network.

the condition of critical assets around the clock, ready to contact individual equipment owners if and when an alarm condition occurs.

MOBILE ASSETS, WIRED INFRASTRUCTURE

As business requirements evolve at Genentech, critical portable lab equipment migrates from one building to another, causing discontinuity and generating the additional paperwork required for the myriad assets that require tracking. Trying to accommodate asset mobility while serving the business and regulatory imperatives associated with centrally monitoring and managing data with a wired infrastructure would be difficult at best. Traditionally, Genentech would decide to shift equipment into a building or lab without an existing facility-monitoring infrastructure. This caused delays because the labs needed to be retrofitted with a new data logger and associated wiring. Cost and delays during equipment migration could add up quickly depending on the condition of the building or lab.

According to Vikas Bakshi, Genentech's monitoring system owner for equipment similar to this, the advantages offered by the wireless technology were multifold. "Significant cost savings realized during the initial implementation due to additional channel capacity were extended by reduced resource requirements for data administration during normal equipment moves," he said.

While there are thousands of critical assets across the site, ultra-low freezers are one of the most common equipment types. Many ultra-low freezers contain aging compressors that can potentially fail at any time. Monitoring the health of these compressors proved to be challenging due to the limited amount of I/O allowed on existing wired infrastructure. As discussed earlier, freezers often migrate from one location to another, so adding additional wiring to monitor the health of compressors helped drive costs higher during equipment migration and implementation. Monitoring specific equipment for compressor status and similar functional conditions like door open/close status was also needed to provide additional data to support predictive maintenance and reliability regimes and identify at-risk equipment prior to failure.

Figure 3: The basic DAWN module connects directly to the sensors through the I/O terminals. It interfaces with the larger network regardless of its location within the campus.

A NEW DAWN

Yokogawa and Genentech partnered to develop DAWN (Data Acquisition Wireless Network). It operates on the 900 MHz frequency band and employs a frequency hopping, self-healing and self-organizing mesh network. This mesh networking strategy allows the radio signals from the equipment to find the closest and most efficient route back to the gateway during migration without any reprogramming or reconfiguration (see sidebar). In addition, mesh networking allows full network redundancy. If an infrastructure repeater goes down, the individual radios automatically connect to the next closest repeater within range.

Genentech's DAWN delivers temperature, compressor condition and alarm status readings from each ultra-low freezer. The radio provides secure, reliable 128-bit encrypted wireless communication. Without additional hardware, each radio has the ability to act as a gateway, access point/repeater, and I/O device based on its configuration. The radio includes eight discrete I/O, four analog I/O and one Type T thermocouple module input. The system supports the Modbus TCP communication protocol.

The majority of non-GMP equipment at Genentech is monitored by DAWN across 15 buildings. Each building is equipped with repeater radios strategically positioned across the facility to ensure wireless coverage for every lab, room and cubicle. The system can handle up to 2,400 radios across the entire site going back to five individual endpoint gateways. Each DAWN radio is configured to monitor temperature, compressor amps and door status to ensure the reliability and health of the equipment.

Endpoint gateways communicate via Modbus TCP and OPC back to the facility monitoring system so operators can monitor the health of each piece of equipment and take action when alarm conditions occur.

Genentech began to immediately realize benefits from its DAWN system despite the fact that its expansion across the campus had not been completed. Seamless equipment migration between buildings without reconfiguration or onerous paperwork generated significant data administration cost savings.

Similarly, managers commissioning new labs no longer have to purchase dedicated data loggers, wiring services and faceplates to network critical assets assigned to that particular lab. The ability to scale and expand the wireless system to monitor virtually any piece of equipment without being limited to the channel capacity of a traditional data logger was another cost-containing aspect of the system's implementation. Live and historical compressor data and trends are monitored by a SCADA system.

Through DAWN and the data it delivers, technicians conducting ultra-low freezer preventive maintenance can predict the potential for compressor failure and prevent the disruptions and losses that might occur if its contents were to thaw.

ACEA BIOSCIENCES INTRODUCES "FAIL IT FAST" ASSAY TECHNOLOGY

New xCELLigence RTCA CardioECR first platform for simultaneous measurement of Cardiomyocyte Contractility and Electrophysiology

By Steven E. Kuehn, editor-in-chief

RESPONDING TO the need for more predictive preclinical assays for cardiac liability, ACEA Biosciences introduced a "ground-breaking" device the company describes as "next generation." Designated the xCELLigence RTCA CardioECR System, it is building on the success of its impedance-only RTCA Cardio System, ACEA says. Combining impedance and multi-electrode array (MEA) technology with a pacing function, the RTCA CardioECR system is said to be the first platform to allow simultaneous cardiomyocyte contractility and field potential measurement.

With the added MEA capabilities and pacing stimuli, ACEA's system allows for a deeper, faster assessment of toxicity mechanisms. According to ACEA, the field-potential recording provided by its MEA electrode technology provides a measure of the integrated ion channel activity that may be impacted by the tested compound. Meanwhile, the pacing function allows for controlling the rate of contractility "for a more controlled assay," says ACEA. The system's combined dual readout system also delivers a longer-term measurement of cardiomyocyte viability — something that has the potential to identify compounds that can cause longer-term structural damage to cardiomyocytes. With its ability to accelerate cardiomyocyte evaluation across multiple compounds by orders of magnitude, the platform introduces distinct "Fail-it-Fast" innovation to R&D operations.

Yama Abassi, ACEA Biosciences' vice president of global operations agrees: "There has been a push by the pharmaceutical industry over the last few years to pursue a 'fail early, fail cheap,' strategy. The earlier that one can eliminate a compound that may have potential [negative] side effects, the better it is. I think it's obviously the earlier one can kill a compound with some potential toxicities, the better."

That concept, says Abassi, is the model now "but the most important thing about it is that you want to have a

very predictive assay. The danger is that you don't want to kill good compounds. But if your [acid] is not predictive enough, the likelihood that you will eliminate some really good beneficial compounds is also very high. That's the dangerous side of the 'fail fast, fail cheap' mentality. It's really important for the pharma industry to use highly, highly predictive assays that are really reflective of the human condition. For example, if they're using cells, it has to be very relevant cell types. In this case, once again, we are using use human stem cell cardiomyocytes. I just cannot see this type of assay being done even five years ago. Five years ago these technologies were not available."

Founded in 2002, ACEA Biosciences has been developing and commercializing cell analysis platforms for life science research. According to ACEA researchers, they are continuing to advance their studies via the 1,300-plus instruments the company has sold for a broad range of diverse applications. According to Abassi, the technology has been cited in more than 500 peer-reviewed publications. ACEA's innovation in this area began with the introduction of its NovoCyt flow cytometers now used in pre-clinical drug discovery and development, toxicity, safety pharmacology and basic academic research.

CARDIOVASCULAR TOXICITY BAD

Cardiovascular toxicity is consistently identified as a leading cause of drug attrition and withdrawal, notes Abassi, explaining that "a number of drugs have been withdrawn from the market due to the risk of causing a potentially fatal form of ventricular arrhythmia referred to as Torsades de Pointes (TdP). The xCELLigence system provides a higher throughput and more predictive approach that can be used earlier in drug development to reduce both cost and risk." Abassi says the company is confident the new system will deliver significant benefit to the pharmaceutical industry and that it is well aligned with the FDA CiPA initiative. With its purported speed, combined sensing abilities and fortune-telling predictive analysis capabilities, the RTCA CardioECR System is indeed revolutionary and Abassi explains why:

"I would describe it as cutting-edge as one can get, says Abassi. "It's absolutely revolutionary in the sense

Combining impedance and multi-electrode array (MEA) technology with a pacing function, the RTCA CardioECR system is the first platform to allow simultaneous cardiomyocyte contractility and field potential measurement.

that it combines multiple technologies to give additional information about the risk of compounds." Abassi notes ACEA's system uses induced pluripotent stem cell-derived cardiomyocytes. "This is as revolutionary and cutting-edge as one can get," he says, noting that commercial stem-cell-derived technologies have only recently emerged. "Obviously with the emergence of [these types of stem cells] the application that everybody thought about was more therapeutic nature, but the more immediate application is to use stem cells to derive relevant human cell types, such as liver cells and cardiomyocytes."

Abassi says that with these model systems the industry is now in a position to start testing the toxic side effects of drugs because relevant human model systems are commercially available and viable; previously the pharmaceutical industry had to rely on animal testing. "Now we have relevant human model systems in scalable quantities that we can use for high-throughput screening potentially to screen hundreds, if not thousands, of compounds on a daily basis and get [large amounts] of relevant information from them."

ACEA's xCELLigence is groundbreaking considering it can generate incisive information from cardiac cells —

FDA INITIATIVE SEEKS CARDIAC SAFETY EVALUATION OF NEW DRUGS

The Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative by the FDA seeks to develop a new paradigm for cardiac safety evaluation of new drugs that utilizes high throughput, predictive and mechanistic assays which can identify pro-arrhythmic compounds earlier in the drug discovery process. An important part of this initiative is to use cardiomyocyte model systems together with platforms that can provide incisive information on the pro-arrhythmic risk of compounds, according to a meeting report in March 2014 from the Cardiac Safety Research Consortium.

Each of the 48 wells of the microtiter array can be treated essentially as a separate experiment. A technician can feed the cells in each of the wells and let the cells grow.

cells basically grown in a dish but ones that behave very much like a normal human heart. For example, the cells beat spontaneously in culture, just like a regular, normal cardiac cell. Abassi explains that the system's sensors are a key element of the testing platform. "These sensors allow us to look at both the contractility of cardiomyocytes and its electrophysiological aspects," says Abassi. "We can quantify cardiomyocyte contraction and derive critical information from it, including the beating rate." The other sensor provides mechanistic information about how the compound may be impacting these cells at the molecular level.

"We can look at two things — contractility on one hand, the typical beating of the heart cells; and on the other, we can look at it from an electrophysiological angle, which gives us once again, more mechanistic information about the proteins of the molecules that are actually involved," notes Abassi. "You get a really quick and clear view of any compound's effect on cardiac cells, hence the human heart."

The system is designed around a microtiter plate format with multiple wells. "You can test lots of compounds," says Abassi, and "you can test different concentrations." Noteworthy also is the fact that the system's sensors generate a readout noninvasively, which means the sensors themselves will not harm the cells. The noninvasive nature of the testing regime means study times can be extended, which is especially important when it comes to understanding toxicity. A lot of people, including the pharma industry, tend to look at toxicity on a minute-to-hour scale. But a lot of times toxicity actually emerges after many days or even many weeks.

"Sometimes toxicities take time to accumulate," says Abassi. "With our system, we can follow how people actually take the drug in the clinic. We can do chronic dosing and see if, over time, there is a cumulative toxicity that could be extracted. With one dose or two doses, you may not see the toxicity, but over time as the dose is continued you might see a cumulative type of toxicity. Otherwise, with other assays one can miss this easily." Because ACEA's system is noninvasive, a lab technician can continue to monitor cells over hours, days or weeks and beyond.

Each of the wells, 48 to be precise, can be treated essentially as a separate experiment. A technician can feed the cells in each of the wells, and let the cells grow. "Because these are cardiac cells," explains Abassi, "we allow them to become synchronous — in terms of beating. Just like a heart cell. Then we monitor that and can quantify it using the system's software." According to Abassi, the system is straightforward to configure and to use. Within 30 minutes one can put the system together. The typical workflow involves plating the cells onto the microtiter plates, then placing the system inside a CO2 tissue culture incubator to grow the cells.

Abassi says the economies and efficiencies that this will allow downstream will quickly provide any lab deploying the technology a return on the investment. "Without a doubt, it's a cost-effective alternative," says Abassi, explaining that without ACEA's system, the alternative is to use whole heart systems from rabbits or monkeys. "Can you imagine how much time and effort it takes to obtain animal hearts and to infuse them with the drugs? You can only do that procedure one at a time," notes Abassi. "The time, effort, energy [and money] that's spent is enormous."

That's why, Abassi explains, pharma companies wait a long time before they attempt these types of tests because it costs so much. "They can only do it with only a handful of compounds. Now because these tests are available in large enough quantities in the drug discovery process, [researchers] can start screening these compounds much earlier and gain a lot of information about the compounds that are being taken through the development phase, says Abassi. "That's the really nice aspect; the alternative's cost — and the system's benefits especially justify the upfront investment."

According to ACEA the FDA also has taken notice of this technology (see sidebar), especially because of the availability of stem cells. "What the FDA wants to do is actually include these tests as part of the safety guidelines, explains Abassi. "The FDA typically issues these guidelines for testing pharmaceuticals. Now the FDA is evaluating our technology as well as other technologies for safety assessment. If all goes well, they can actually recommend these kinds of tests as part of the cardiac safety guidelines, which will come out in 2016."

TECHNOLOGY AT WORK

AUTOMATING BLOOD CELL POPULATION SEPARATION

Industry collaboration delivers good manufacturing practices approach to peripheral blood mononuclear cells separation

By Arnaud Foussat, VP research and new products, TxCell; and Sébastien Olivier, sales manager, Biosafe

CELLULAR IMMUNOTHERAPY is a rapidly developing field that holds great promise in oncology, autoimmunity and chronic inflammation as well as transplantation. As one example, cancer immunotherapy research was awarded the scientific breakthrough of the year by the journal Science. In addition, the recent deals between biotechs and academic centers developing cellular immunotherapies and pharmaceutical companies highlight the interest of pharmaceutical industry stakeholders for these new therapeutic approaches.

Cellular immunotherapy uses the properties of cells from the immune system either to fight tumors through cytotoxicity mechanisms involving effect or T cells or to decrease the immune mediated pro-inflammatory processes in patients with autoimmune and chronic inflammatory diseases using regulatory T cells. A recent boost in the field has been observed with significant results of remission in late stage lymphoma patients treated with engineered T cells. This is the most recent demonstration of the huge promise of immunotherapies where classical treatments have failed.

ONE KEY CHALLENGE

One key challenge faced by cellular immunotherapies is the standardization of the cell processing procedures. These procedures are an integral part of the manufacturing process. So far there are few tools that allow cell therapy production methods to achieve a high scale production capacity that includes process robustness and pharmaceutical grade.

Peripheral blood mononuclear cells (PBMC) represent the most easily accessible source of immune cells. Consequently, the common first manufacturing step for many cellular immunotherapies is the isolation of PBMCs from whole blood collections. The classical method for PBMC separation is performed using centrifugation in gradient density media such as Ficoll, Percoll or Optiprep. This allows the separation of blood cell populations according to their respective density.

In the Ficoll procedure, the platelets, red blood cells, granulocytes and blood dendritic cells are pelleted in the bottom of the centrifuge tube. A ring of mononuclear cells comprising T cells, B cells, NK cells and monocytes are kept in suspension in the diluted centrifuged Ficoll medium allowing their harvest for further manufacturing steps. This procedure is routinely used manually worldwide as no specific device has yet been set up to standardize this separation procedure.

As a result, however, operator-dependent variability can be observed on top of the starting material variability, in terms of cellular impurities (i.e., residual red blood cells and granulocytes in the mononuclear cell ring) and separation performance (mononuclear cell yield). Such variation can dramatically impair the manufacturing robustness of cellular immunotherapy products. Indeed, in these types of products, where significant donor-derived variability can be already expected due to starting material, any further variability caused by the manufacturing procedures should be avoided.

TEAMED TO TACKLE THE CHALLENGE

TxCell and Biosafe, two companies well-established in the field of cell therapy decided to jointly tackle this challenge with the aim of offering a standardized and automated solution for this common first step of most cellular immunotherapies. Indeed, besides the need to increase the robustness and productivity of cell therapy production processes through automation, the regulation of medicinal cell therapy products as part of the Advanced Therapy Medicinal Product (ATMP) directives and guidelines requires production of these innovative treatments under Good Manufacturing Practices (GMP). Full environmental monitoring and control for the absence of microbiological contamination are critical elements for GMP production of cell based ATMP. This is because these products are made from living materials and cannot be sterilized before release. As a consequence, standardization of cell processing procedures should include, in addition to automation, systems to control these parameters, for example, by implementing closed systems.

French biotech company TxCell is developing economically viable, autologous cellular immunotherapies for chronic inflammation and autoimmune diseases. TxCell's products are based on the anti-inflammatory and immuno-modulatory properties of a subtype of blood leucocytes called antigen-specific regulatory T cells (Ag-Treg). Through ASTrIA, its proprietary discovery and manufacturing platform of Ag-Tregs, TxCell has already advanced its first Ag-Treg product candidate, Ova save, into the clinic stage. TxCell has also demonstrated the tolerability and potential benefit of this product for Crohn's disease patients refractory to existing treatments. TxCell is also already authorized by the French regulatory agency (ANSM) to produce cellular immunotherapy products for clinical use in its GMP-certified manufacturing site in Besançon, France.

With 17 years of experience, Swiss company Biosafe's cell-processing technology supports the automation and standardization of cellular immunization therapy production. SEPAX 2, Biosafe's automated technology is commonly used for stem cell processing and is a recognized and efficient tool for stem cell isolation. More recently, pharmaceutical and biotech companies working in the cell therapy area are increasingly adopting SEPAX 2 technology.

TxCell and Biosafe's Project "POSITIVE" includes the participation of the cell and gene therapy unit of the CHU (University Hospital) of Nice, France. It aims at standardizing the PBMC separation procedure using Biosafe's SEPAX 2 device (shown here) to produce cellular immunotherapies under GMP.

TxCell manufacturing technicians performing antigen-specific Treg cells expansion in aseptic conditions as required for cell-based ATMP products.

KNOWN AS POSITIVE

Known as "POSITIVE," the TxCell and Biosafe project includes the participation of the cell and gene therapy unit (CGTU) of the CHU (University Hospital) of Nice, France. It aims at standardizing the PBMC separation procedure using Biosafe's device to produce cellular immunotherapies under GMP. The project has been awarded a grant by the French Provence-Alpes-Côte d'Azurregion.

Biosafe is contributing its expertise in automated cell processing and cell separation techniques. This will allow fine-tuning of the device software and processing kits for GMP manufacturing of therapeutic immune cells. TxCell will add its expertise in clinical-grade GMP manufacturing of regulatory T cells from peripheral blood. Lastly, the Nice CGTU will offer its expertise on clinical grade production of effector T cells.

The primary objective of the project is to bring performance consistency and promote separated PBMC purity levels. This will ensure suitable properties of the PBMC preparations for further cell processing steps that can involve cell-specific stimulation steps. It will also enable GMP compliance by ensuring aseptic handling of cells in a closed system.

One of the first R&D steps will evaluate the parameters to be fine-tuned as well as the suitability of the procedure for immune cell therapy production. A second step involves concentrating on validating the new, improved PBMC separation method in one of TxCell's upcoming clinical trials.

Ultimately, the standardization of this procedure will benefit all developers and manufacturers of cellular immunotherapies, as standardization will allow scale-up with robust and automated cell processing methods.

By bringing together an industrial developer of innovative treatments, an academic cell therapy unit and a developer of devices, the project provides a demonstration of how different stakeholders can overcome a scientific and industrial challenge by sharing their strengths for a common goal. This collaboration demonstrates how teamwork can push forward a field like cellular immunotherapy to fulfill the requirements of pharmaceutical industrial commercialization and distribution. Most importantly, the project leaders hope the project will prove an ideal route to ultimately bring new, innovative treatment solutions for patients.

MULTIVARIATE DATA ANALYSIS FOR BIOTECHNOLOGY, BIO-PROCESSING

Powerful MVA and DoE methods are giving biotech companies greater insights from complex data

By Brad Swarbrick, vice president business development, CAMO Software

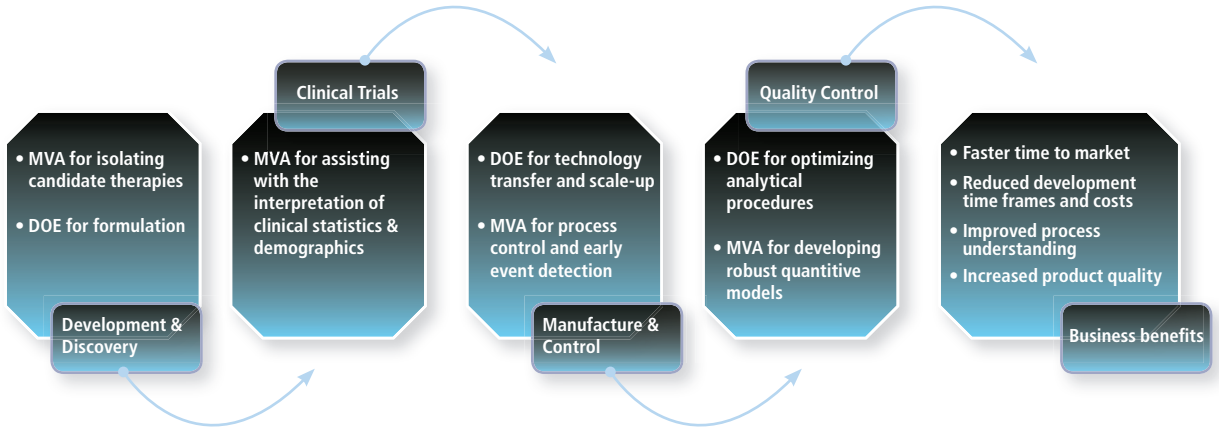
THE MODERN biopharmaceutical/biotechnology manufacturing facility contains many sophisticated control, data logging and data archiving systems. Massive amounts of data are collected from sources such as raw materials analysis, process outputs and final quality assessments, which are stored in data warehouses.

The sheer volume of data contained in these warehouses makes it a near impossible task to extract the information using simple charting and univariate methods of analysis. Such complex data requires methods of analysis that can cope with multiple variables simultaneously that not only reveal influential variables, but also reveal the relationship such variables have with each other. This is where Multivariate Analysis (MVA) is finding a much greater role in the analysis of complex bioprocess data.

Much more effort is being put into the discovery and development of biotherapies and personalized medicines. Biopharmaceutical and biotechnology companies are looking for ways to accelerate drug discovery, and through quality and compliance initiatives such as the Food and Drug Administration's (FDA) current Good Manufacturing Practice (cGMP) and Quality by Design (QbD) principles, and Data Driven Knowledge Discovery, reduce the regulatory approval time and be first to market. This means that data collected throughout the entire product lifecycle must be analyzed and interpreted in order to gain extensive product and process understanding. This, in turn, leads to improved quality, greater confidence in the market for a company's products and ultimately market capitalization.

It is estimated that the time it takes to bring a new drug or therapy to market is approximately 12 years. This usually involves three phases: discovery, clinical trials and registration.

Coupled with these phases is the development of a suitable manufacturing process that can consistently



THE APPLICATION OF MVA AND DOE IN THE BIOTECH PRODUCT LIFECYCLE.

Figure 1: Biotechnology companies can realize significant benefits using MVA and DoE from product development through to manufacturing and quality control.

produce the highest quality product and be compliant with FDA current Good Manufacturing Practice (cGMP) guidance. This includes the development of a formulation that is robust under processing conditions, scale up considerations and technology transfer from facility to facility or even between different types of manufacturing equipment. Each of these phases can be improved and accelerated through the use of the tools of MVA and Design of Experiments (DoE).

Even before data is analyzed, one of the biggest challenges facing the industry is getting this data into a format that is amenable to MVA. Many data collection and agglomeration systems are commercially available for compiling various forms of data and these can be seamlessly integrated into MVA packages so that the vast array of graphical and analytical approaches can be applied to reveal the information it contains. The general statement is data is only data until the information is extracted from it, and from there, information leads to knowledge.

MVA IN THE PRODUCT LIFECYCLE

Unlike small molecule drug product development, biotherapies are fundamentally more complex in terms of structure and application and suffer greatly from natural biological variability. For example, isolating and selecting cell cultures or bacterial strains to further develop into future products is aided greatly by the tools of MVA, including the monitoring of the processes (e.g., fermentation reactions) used to produce them. From there, the tools of DoE can be used to devise formulations that stabilize the active component(s) during manufacture and are also useful in product scale-up studies.

Once the candidate therapy (cell cultures, antibody, virus strain, etc.) has been formulated into a stable matrix, MVA can be used to assist in the interpretation of clinical trial data and can even lead to accelerating the lengthy process through a much more comprehensive and overall approach to data analysis, especially when combined with the principles of adaptive designs and the Critical Path Initiative endorsed by FDA.

When the candidate therapy has been approved for market release, the tools of MVA are useful for assessing the success of technology transfer from R&D to production, or from one manufacturing facility to another. In the production environment, MVA is useful for assessing incoming or internally produced raw material quality and characteristics. Combined with rapid spectroscopic (or other characterization methods) control strategies for the real-time monitoring and adjustment of processes within the so-called "design space" can be devised so that proactive quality control can be realized. DoE and MVA are then used in developing robust analytical methods for stability studies and other post-production analyses.

Data collected over time from a manufacturing facility can be modeled to assess batch-to-batch consistency and facilitate continuous improvement (CI) and preventive maintenance and corrective action (CAPA) programs. The entire process is summarized in Figure 1.

Candidate Therapy Discovery: During the initial development of new therapies, there is usually much information available on candidate cultures, antibodies, etc., in respect to their chemical, biological and toxicological properties. Combined with information

from origin and other background information, the method of Principal Component Analysis (PCA) provides a key data mining tool for the development scientist to not only classify candidates of similar properties and characteristics, but also to discover unique classes that may be better suited to the treatment of specific conditions.

PCA provides a visual map of the sample groupings, allowing for the more efficient selection of real candidate therapies, but it also provides a map of the input variables and their relationships that cause the samples to group the way they do. Figure 2 provides an example of the outputs of a PCA in the form of the scores and loadings plots. The scores provide a map of the samples and the loadings provide a map of the input variables.

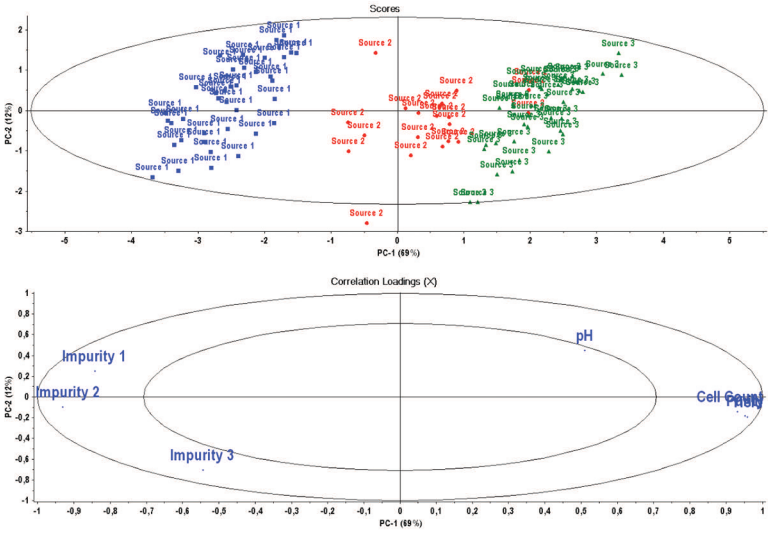
PCA (or more generally MVA) applied to this kind of data is sometimes referred to as Quantitative Structure Activity Relationships (QSAR) and has helped some companies to significantly reduce the time and effort required to isolate suitable candidates for further development.

Formulation of suitable products: Stabilizing the candidate into a suitable matrix for manufacturing and delivery is best approached using DoE and, in particular, excipient screening and mixture designs. Excipient screening designs allow the formulation scientist to select the best components that will preserve the nature of the candidate, while mixture designs allow for the development of the best combination that will not only stabilize the candidate, but also protect it during subsequent manufacturing processes.

CLINICAL TRIALS

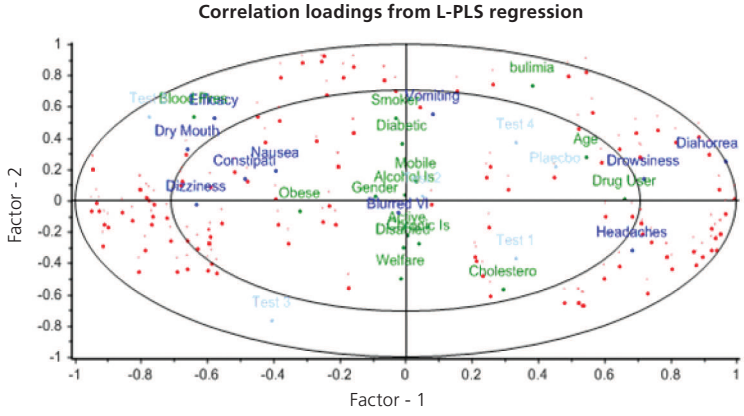
Clinical trials have traditionally been the domain of univariate statistical approaches (in particular clinical statistics) where statistical significance is assessed for parameters such as efficacy and major side effects. The tools of MVA can be used to complement the findings generated by clinical trial statistics to further confirm and accelerate key findings through this phase of product development.

The ability to incorporate demographic, age, sex and patient history into predictive or



SCORES AND LOADINGS PLOTS FOR A CANDIDATE SELECTION STUDY

Figure 2: In this example, Source 1 samples have high amounts of impurities whereas Source 3 samples have the highest cell count. As a rule of thumb, variables located outside the inner ellipse are regarded as being important in interpretation of clusters in the Scores plot.



THE L-PLS MODEL AND ITS POTENTIAL FOR CLINICAL TRIAL DATA ANALYSIS.

Figure 3: In this example, the variables in green describe the background information of the patients, the variables in blue are the side effects of the formulations (the actual formulations in light blue) and the red dots indicate patient groups. This combined plot is the most informative way of displaying the relationship between the three data tables depicted in the frame above.

exploratory models is a unique feature of the MVA method, and approaches such as the L-PLS model can provide an overall picture of the patient groups, disease markers and the candidate properties to better assess the effect of the therapy on specific patient groups. Figure 3 provides an example of the L-PLS model structure and an example output.

Through the use of MVA tools for monitoring and controlling bioprocesses, manufacturers worldwide have realized significant cost savings through proactive quality control. During the scale-up and technology transfer of a process from R&D to full scale manufacturing, the use of DoE is a critical strategy for assessing the effect of changing process and equipment variables. This allows the definition of the Design Space, which defines the most effective control strategy for the process. Multivariate Statistical Process Control (MSPC) uses multivariate exploratory and predictive models and integrates them into the entire data collection and process control system.

This allows manufacturers to be more innovative in their approach to quality combining in-line process analytics into single or holistic process models that better assess the quality of production than single measurements in isolation. Two particular processes that are commonly used in biotherapy manufacture are fermentation and lyophilization. Some applications of MVA to these are discussed in the following sections.

MVA FOR FERMENTATION MONITORING

For many years manufacturers have been challenged with the development of suitable models for monitoring the progress of batch processes, fermentation being one such process. These batch models aim to establish a process trajectory and associated limits around the trajectory that define the bounds of acceptable product quality.

Methods exist that unfold batch data and use so-called "maturity indices" to model the process. However, the major drawback of these methods is that they assume linear relationships in the processes, which are fundamentally incorrect and have only partially solved the batch problem. Other approaches use time warping to distort the time scale and align batch trajectories. Again, these approaches also suffer fundamentally as they distort the chemistry or biology of the system and hence do not describe the true state of the process.

Relative Time Mapping (RTM) addresses the shortcomings of the previously defined methods by keeping the chemistry/biology of the system intact, while at the same time, providing the usual batch trajectory plots and associated diagnostics that have become synonymous with this type of analysis.

Whether batch models or traditional Statistical Process Control (SPC) charts are used to assess the progress of a bioprocess, there are many diagnostics available in multivariate models that can be used to determine the onset of process failure.

EARLY EVENT DETECTION

The term Early Event Detection (EED) is being increasingly used to describe the application of Multivariate Statistical Process Control for the detection of process faults. The diagnostics from these models can be fed back into the manufacturing control systems using protocols such as OPC to automate process adjustments and therefore maximize the quality of the final product.

An extension of MSPC is the use of Hierarchical Models (HM). These models provide an excellent way of classifying the state of discrete phases of processes such as fermentation and adapt to changing conditions as they occur. HMs can be set up as Classification — Classification, Classification — Prediction and Projection — Prediction models which can be adapted to applications such as analysis of raw materials, process monitoring and quality-control applications.

Near Infrared (NIR) spectroscopy has been used for many years with multivariate predictive and exploratory models for the rapid, non-destructive assessment of product quality. One common application of the NIR method is the quantitative analysis of residual moisture in lyophilized products.

Lyophilization is a common method used in the manufacture of biopharmaceutical products as it uses low temperatures to remove residual moisture, thus preserving the structure of the active components and allowing their storage at room temperature. The traditional method of analysis for residual moisture in lyophilized product is Karl Fischer (KF) titration which is a destructive test and can only be applied to a small number of samples.

Replacement of the KF method with NIR not only results in non-destructive testing, but also allows for

100% inspection systems to be put in place. These systems use MVA predictive models to transform the NIR spectrum into a single value for residual moisture (or other properties) and are used to accept and reject product as it is being manufactured.

In one case, a biopharma manufacturer saved about $1 million by using the NIR method combined with PCA to validate the performance of a new freeze dryer. They also developed a quantitative Partial Least Squares Regression (PLSR) model to replace the KF method in the laboratory. This method saves them $1,000 per sample and provides more confidence when releasing the batch to market.

QUALITY CONTROL

Although initiatives such as Process Analytical Technology (PAT) have been used by many manufacturers globally to assess product and process quality at the point of manufacture, not every process measurement can be replaced at the point of manufacture. Quality Control (QC) operations are still vital in the final release stage of some, if not all, products.

Due to the high variability in many biological assays, DoE and MVA can be used to design and refine the analytical methods used in the QC laboratory and has been successfully applied to the optimization of chromatographic methods, the refinement of sampling procedures and the analysis of complex data produced by mass spectrometers.

Another advantage of combining spectroscopic analysis with MVA methods is in stability studies. Since the NIR method is non-destructive and is sensitive to changes in the product and its matrix, the same sample can be assessed over the entire timeframe of the study. Where applicable, this avoids the destruction of product, and the results are completely representative as the same sample is being assessed each time.

MVA and DoE are fast becoming essential tools for all process development and monitoring applications. Bioprocesses provide an excellent but challenging application area. Modern manufacturing execution systems and control platforms produce a massive amount of data that requires the tools of MVA to fully "data mine" the most important information and make real-time quality decisions.

From raw material analysis to final product release, MVA models can be integrated into the total Quality Management System (QMS), allowing manufacturers to realize the benefits of the Quality by Design (QbD) initiative.

Multivariate data analysis and DoE are powerful tools ideally suited for understanding the complex behavior and relationships in biological systems. These methods can be used across the full biotech product lifecycle, from discovery and development, to scale up, production and quality control. Today's leading MVA and DoE solutions can be seamlessly integrated with other systems including process equipment, laboratory and spectroscopy instruments, enabling faster and more informed decision making.

Leading biotechnology companies that implement and exploit the power of MVA and DoE can realize substantial benefits including lower development and production costs, improved product quality and compliance, technology transfer, faster time to market and ultimately increased business value.

"PHARMONICS" AND THE OPERATOR INTERFACE

Pepperl+Fuchs' Aseptic Operator Interface Terminal offers a compelling value prop for biopharma production environments

By Steven E. Kuehn, Editor in Chief

TECHNOLOGICAL INNOVATION can be dramatic; it can also be over-hyped (think Segway). Other times technical innovation comes with less drama, often the result of a couple of engineers and their product managers thinking deeply about how to make their design even better for users and those who authorize the purchase — more functional, easier to operate, simpler and cheaper to implement and maintain and so forth. Of course, this is the way of most companies in the business of creating and selling ubiquitous industrial technologies including Pepperl+Fuchs, who recently introduced a highly refined operator interface terminal (OIT) purpose-built for sterile, cleanroom pharma processing environments.

Without being overly remedial, a clean room's primary function in Pharma is to assure a sterile production environment to prevent products from being contaminated. Further, regulators classify these environments and compel Pharma to follow their specific mandates to control particulate and microbial contamination and assure the public's safety. The FDA recommends that the area immediately adjacent to the aseptic processing line meet, at a minimum, Class 10,000 (ISO 7) standards during production. Drug makers can also classify this area as Class 1,000 (ISO 6) or keep the entire aseptic filling room at Class 100 (ISO 5). An area classified at an air cleanliness level of Class 100,000 (ISO 8) is appropriate for less critical activities such as equipment cleaning.

IT'S THE PEOPLE

According to P+F, clean room workers are a clean room's largest contamination source. "People generate particles in the form of lint, skin flakes, cosmetics and respiratory emissions," says P+F's Lou Szabo. "To prevent particulates and particles from settling and accumulating on equipment, housing finishes must be hard, polished and free of corners, crevices or seams where dirt and other unwelcome visitors like bacteria might collect." Szabo

notes that the OIT can be a flashpoint of contamination "because that's where humans tend to spend the most time." Szabo explains that OITs must be designed, first, to eliminate any feature that promotes the accumulation of contaminates and be able to withstand the rigors of aseptic cleaning. "Housings must resist high-pressure, high-temperature washdowns, including live steam and aggressive cleaning chemicals as well as simpler SOPs such as spray and wipe," says Szabo.

Pepperl+Fuchs say a major pharmaceutical company with extensive biopharmaceutical operations (one that shall not be named), recently embarked on a program to expand their aseptic manufacturing space to meet demand for a new drug. Operations quality supported by information systems and process controls was a priority, says P+F, and their customer wanted these systems to be accessed by OITs in its Grade A and B spaces mounted flush with the surface of the new space's modular walls with minimal protrusion from behind. Plant requirements, as well as lessons learned from the initial plant construction, called for two aseptically designed OIT panels in theses spaces: One to communicate with the DCS and a second to communicate with the manufacturing execution system (MES) in a virtualized environment. Additional terminals were also specified to provide access to company intranets and corporate applications such as email, as well as room status displays (RSD). Pepperl+Fuchs' customer, as well as the firm engineering the new capacity, both wanted the installation and maintenance of the OITs to be more cost-efficient.

Operator interface terminals, Like P+F's unit shown here, must be designed to eliminate any feature that promotes the accumulation of contaminates and be able to withstand the rigors of aggressive aseptic cleaning.

PANEL DESIGN'S INHERENT EFFICIENCY

According to Pepperl+Fuchs, the existing workstation's installation cycle time was long — between six and eight hours per unit for Grade B and A spaces, respectively. "A good deal of time was spent aligning templates, drilling holes, aligning fixtures, affixing rear fixing plates, and finally, sealing all exposed seams with a silicone room temperature vulcanizing (RTV) elastomer sealant/encapsulant," says Szabo, "This translates to one workstation installation per day, or in the case where 20 or more are being installed, a 'critical path item' in the project schedule."

The company's improved panel design incorporates some well-refined installation features. To start, the OIT requires mounting the enclosure shell to the studs in the wall. The unit is then secured from the inside of the enclosure shell with a torque-limited drill. As the screws are tightened, a clever spring-activated latch deploys and tightens against the rear of the modular wall. "The shell can be secured in two minutes," says Szabo, then the integral FDA-grade silicone gasket forms an air/bacteria seal between the shell and wall."

The company says the door is never removed from the shell, so no electrical connections are disrupted, minimizing commissioning time. Power and Cat5 connections are made, power applied, and the single

The company says the door is never removed from the shell, so no electrical connections are disrupted, minimizing commissioning time.

vault-like hinge swings the door back in place and the latches set, pulling the door firmly against the second layer of the silicone gasket. In the process, an air/bacteria seal between the door and the shell is completed. "Clean rooms are expensive to design, construct and operate," says Szabo, "and reducing labor-intensive installation time to under an hour and reducing maintenance time by at least 50 percent is certain to save CAPEX and OPEX."

DUAL-SEALING CUTAWAY

With the new, enhanced unit, an MTTR (mean time to repair) of 10 minutes is achievable with the Pepperl+Fuchs' dual-seal gasket and latching mechanism system.

MAINTENANCE REGIME STREAMLINED

The existing workstation's preventive maintenance (PM) cycle regime was relatively time consuming as well, between two and four hours per unit for Grade A spaces. First a technician had to tediously and thoroughly remove the silicone RTV sealant around the door frame. Then, each unit underwent a maintenance function, primarily recalibrating the capacitive touchscreen. Once that was accomplished, all exposed seams had to be resealed. "The PM cycle translated roughly to two workstation PMs per day," says Szabo "or in the case where 20 or more are installed, that meant up to 10 days of downtime." With the new, enhanced unit, Szabo explained, an MTTR (mean time to repair) of 10 minutes is achievable with the Pepperl+Fuchs' dual-seal gasket and latching mechanism system.

PHARMANOMICS

There is another benefit to this design, the company says. "Installation cost and impact on project schedules," notes Szabo. "For the traditional installation, each unit requires up to a day to install, and with more than 20 units, that can take up to a month — likely placing the workstation installation on the critical path list."

As far as Pepperl+Fuchs' reckons, a traditional OIT panel requires a 6- to 8-hour installation and two people to install it, characterizing it as a "one-a-day" approach. To help understand the math, the company's marketers projected associated expenses and created a table to illustrate the installed cost at a burdened hourly rate of $100. Multiply this across 20+ units and one can see the total price tag for installation grows significantly as the number of units climb. "A secondary point, but perhaps more significant," emphasizes Szabo, "is that engineering firms are often incentivized to deliver a facility project on time, ahead of schedule and/or under budget. These incentives can range upwards of $100,000 per day." Szabo explains that the chart shows that specifying the Pepperl+Fuchs solution could shave enough time off the critical path to generate savings and contribute to a substantial (net) early completion bonus. "In our example," says Szabo, "at $20,000 per day, the net savings of using this enhanced workstation over the conventional bolt-in-RTV goop version pays for the workstations."

Additionally, during this expansion, the customer noted the thin clients from the first phase were no longer available, while their industrial grade thin client was unchanged for seven years. The difference is in the industrial world, where they design for long lifecycles and purchase embedded processors at the beginning of their lifecycle, while in the consumer world, their design is based on end-of-life purchases of processors and an 18- to 24-month product lifecycle. Additionally, these COTS clients and KVM extenders do not have the temperature characteristics required for enclosure mounted equipment with no airflow and a 27°F temperature rise over ambient as design criteria.

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	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Data
15. Extent and Nature of Circulation		
a. Total Number of Copies (Net press run)	21,835	22,149
b. Legitimate Paid and/or Requested Distribution (By Mail and Outside the Mail)		
(1) Outside County Paid /Requested Mail Subscriptions Stated on PS Form 3541. (Include direct written request from recipient, telemarketing and Internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof and exchange copies).	13,742	13,860
(2) In-County Paid /Requested Mail Subscriptions Stated on PS Form 3541. (Include direct written request from recipient, telemarketing and Internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof and exchange copies).		
(3) Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid or Requested Distribution Outside USPS	150	156
(4) Requested Copies Distributed by Other Mail Classes through the USPS		
c. Total Paid and/or Requested Circulation [Sum of 15b. (1), (2), (3), and (4)]	13,892	14,016
d. Non-requested Distribution (By Mail and Outside the Mail)		
(1) Outside-County Non-requested Copies Stated on Form 3541 (include Sample copies, Requests Over 3 years old, Requests induced by a Premium, Bulk Sales and Requests including Association Requests, Names obtained from Business Directories, Lists, and other sources)	6,062	5,858
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(4) Requested Copies Distributed Outside the Mail (Include Pickup stands, Trade shows, Showrooms and Other Sources)	263	375
e. Total Non-requested Distribution (Sum of 15d (1), (2), and (3))	6,289	6,223
f. Total Distribution (Sum of 15c. and e.)	20,181	20,249
g. Copies Not Distributed	1,655	1,900
h. Total (Sum of 15f and g)	21,836	22,149
i. Percent Paid and/or Requested Circulation (15c divided by f times 100)	68.84%	69.22%

16. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the November 2014 issue of this publication.
17. Signature and Title of Editor, Publisher, Business Manager, or Owner

Jeremy L. Clark, VP of Circulation Date 9/30/14
I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

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