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BIOPHARMACEUTICAL TECHNICAL RESOURCE GUIDE

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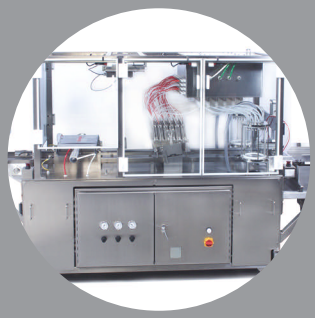

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Large Molecules,

The biopharma industry remains one of the most robust and healthy of industries, not only in the states, but also around the world

IF THERE'S a bright spot in Pharma these days, it's the light shining from the biopharmaceuticals sector. Most professionals observing this aspect of pharmacopeia agree that the biopharmaceutical industry remains one of the most robust and healthy of industries, not only in the U.S., but arguably around the world. The global market for biopharmaceuticals is quite large; north of $165 billion and growing at some 15 percent annually. Sources say of the top 100 prescription products, by 2018, biologics will account for 50% of sales.

By Steven E. Kuehn
Editor in Chief

Accenture analyzed the 16 largest pure biopharmaceutical companies and found that collectively at some $487 billion in aggregate 2011 revenue, these companies represented 54 percent of the global pharmaceutical market. That's pretty impressive and reveals the dominance the sector is creating for itself even in the face of patent expiry, which Accenture says hit its peak in 2012. In its overview of market trends, Bioplan Associates Inc.'s *10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity*, finds that the biopharmaceutical industry did more than survive the downturn. "In fact," says the report, "the industry has done rather well for itself during this period — not contracting or losing much at all in recent years — and is now showing clear signs of full recovery and growth." Clearly the industry's momentum shows little sign of doing anything but accelerating.

As an industry, biopharmaceuticals have become a significant economic driver, especially in the United States. In its 2013 *Profile* report, The Pharmaceutical Research and Manufacturers of America, (PhRMA), notes that the biopharmaceutical industry continues to make major contributions to the U.S. economy. "The U.S. biopharmaceutical sector employs more than 810,000 workers, supports a total of 3.4 million jobs across the country and contributes nearly $790 billion in economic output on an annual basis …" According to PhRMA, those workers earned a collective $89.9 billion in pay, averaging slightly more than $110,000 in wages and benefits per worker. Those kinds of wages buy a lot of toasters and SUVs as well as health care.

The industry's growth, the effectiveness of its therapies, and its continued health and vitality are linked very directly to the industry's growing investments in R&D and technology. In 2012 the industry invested $8.5 billion in R&D, says PhRMA's report, representing more than 20% of sales when it comes to domestic R&D spending and defines the largest R&D investment of any sector of the U.S. economy. Since 2000, PhRMA members spent $500 billion in R&D and it is paying off. Fostering a decade of innovation that produced the first anti-angiogenic medicine for cancer (2004), the first new kidney cancer Rx in a decade, three new diabetes therapies (2005), first once-a-day HIV medicine (2006), first fibromyalgia treatment (2007), the first new Rx for gout in 40 years (2009), two new multiple sclerosis drugs (2010), first lupis drug in 50 years (2011), 43 new approvals (2012) and as of 2013, more than 5,000 medicines in development globally.

This robust activity provides real testimony to the efforts of the industry, but it's not all a bed of roses. As John Castellani, president and CEO of PhRMA notes in his intro letter to the report, "Researchers continue to work toward these goals in spite of many barriers. The science and technology of drug development are increasingly complex, and the length and cost of research and development have continued to grow. Regulatory and business environments add uncertainty to the process."

Adding to CFO heartburn is the advance of biosimilars. In its recent report *Shaping the Biosimilars Opportunity: A Global Perspective on the Evolving Biosimilars Landscape*, research firm IMS says: "By 2015, sales of

Larger Impact

biosimilars are expected to reach between $1.9 to $2.6 billion, up from $378 million for the year to the first half of 2011. Potentially, this market could be the single fastest-growing biologics sector in the next five years — albeit from a small base — spurred by the convergence of major dynamics that will see new biosimilars enter the U.S. market by 2014, bring additional molecules to Europe through 2015, and open up oncology and autoimmune disease areas to biosimilars for the first time ever." The IMS report finds that society is putting pressure on Pharma to continue to lower the cost of drugs and increase access to effective but expensive biologic therapies. What's going to be tricky for the biopharmaceutical industry is how to answer that demand for generic therapies without going broke; one prominent analyst noted that the costs to commercially develop and produce biosimilars is, well, similar to that of its branded counterparts.

In spite of the complexities and costs associated with biopharmaceutical drug development, the expense associated with clinical trials, etc., the biopharmaceutical industry is fueling its growth and financial success by investing heavily in the process and analytical technologies that support innovative, cost-effective cGMP-based manufacturing environments. In fact, the industry is demanding effective technologies to drive efficiency and productivity in and costs out of biopharmaceutical processing. They're looking for increased manufacturing performance, especially in clinical-scale scenarios.

To that end, the editors of *Pharmaceutical Manufacturing* and PharmaManufacturing.com have compiled this special issue to hopefully provide readers fresh technological insight as well as a few best practices to help better understand biopharma processes and generate the manufacturing performance the industry is demanding. Welcome to *Pharmaceutical Manufacturing*'s Biopharmaceutical Technical Resource Guide.

Seeking Innovation to Solve Persistent Problems

Study reveals biopharma's growing demand for effective technologies to drive efficiency and productivity in and cost out of biopharmaceutical processing

By Eric S. Langer, president and managing partner, BioPlan Associates Inc.

IT'S PROBABLY fair to say that innovation in the biopharmaceutical manufacturing industry is a slow cycle. But that would ignore the many changes in biomanufacturing over the past 5 to 10 years: Better expression systems, widespread adoption of novel single-use applications, re-emergence of perfusion technologies, new modular and flexible facilities, better sensors, control systems and downstream technologies.

The industry now finds itself very aware of the promise new technologies carry in terms of optimizing, and in some cases revolutionizing existing processes. Results from our "10th Annual Report and Survey of Biopharmaceutical Manufacturers"[1], in which we surveyed 238 biomanufacturers, indicate that end-users are still actively looking for a range of new technologies to solve persistent problems.

MORE FOR LESS

The driving factors today in bioprocessing innovation, according to our study, involve improving efficiency and productivity. This equates to getting more out of existing processes for less money. For example, roughly two-thirds of the industry attributes improvements in manufacturing performance to single-use systems and applications. But most of the recognized benefits involve improved efficiency, especially in clinical-scale processes. Single-use devices shorten the time getting facilities up and running and reduce capital investments necessary for new plants. New facilities offer more flexibility, and "modular" approaches along with faster campaign turnaround times and lower annual maintenance costs.

Similarly, the industry is demanding better downstream processes — demands that are generally focused on cheaper, equally effective chromatography, protein-A and purification steps. Again, innovations need to be about cost effectiveness. So as innovators and suppliers develop new products, they'll need to demonstrate their technologies are actually better than current approaches.

PRODUCTIVITY INNOVATION 2013

In a separate survey Bioplan Associate's ran late last year, among the more than 450 global subject matter experts and senior participants who make up our Biotechnology Industry Council,[2] the study found consistent expectations regarding improvements in productivity. Again, improvements in downstream processing and single-use technologies ranked as the top 3 trends for 2013, these were followed by demands for better analytical methods. New analytical methods are required for better process monitor-

Biopharmaceutical manufacturers are seeking new modular and flexible facilities with better sensors, control systems and downstream technologies.

ing and process improvements. In addition, to develop biosimilars, the industry needs better characterization techniques, and better processes. Otherwise, even if "similarity" with a reference biologics could be shown, the cost of producing a new biosimilar might not be much lower than the original; this could dramatically reduce the attractiveness of any such high-cost generic version.

Returning to the attractiveness of single-use technologies, we found in our annual survey that respondents today estimate 35% of their upstream clinical production operations to be single-use. This compares with 25% of respondents that said more than 80% of their downstream clinical production steps are now single-use. The number is 16% of downstream commercial-scale production. This wasn't surprising to see that the lowest use was for downstream commercial production, which remains mostly fixed stainless-steel equipment. It was also fairly consistent to see the highest adoption rate be for downstream clinical production, likely due to broader use of disposable tubing and filters, buffer containers, etc.

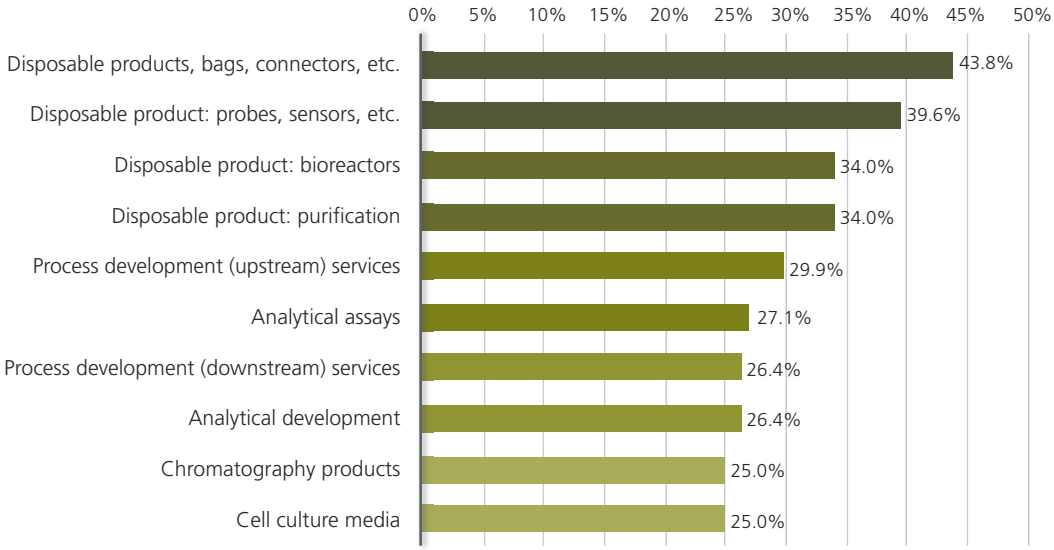
FOCUS SUPPLIERS, FOCUS

Researchers asked respondents to consider new product and services developed by suppliers and to identify the top areas they want suppliers to focus their development efforts on. This year, of the 21 areas the study listed, the areas highlighted in prior years, and other studies continue to occupy the top position. Specifically:

- Disposable products, including bags, connectors and other devices
- Better probes and sensors
- Process development services (up- and down-stream)
- Chromatography products

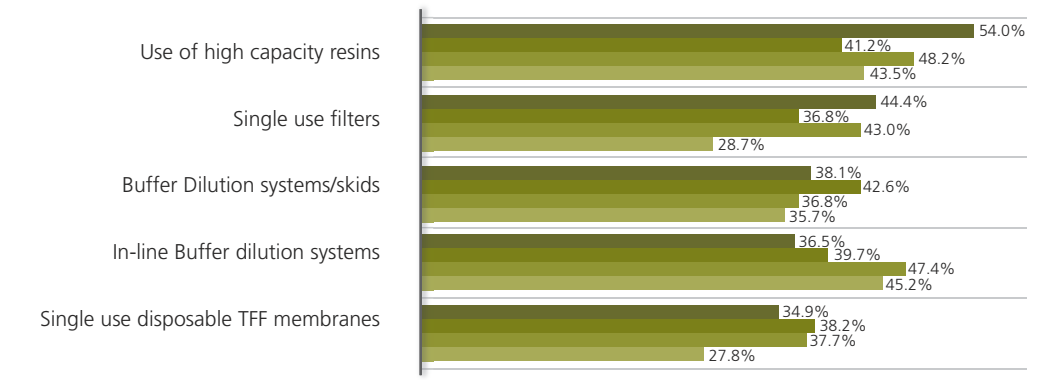
Some of the specific new product development areas being demanded by biopharma's operational managers are included in Figure 1. Identification of these areas by end-users is not a reflection of their need for technical advances to produce drugs that otherwise wouldn't be possible. Rather it mirrors their requirements to produce more efficiently and less expensively. This shift in focus on manufacturing is a maturation process that has been growing over the past 10 years.

SELECTED NEW PRODUCT DEVELOPMENT FOCUS AREAS



ADOPTING NEW DSP TECHNOLOGIES 2010 VS 2013

"Downstream Purification (DSP) technologies being considered"



Source: 10th Annual Report and Survey, Biopharmaceutical Manufacturing and Capacity, www.BioPlanAssociates.com, April 2013

TRENDS OVER TIME

Looking at responses from the past four years, the study shows that interest in more innovative approaches to bioprocessing, again, centers on process improvements. For example, demand for better upstream process development services has increased five percentage points over the past four years, while interest in downstream PD has decreased from a high of 35% in 2008, down to 26% this year. Similar declines in interest in new chromatography products are evident. This suggests the acute bottlenecks created around downstream operations have been abating, while the chronic need for improved productivity has not.

Better disposable devices, including bags and connectors, has increased by about five percentage points from 2008. Demand for disposable probes and sensors is up by roughly 10 percentage points, while interest in new bioreactors and purification products has remained steady during the period.

Predictably, interest in various new technologies varies by business model — and even geography — and the study's results offer a window into how different parts of the industry are looking at innovation. When comparing biomanufacturing developers to contract manufacturing service providers (CMOs), for example, the study found

Among the technologies biopharmaceutical manufacturers want suppliers to focus innovation and development on are single-use technologies including bags, connectors and other devices.

that while the former were more interested in disposable probes and sensors (41.3% vs. 27.8%), the latter were twice as interested in disposable purification products (61.1% vs. 30.2%). Again, this is likely the result of CMOs' need for efficiency to remain competitive.

THE INNOVATION PENDULUM

Although bioprocessing industry growth isn't as radical as in semiconductors (where Moore's Law proposed that the number of transistors on a chip doubles every 18 months), demand for innovation that improves efficiency is similar in respect to how new product developments swing from one bottleneck to the next. This year, single-use applications are clearly the subject of much interest when it comes to innovation; in prior years, and likely in the future, other technology areas will bounce back. Downstream purification, new and better analytical tools, and improved services offerings for example are likely to re-emerge as urgent problems as the industry resolves current, more acute, issues.

For example, separately in our study we asked respondents which of 21 different, novel downstream purification (DSP) technologies they were actively considering to address bioprocessing problems (see Figure 2). The responses are indicative of potential future adoption and do not take into account respondents already having adopted these technologies or those who are considering but not actively pursuing them.

Topping the list of new downstream processing solutions being considered this year are high capacity resins, by 54% of respondents. Following are single-use filters (44.4%), buffer dilution systems/skids (38.1%), in-line buffer dilution systems (36.5%) and single-use disposable TFF membranes (34.9%).

Compared with years past, we see a greater interest in the use of high capacity resins (this year's 54% being up from 41% in 2010) and single-use filters (44.4%, up from 28.7% in 2010). Some downstream areas are showing a trend toward decreased consideration. For example, the 36% actively considering in-line buffer dilution systems

The biopharmaceutical manufacturing industry is actively considering and adopting a range of new technologies for all facets of the manufacturing process. (Photo: Boehringer Ingelheim)

is down from 48% a couple of years ago. These declines may also reflect greater adoption of these technologies in the past few years, with fewer respondents falling into the "actively considering" column as a result of following through on those considerations. It may also be that incremental improvements in processes, elimination of purification steps and a diminished interest in alternatives for current technologies (such as Protein A alternatives) have weakened the urgency for new solutions.

Our analysis finds that CMOs may be a leading-edge indicator regarding plans for adoption of alternative downstream processing technologies. Results offer some insight into which markets are likely to expand in the coming months and years. For example, CMOs are far more likely to be considering single-use disposable TFF membranes (50% vs. 32%) and disposable UF systems (40% vs. 28%).

We also found significant differences on a regional basis, with U.S. respondents generally more likely than Western European respondents to be considering a range of technologies. For example, use of high capacity resins (71% U.S. vs. 33% W Europe), a 37.3 point gap; and In-line buffer dilution systems (53% U.S. vs. 11% W Europe). On the other hand, Western Europeans demonstrated significantly more active consideration for membrane technologies, alternatives to chromatography and precipitation.

WHAT'S AHEAD FOR NEW TECHNOLOGIES

The biopharmaceutical manufacturing industry is actively considering and adopting a range of new technologies for all facets of the manufacturing process. Single-use devices continue to crop up in any conversation about new technologies and a move towards leaner, more flexible and "modular" systems seems likely in biopharma's future.

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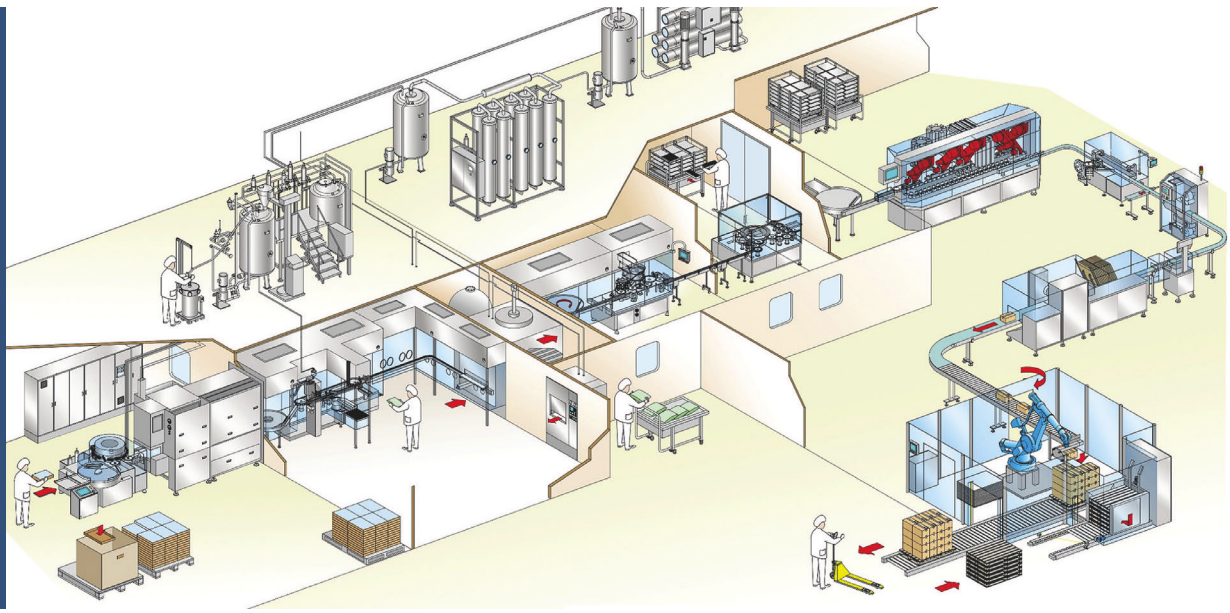

Demand for disposable probes and sensors is up by roughly 10 percentage points, while interest in new bioreactors and purification products has remained steady.

It is also important to note that introduction of innovations is not at all easy in this industry, and there are many obstacles to new technology introductions. Regulatory issues force biomanufacturers to stabilize bioprocessing systems early on, so processes can remain largely unaltered through a drug product's lifetime. This can make manufacturers less receptive to improvements. Thus, manufacturing strategy takes a long view when it comes to adoption of innovation.

On the other side, vendors, larger ones in particular, invest significantly in R&D and product lines. They have a vested interest in evaluating where future adoptions will be needed, and how rapidly they will be taken up.

Economic conditions can also play a role. While budgets are again expanding, tighter conditions continue to discourage the financing — and entrance — of smaller suppliers in the market, reducing the pool of likely contributors to innovation. Even so, biomanufacturers are showing a renewed urgency to improve productivity, reduce costs while boosting quality. This is reflected in increasing budgets over the past four years supporting activities focused on production efficiency.

Given the complexity, and the long product development cycle, the only way to ensure efficient process is for industry suppliers and vendors to continue to identify and meet the demands of end-users. This will drive future investing in the development of new technologies. And supporting this, on the suppliers' side, we find that vendors' R&D budgets for new product development have also expanded over the four years.

So, with increased budgets and interest from both manufacturers and vendors on innovation that boost efficiency, it's easy to visualize a robust future for the industry. For biomanufacturers to truly push forward innovation and remain competitive as cost pressures increase, and biosimilars evolve, they will continue to demand better ways of evaluating new technologies to cut downtime to market and streamline the overall testing process.

Survey Methodology: The 2013 "10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production" yields a composite view and trend analysis from 238 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 30 countries. The methodology also included over 158 direct suppliers of materials, services and equipment to this industry. This year's study covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time, and assesses differences in the world's major markets in the U.S. and Europe.

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Control Valve Replacement: Alternative to Globe Valves

An 18-year-old biopharmaceutical plant evaluated existing process conditions and devised a solution to replace its outdated valves

By Shamai Cylich, PE,
RPA Engineering

A BIOPHARMACEUTICAL plant in the United States was operating a cold/chilled glycol (CG) system to cool approximately 50 process vessels, mainly jacketed tanks (250 – 3500 L), and several heat exchangers to produce its products. The plant was approximately 18 years old and circulated propylene glycol (40%) and water (60%) as the heat transfer medium. Chillers in the basement generated 28 F (-2 C) cold glycol, which was then circulated by three constant-speed centrifugal pumps to the distribution network. System differential pressure control was achieved with a bypass valve that short-circuited the CG supply to the return side during periods of low demand.

Globe-style control valves, located in the mechanical rooms, provided temperature control of the process vessels. The valves were automated (PID control) through the plant's distributed control system (DCS).

However, being 18 years old, the original valves were providing inadequate positive shut-off as required for their application. Specifically, the plant experienced a temperature excursion in one of the tanks, because cooling fluid passed through a closed control valve, resulting in over-cooling of the tank and product. In addition, many of the valves were leaking externally through their (re-built) packing, causing accelerated corrosion of the carbon steel valves. Obsolete and non-maintainable, the original valves had become a real liability.

SELECTION CRITERIA

The biopharmaceutical company in question hired RPA Engineering to evaluate the existing process conditions and provide a solution for the passing control valves. The criteria was to maintain the existing temperature control scheme, provide tight shutoff (Class VI or better), and match the existing flow capability (flow coefficient, Cv), all with a standard platform and manufacturer that would be fully supported for the foreseeable future (10-20 years).

VALVE ASSESSMENT

Globe valves require resilient seats mated to stainless-steel plugs to achieve a class VI shutoff. However, the softer, resilient seats are susceptible to wear and tear and, consequently, more maintenance over time.

When new, the existing valves (equipped with stainless-steel seats and plugs) provided Class IV shut-off. As an alternative, RPA engineers considered replacing the obsolete Class IV globe valves with similar Class IV globe valves and installing additional block valves into the piping. The block valves would handle the tight shut-off duty, while the globe valves would continue with their true control function.

This flow control strategy is well suited to short-term batch type operations with discrete start/stop of the temperature control function.

However, the plant required tank temperature control for extended and unidentified periods of time (up to 30 days), during which the valves would continuously cycle through closed and partially open positions. Inefficient and cumbersome, this solution required additional programming and associated change control documentation — a task that generates considerable time and expense. RPA system designers opted for a less complex and, therefore, less costly solution.

Because the original globe valves were outdated and were in a supporting utility system — as opposed to being directly involved a product processing train — it was feasible to replace them with functionally "like-for-like" valves in lieu of an exact match. For this application, RPA engineers evaluated the functionality of ball valves with a "V" cut, otherwise known as V-ball valves. Capable of both modulating control and positive shut-off, V-ball style control valves met the functionality requirements that would be provided by any "like-for-like" replacements of the failing, end-of-service-life control valves.

V-BALL BENEFITS

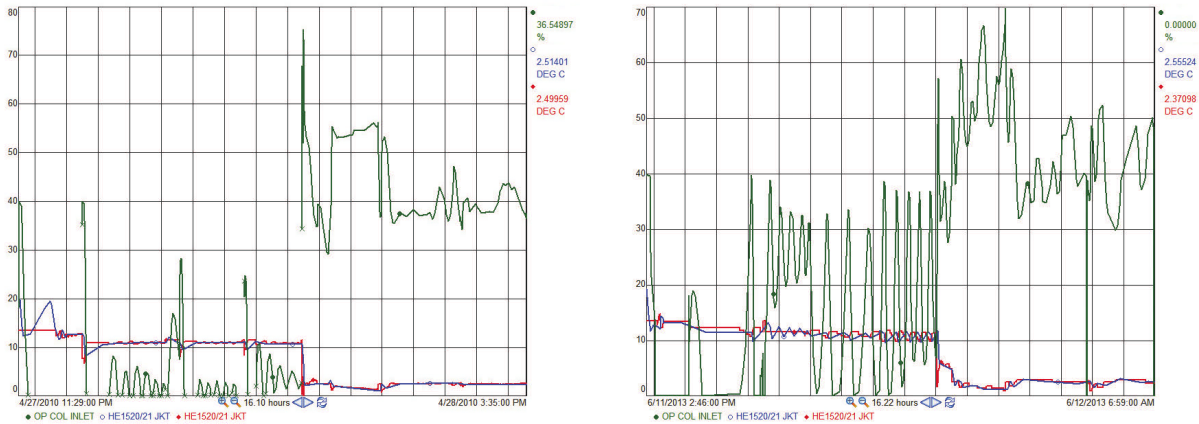
For this biopharmaceutical processor, V-ball valves offered additional operational benefits including high turndown capability and longevity of service: The rotary motion of the V-ball valves swipes the seats clean with every stroke, which serves to help maintain a tighter seal. Due to its rising and falling action, globe valves are more susceptible to accumulating material on plug/seat surfaces and wire-drawing, thereby reducing sealing capability. Functionally, V-ball valves offer an appealing alternative, especially since they are established in the market and have excellent performance records.

Globe valve packing is more susceptible to leaks due to the linear up/down action of the valve shaft versus the rotary action of the V-ball valves. As the globe valve shaft rises up, the cold, exposed shaft can sweat, and consequently this condensation drips down on to the carbon steel valve body and insulation. In addition, as the packing deteriorates, some of the glycol/water remains on the shaft. As the glycol/water mixture evaporates, crusty deposits form on the shaft. On the next down stroke, these deposits often enter the packing, further impairing the valve's ability to seal. As the cycle continues to expose the carbon steel valve body to water, corrosion accelerates. Because of its design, the rotating action of V-ball valve shaft mitigates these problems.

Original Buffer Prep Tank Cold Glycol Temperature Control Valve: Before

Close-up of a Typical Buffer Tank Glycol Temperature Control Valve: Before

Knew Buffer Prep Tank Cold Glycol Temperature Control Valve: After



Original valve HE Temperature Control Loop performance test (left) and after V-ball valve installation (right). Testing revealed benefits of the specified valve and control strategy, including slightly better cool-down capability, a higher Cv rating at full open and an equal percentage characteristic flow curve relative to the original process' flow parameters.

Historically, it's been easier to establish control loop position feedback with globe style valves as compared to rotary valves due to the type's linear, rising stem action. However, recent advances in electronics have increased the control capabilities of rotary (i.e., ball) valves while simultaneously reducing the cost of rotary valve positioners, which helps make them cost-competitive with traditional globe style control valves. New, digital, smart positioners offer a host of capabilities, most of which will ultimately never be fully realized in this application.

Lastly, the ball valve's assembly (valve, actuator and positioner) is smaller than that of the globe valve and can easily replace valves in circumstances where space and size limitations are a critical factor.

PILOT STUDY

First, a pilot study on one of the process jacketed tanks was performed with the new V-Ball valve (see photos) to prove the concept. The starting point for the selection of the new valve was to accept that the existing control capability was adequate with, of course, the exception of positive shut-off. The new valve also needed to maintain the existing performance level without requiring re-tuning of the PID constants already programmed in the DCS.

THE NEW VALVES WERE TRACKING ON THE SAME CONTROL CURVE AS THE ORIGINALS, ALLOWING FOR ONLY A MINOR OFFSET DUE TO THEIR HIGHER CV.

In order to specify the new valves, RPA performed a walkdown of the existing valve to verify the installed piping configuration and obtain nameplate data. In addition, the original design calculations were reviewed in conjunction with the piping and instrumentation diagram's (P&ID's), historical process data, Master Batch Records and P&ID constant settings. RPA also conducted interviews with the production staff to assess the performance level (robustness of control).This information was then analyzed to determine whether a standard selection (close enough) or custom selection (exact match) was required for each of the replacement valves. Valves were then selected from the manufacturer's standard offerings with a Cv that was closest to the Cv of the original globe valve.

After the valve was installed, RPA performed operational and performance testing with very positive results, as summarized below:

- Cool-down capability was actually slightly better than the globe valves due to slightly higher Cv rating at full open.
- The replacement valves have equal percentage characteristic flow curves. This provides similarity with the equal percentage characteristic flow curves of the original globe valves. The new valves were essentially tracking on the same control curve as the originals, allowing for only a minor, but acceptable, offset due to their higher Cv.

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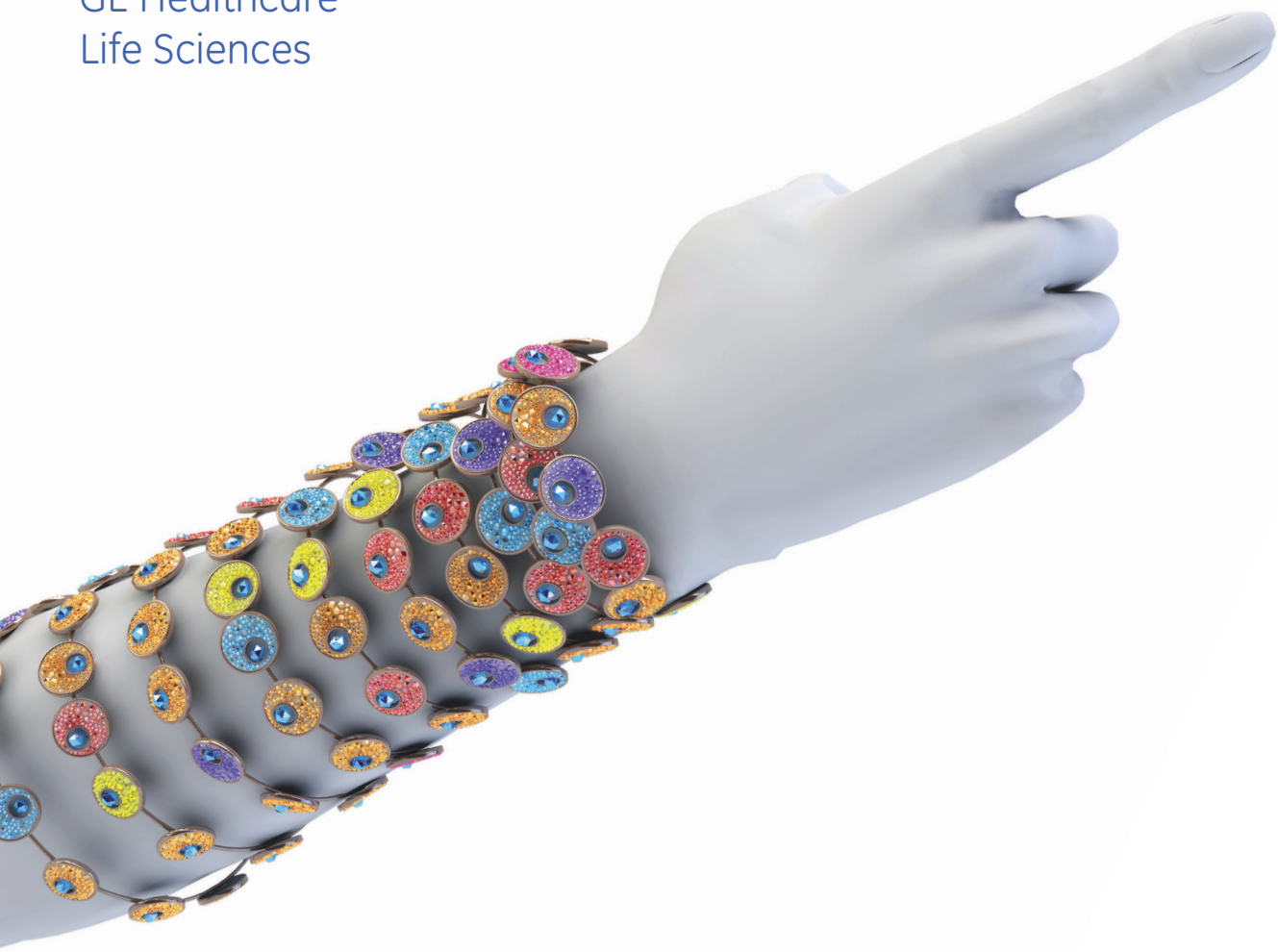

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PRODUCT SPOTLIGHT

RPA evaluated several manufacturers and selected the Flowserve CPT valve line for the following reasons: The V-cut is incorporated into the downstream seat rather than the ball of the valve. This aspect permits the manufacturer to laser cut the flow opening to meet a broad range of flow requirements. As such, they can offer a large selection of standard openings for the "characterized seat," making it easier to match the existing valves, including their equal percentage flow characteristic. Therefore, standard valve and seat configurations may be selected with flow coefficients (Cv) close enough to the existing that the level of control will not be compromised. The characterized seats are also retrofittable. Should the valve performance not meet the requirements, a new seat can be ordered and readily changed in the field. Additionally, the manufacturer offers customized cuts to meet non-standard flow requirements. Flowserve CPT valves are manufactured with high grade materials, including nickel-plated 316 stainless steel ball, 316 stainless steel body, and TFE impregnated sintered stainless-steel seat (for the characterized seat).

ROTARY VALVES CAN BE CONSIDERED IN APPLICATIONS THAT HAD TRADITIONALLY BEEN THE DOMAIN OF GLOBE STYLE CONTROL VALVES.

- The above control was achieved without changing the PID loop constants — the valves were essentially a drop-in, "plug-n-play" replacement.
- After the successful completion of the pilot testing above, all of the temperature control valves — plus a few steam and hot glycol valves as well — were replaced with the new standard.

SELECTION METHODOLOGY FOR BALANCE OF PLANT

RPA applied the same methodology used in the pilot study to the balance of the system's valves. Review of the historical process data on the PI historian indicated that there were essentially two different types of temperature versus valve position curves:

Tanks: After the tanks were steam sanitized (~ 122 C) glycol was applied to the jacket for cool-down. Tanks with hot glycol service were cooled down to below 100 C with hot glycol (80 C), and then the cold glycol was introduced. During the cool-down phase, the temperature control valves were commanded wide open via the DCS. As the final hold temperature was approached, the valves slowly throttled closed. During extended hold periods, the control valves would maintain the tank temperature through short bursts of activity, opening quickly to ~ 15%-30% open and then closing over the span of a few minutes. This opening/closing process repeated during the course of the holding period, thereby maintaining the tank temperature within +/- 1 C. The control process was easy to duplicate and fell within the capability of the Flowserve CPT valve standard line.

Heat exchangers: During processing phases for typical heat exchangers, the valves remain in control, modulating as required to maintain process temperature. One of the more difficult control schemes incorporated a cascading loop, where the outlet of the heat exchanger (which was the inlet to the processing column) reset the supply temperature. The temperature control valve then controlled the flow of CG to the heat exchanger's supply pump.

INSTALLATION AND TESTING

Installation of the valves included minor pipe reconfigurations to allow for improved maintenance and troubleshooting. RPA developed testing plans and executed them for each valve type prior to being placed back into full production. In total, 49 CG control valves for tanks and heat exchangers were replaced under the program, as well as four steam (15 psig) valves and four hot glycol (80°C) valves. The valves were replaced from the end of 2012 through 2013.

Recent advances in electronics and materials technology have not only reduced the cost, but also increased the capability of rotary style valves for dual service applications — tight shut-off and control — which previously required two valves. Therefore, rotary valves can now be considered in applications that had traditionally been the domain of globe style control valves. Of course, due diligence is required and the owner should review the merits of their valve selection on a case-by-case basis to ensure proper application.

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Four Keys to Effective **Raw Material Containment**

Solutions to protect raw bio materials in storage and conveyance

By Mark Hoffman, PE, SSOE Group

ANY PROCESS that manufactures a biotherapeutic, biodiagnostic, or other bio-based solution requires a well-designed bulk material storage and handling environment. Without such technology, the manufacturing process can be sidelined by raw material breakdown, spoilage, exposure to moisture or contamination or pest infestation. Assuring the reliability of a storage and conveyance environment is based on four key concepts:

1) A well-designed storage container system
2) Effective climate control
3) Smooth conveyance of the material in and out of the container
4) Cleanability for quality assurance and operational efficiency

A WELL-DESIGNED SILO

A well-designed bulk material storage and handling environment must balance cost with the size needed for the raw material. Containers must be large enough to achieve economies of scale, and to allow easy emptying and refilling, and its surfaces must be compatible with the characteristics of the raw material. Striking this balance requires an integrated assessment of the plant, its site and the material to be contained.

Unfortunately, there are currently no universally accepted design standards for the bulk material storage and handling environment. Although many equipment vendors provide a turnkey package — silo, peripheral equipment and design — there are pitfalls to this type of solution. Shortcomings with this approach include oversimplification, which can result in system performance issues and also a tendency to use standard or off-the-shelf solutions, which may not provide the best solution. An experienced bioprocess engineer can offer a custom design that meets the unique operational needs of the owner and facility.

First of all, bin activation and fluidizing systems must be configured to match the characteristics of the raw material. If the owner or vendor can provide the material's physical characteristics, great. If not, materials testing will be needed to determine the material's angle of repose, its hygroscopic parameters and particle size, all of which are related to flow.

Some raw materials flow easily out of a cone bottom, whereas others tend to bridge and obstruct free flow. An example of the latter is soy meal, which forms clumps when damp. To keep the material dry, the silo's designer can envelop the silo in dehumidified air and use air pads on the silo's cone bottom to facilitate flow.

Other bio-based materials require bin activation using a vibratory or a screw conveyor.

Unfortunately, if the system can't be easily cleaned, the raw material may build up, especially at transition points. In that situation, fluidizing may be a better solution. Solimar Pneumatics, for example, offers a fluidizing disk that is compact, self-cleaning and economical.

A design consideration that is equally critical to flow maintenance is the interface between the container's surface and the contained material. Given a corrosive material such as urea, for example, stainless steel would unquestionably make a more durable and cleanable containment surface than fiberglass. Furthermore, using stainless steel may be the most cost-effective choice in the long run. It is far less likely to need replacing if the process will be using a corrosive raw material in the future.

A well-designed bulk material storage and handling environment must balance cost with the capacity needed for the raw material while taking advantage of both off-the-shelf and custom-engineered technologies and solutions.

The next design challenge to consider is the conveyance of the bio-based material into and out of the silo. If the material is subject to molecular decomposition or other damaging transformation, the process engineer must be careful with the design of any pneumatic conveyance. It has an inherent tendency to abrade or heat the material. With such materials, the engineer must not allow too high of a conveying velocity. He or she must also use appropriate piping components and employ cooling heat exchangers in the conveying air stream.

The climate control system of a container must be designed around the susceptibility of the raw material to humidity, airborne microbes and extreme temperature. To prevent a hygroscopic material from absorbing water and clumping or degrading, humidity must be kept low. Sugars, for example, are very hygroscopic and can easily clump and interrupt flow. For materials that are vulnerable to microbes engineers can use HEPA filtration or UV treatment of the air in the top of the bin. Temperature control is obligatory for heat-sensitive materials such as glucose.

Cleanability is important for reasons of safety and performance. A clean system prevents contamination by microorganisms, insects, rodents and other animals. A clean system protects the flow of material against clumping or dredging. An effective design streamlines both the container and conveyance system to limit transition points. When transition points cannot be eliminated, they should be designed with maximum bending radii so that material flows smoothly and does not build up.

Good cleanability can also avoid the need for extra steps. For example, many bioprocess manufacturers will, as a hedge against contamination in unreliable storage conditions, heat a slurry to sterilize it before adding it to their fermenters. Proper system design may eliminate certain sterilization steps, which can reduce operating cost and improved quality control. Finally, the system's design must allow operators to take its components apart and reassemble them quickly by hand. This keeps downtime for cleaning and maintenance to a minimum.

REAL-WORLD SOLUTIONS

Innovative solutions for containment and conveyance can confer benefits well beyond protecting the integrity of bio-based materials. They can also reduce costs, compress the construction and installation schedule, improve quality control and enable expansions to be completed while maintaining production. In the following cases, strategies included holistic assessment, the use of carefully selected "off-the-shelf" equipment and prefabricated components, and the expansion of storage capabilities while maintaining operation:

Looking first at the entire process. How did a bioprocessing firm that uses soy meal in a fermentation system to produce an enzyme achieve a technically sound and cost-effective climate control system? It combined a thorough needs and site assessment with the transfer of knowledge from the food industry. Although the end-product of this process is not used for human food production, bioprocess engineers with SSOE Group designed the storage environment as if its contents were intended for human consumption. Going this extra mile reflected SSOE's respect for the potential negative impact of contaminating a batch of expensive product.

In this case, the soy meal was received in bulk and stored in a bin. Although it was not especially sensitive to degradation, humidity and the resultant clumping were still problematic. The conventional solution? A cooling coil and reheat coil system, or a desiccant system. However, because this manufacturer used dry nitrogen in other parts of its process, the SSOE engineers designed a dry nitrogen purge system to control humidity within the ideal range. The capital outlay for this innovation was one-third that of the conventional cooling or drying technology.

Using small containers and off-the-shelf equipment for an offshore pilot plant. Practical and economic constraints created challenges for SSOE process engineers when asked to design a raw material storage and handling system for a biofuel pilot plant at an offshore location. Both the equipment for the plant and the raw materials were to be delivered by container ships. The engineers' solution enabled the owner to use bulk bags, totes and drums, and it incorporated off-the-shelf equipment to handle dumping, pumping out, emptying and hanging these containers.

It was elegant simplicity. Bulk bags arrived by ship; fork trucks unloaded and delivered bulk bags to the storage and handling area; the bags were hung on an emptying station; contents were emptied into a conveying system; and raw materials were conveyed to a slurry-mixing tank. In addition to handling the raw material, the solution minimized capital cost, achieved cleanability and optimized efficiency. There is no master specification for such equipment. Because this was a pilot plant, the engineers also maximized its flexibility to safely process new and possibly more corrosive materials in the future.

Pre-fabricate to reduce cost, accelerate schedule and improve QC. Another manufacturer had to double its plant capacity, including raw material storage, to keep pace with forecasted market trends. With the plant remaining in operation, SSOE completed the project in 11 months. To do this, the engineering firm partnered with two contractors to execute a design-build plan that used prefabricated components. While one contractor worked on slip forms for the silos, the other worked on the conveying system using prefabricated pipe and other components. Tie-ins were made during scheduled process shutdowns. The parallel team approach not only cut 25% off the original construction schedule, it improved QC because shop fabrication allowed greater control conditions.

In the bioprocessing industry, well-designed bulk material storage and handling environment are essential in preventing raw material breakdown, spoilage, exposure to moisture or contamination or pest infestation. The components of such an environment include: a well-designed silo or other storage container system; effective climate control; smooth conveyance of the material in and out of the container; and cleanability for quality assurance and operational efficiency. When innovative thinking is combined with a technically sound design, the result can save bio-processor's time, trouble and money.

Mark Hoffman, PE, is an engineering manager at SSOE Group (www.ssoe.com). He has more than 30 years of experience in project/engineering management in many industries. Hoffman can be reached at 651-726-7660 or Mark.Hoffman@ssoe.com.

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Biotech R&D Demands New Techniques, Technologies

Q&A with Dr E. Neil Lewis, Chief Technology Officer, Malvern Instruments

By Emil Ciurzak, Contributing Editor

INVESTMENT IN biotech R&D is reportedly now outpacing that of big pharma (http://bit.ly/19PPRKT) and is driving rapid developments across the biopharmaceuticals sector. The race to identify candidates and to produce effective biological therapeutics is intense and brings unprecedented challenges. Even with traditional small molecule drugs, the route from candidate selection through formulation and into manufacturing is often difficult to negotiate. When it comes to biologics, it may well be a journey into the unknown where, for example, traditional analytical methodologies don't apply and where many of the rules are still being written by the regulators. Dr. E. Neil Lewis, chief technology officer at Malvern Instruments, leads the company's Bioscience Development Initiative, established to work in tandem with the biotechnology and biopharmaceutical industries to rapidly identify, evaluate and deliver the new analytical technologies they need, when they need them.

Pharmaceutical Manufacturing: What is driving the demand for new analytical techniques in biopharmaceutical development?

"Unlike chemical entities, large biological molecules cannot be delivered as powders or tablets and instead, are delivered in suspension via injection. Large biological molecules are heterogeneous in nature, and the therapeutic molecule itself may become misfolded, aggregated or denaturated. Consequently, biological materials bring a level of complexity to the development process that is simply not present for small molecule drugs. Safety and efficacy of the final product are paramount, and have been driving analytical requirements to this point. However, as the industry grows, the analytical expectations throughout the development cycle will mature. Potentially, a suite of analyses will be applied at all stages of development, evolving into the biopharmaceutical analogue to Quality by Design. This includes pre-formulation and formulation stages, where critical decisions must be made as to the likely downstream suitability of a molecule.

In this fast-moving environment, some of the biggest challenges lie in understanding not only what can be measured but what will provide meaningful, predictive information as to quality, and finally anticipating what measurements you will be required to make in the future. Such dynamism is pretty exciting and is stimulating some significant scientific advances, but means that we have to keep defining and redefining the metrics, and as analytical instrument providers we have to deliver the necessary tools."

PhM: How is Malvern addressing these challenges?

"We at Malvern believe that the traditional model of getting an analytical instrument into the hands of the people who need it, where it can take a number of years to perfect a market acceptable product, needs to be bypassed. In the rapidly changing environment of biopharmaceutical development there is a high risk that by the time an instrument developed the 'old' way gets to market, analytical requirements will have advanced beyond the original capabilities. The Bioscience Development Initiative has been established to encourage industry players to partner and share with us their challenges, to provide a vehicle for us to identify and target emerging technologies and to provide fast-moving, agile technology development. Our team engages on both sides of the market. We work with the end customers, those biopharmaceutical companies who have the analytical needs, as well as the leaders on the sharp edge of technology development who have a strong in-house team of scientists and engineers, and with those in small companies and academia.

We gain a real-time understanding of the biopharmaceutical industry's needs and have the ability to access emerging technologies from a variety of sources, through in-house development, partnership, licensing and/or acquisition. We can quickly test concepts, build prototypes and take the most promising designs forward. As a result, our biopharmaceutical partners get their hands on new technologies at a much earlier stage than compared to traditional product-development cycles. Their iterative feedback then shapes further development, or alternatively, will accelerate the decision to cease work on a concept that fails to deliver on its potential. Such high-level partnering allows Malvern and its affiliates to take the risks needed, to explore technologies that traditionally would appear at too early a stage for consideration, and to know quickly if these instruments will deliver the information to justify further investment. Malvern is really in the business of accelerating technology evaluation and development, quickly eliminating dead ends, and driving through those products that will provide real value to the biopharmaceutical industry as and when they need it."

Dr E. Neil Lewis
Chief Technology Officer,
Malvern Instruments

PhM: Where is your technology focus at present and can you give examples of successful product development that has come through the Bioscience Development Initiative (BDI)?

"The biopharmaceutical industry has cited analytical testing as one of the bottlenecks in screening new candidate molecules. Selecting suitable biological entities post-discovery involves various physicochemical testing processes that are designed to rule out those that will be 'problem children' in downstream processing. So the question to be answered is 'how will these entities behave in formulation?'

Typically there are only microliter quantities of extremely high-value material available, yet many parameters to be tested. Concerns include stability, propensity to aggregate, structural integrity of the molecule, and viscosity of the formulation. All of these critical to quality attributes should influence whether or not a candidate entity is advanced, but sometimes it is not possible to characterize all of them with the small quantities of material available.

For example, protein aggregation is a ubiquitous problem, as aggregates have the potential to trigger an immune response in the recipient. Malvern has established solutions for measuring protein aggregation, including Size Exclusion Chromatography and Dynamic Light Scattering techniques. However, to provide complementary and additional characterization capability, the company has negotiated an exclusive distribution agreement with Affinity Biosensors to employ their Resonant Mass Measurement technology to detect, in some cases speciate, and more importantly, count particles in the size range 50 nm - 5 µm. It is especially useful for characterizing protein aggregates in a formulation or buffer.

The viscosity of protein and formulations is another area that can critically impact manufacturability and how a drug is delivered, either intravenously or subcutaneously. As a result Malvern also has an ongoing partnership and development program with another company to develop microviscosity measurement technology, with the aim of providing automated screening of extremely small volume samples and formulations. The results of this joint development project will be marketed as a full Malvern product later in 2013."

PhM: Can you provide some thoughts as to what's on the horizon at Malvern?

"One key goal will be to satisfy the industry's need for automation. This is important for analytical techniques that are applied early to determine a molecule's 'developability.' Many pharmaceutical candidates are likely to be under

consideration and the process of applying numerous physicochemical measurements to identify lead candidates can be labor intensive, expensive and perhaps less reproducible than an automated workflow. Therefore the automation and integration of these new technologies with existing workflows and established industry practices will likely be one of the keys driving the molecule's success."

PhM: What about regulatory acceptance?

"Regulatory acceptance is certainly an important aspect to consider. Typically, new technology and instrumentation undergoes a process of validation by the scientific community via peer-reviewed publication before it ultimately garners the attention of industry, and ultimately, the regulator. This process can take a significantly long period of time when it happens 'sequentially.' A program such as BDI aims to compress that time schedule as much as possible so that everybody benefits.

Finally, Malvern will be keeping track of industry trends. The biopharmaceutical industry is changing rapidly and the next generation of biopharmaceutical products is quickly evolving beyond a standard monoclonal antibody. Antibody-drug conjugates, for instance, are a unique combination of a small molecule drug attached to an antibody. A variety of other molecules and delivery technologies are entering the market space as well: bispecific antibodies, antibody fragments, peptides, liposomes, etc. All of these are likely to quickly drive new analytical requirements. The need for an agile analytical instrument development process to support it is clear.

Dr. E. Neil Lewis received his Ph.D. in chemistry from the Polytechnic of Wales in the UK and did his postdoctoral fellowship at the National Institutes of Health (NIH) in the USA. He was tenured by the NIH in 1992 holding the position of Senior Biophysical Researcher. He is the founder of several high technology companies, including Spectral Dimensions Inc., a company that developed hyperspectral imaging systems, and he has been at the forefront of the development of these technologies. He has authored more than 70 papers, book chapters and patents and has received numerous awards for his contributions. After the sale of Spectral Dimensions to Malvern Instruments Ltd., he was appointed to Malvern's Board of Directors and holds the position of Chief Technology Officer. He can be reached at neil.lewis@malvern.com.

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QbD: The Devil Is in the Data

A single data capture and management platform is needed for R&D, pilot, QC/QA and manufacturing to effectively implement a QbD strategy

By John P. Helfrich, Vice President, ADQM Solutions Group, Accelrys Inc.

QUALITY BY Design (QbD) is a strategic concept for operational excellence in any manufacturing operation, and it has become a focused initiative by many of the life science companies that are highly regulated (i.e. pharmaceutical and biotech companies). The goal is to link manufacturing intelligence to product and process research and development (R&D) data in order to streamline the operational changes required to produce a quality product at the lowest manufacturing costs reliably and consistently in a variable environment.

The key challenge is developing the contextual link from routine production/manufacturing data sets to the vast array of experimental data obtained during the product and process development and pilot lifecycle stages. By correlating critical process parameters (CPPs) in the plant with the critical quality attributes (CQAs) and relating the variations to the R&D development data sets, a production facility can define a platform for real-time operational excellence. In addition, the manufacturing intelligence can add a significant knowledge base to the R&D cycles on new products in development. The ultimate benefits are shorter R&D cycle times, improved technology transfer to pilot and manufacturing and significantly reduced operational costs in commercial production. Minor shifts in CPPs can, in as close to real-time as needed, be adjusted to assure CQAs are in line with specifications, saving time and rework loops that add to costs. This is true operational excellence.

The devil, of course, is in the data. Capturing, cataloging and operating on the R&D and QC data become a critical-path requirement for effective QbD. Historically this data resides in numerous data silos and is difficult, if not impossible, to access and use. A single data capture and management platform is needed for R&D, pilot, QC/QA and manufacturing to effectively implement a QbD strategy. This then creates the environment to turn your data assets into information that, when interpreted, forms the knowledge that can create the wisdom for QbD and operational excellence.

THE 2.0 REGULATORY ENVIRONMENT

Recent regulatory initiatives have highlighted the need for science-based process understanding and a culture of continuous improvement in life science manufacturing. The FDA and other regulatory agencies are encouraging the industry to adopt technologies to move from a "quality by inspection" to a "quality by design" operation, with the goal of continuous quality verification (CQV) and ultimately "real-time release." Although QbD and process analytical

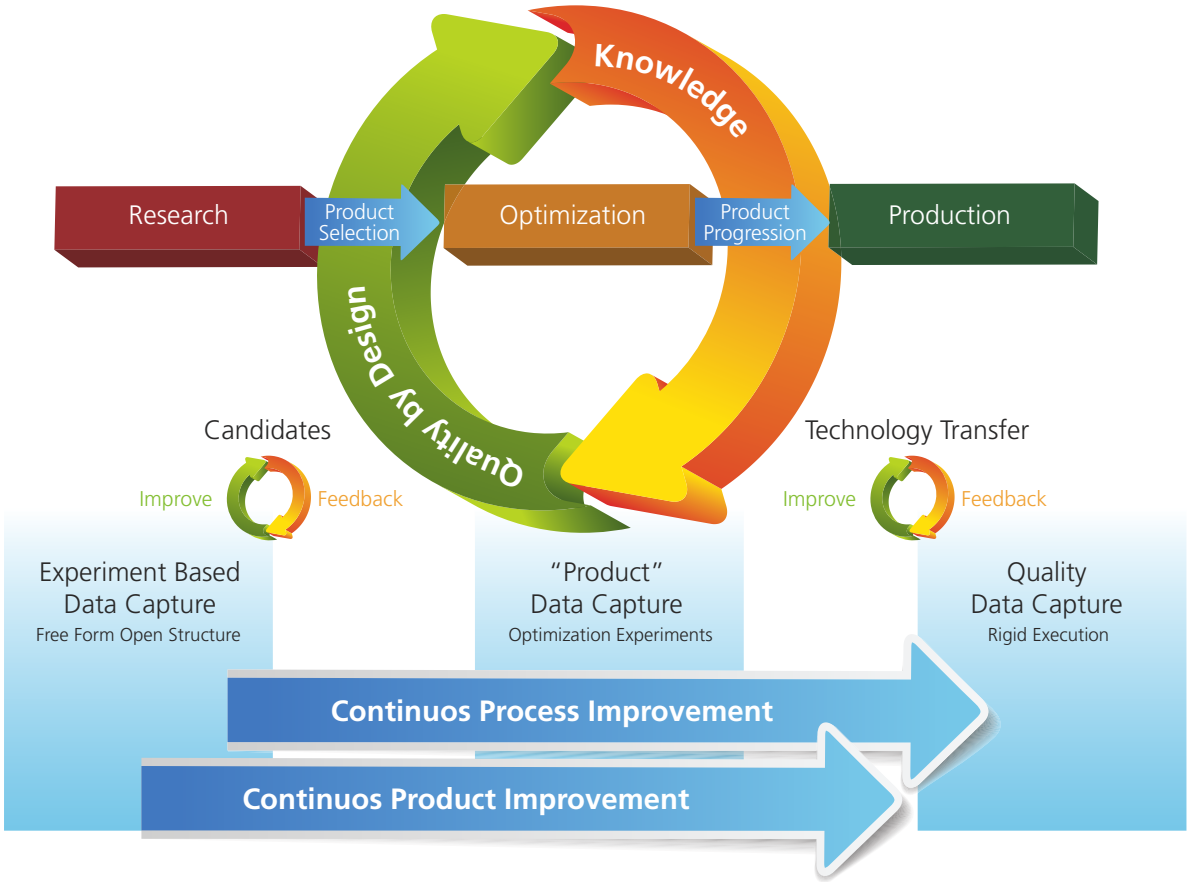


Figure 1. An Informatics infrastructure and strategy that expands research, development and manufacturing enables information from across the organization to support QbD and continuous product and process improvement.

technology (PAT) improvements are not yet regulatory requirements, the original cGMPs specify that "…control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product." Furthermore, rather than being something that happens only during process development and scale-up, there is now an expectation that continuous improvement and the establishment of process consistency are ongoing components of the entire product lifecycle.

Successful approaches to "real-time quality assurance" require that the sources of variability in the CQA be identified and understood so that they can be measured and controlled in real-time using appropriate technologies and equipment. The process parameters that drive this variability are called Critical Process Parameters (CPP). When combined with a culture of continuous improvement and the right supporting technology environment, this initiative can drive adoption of better practices and sustain higher levels of predictability and quality compliance across the entire manufacturing value chain. The resulting business benefits to life science manufacturers are significant:

- Increased predictability of manufacturing output and quality
- Reduced batch failure, final product testing and release costs
- Reduced operating costs from fewer deviations and investigations
- Reduced raw material, WIP and finished product inventory costs
- Greater understanding, control and flexibility within the supply chain
- Faster tech transfer between development, pilot and manufacturing
- Faster regulatory approval of new products and process changes
- Fewer and shorter regulatory inspections of manufacturing sites

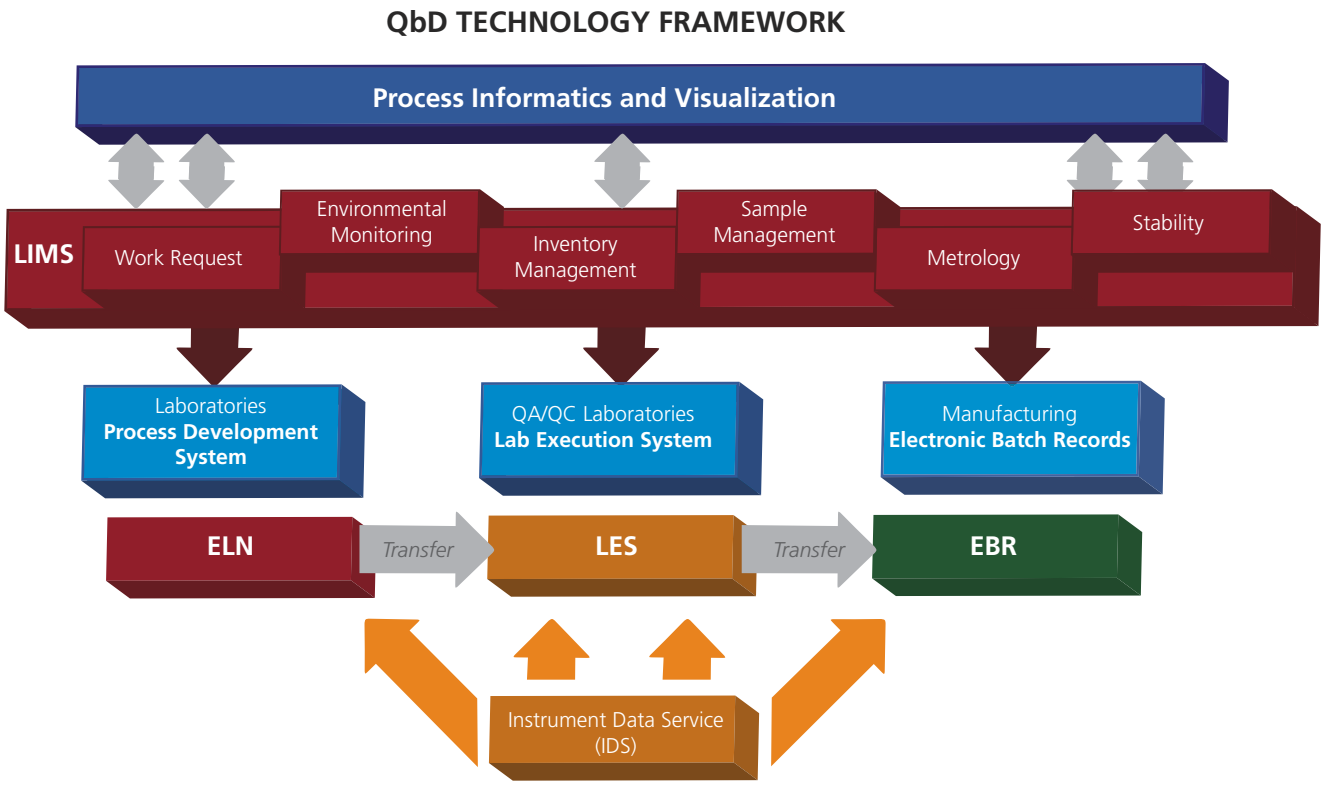


Figure 2. A QbD informatics framework consists of an ELN, LES, EBR, IDS and Process Informatics and Visualization technologies.

These benefits accelerate time to revenue, reduce cost of goods sold (COGS), and address the new regulatory environment in an industry that is feeling pressure from expiring patents and less predictable product pipelines. They also translate into significantly reduced risks and costs to consumers.

QBD INFORMATICS - DATA CAPTURE, CONTEXTUALIZATION, ACCESS AND KNOWLEDGE CREATION

Adopting informatics to support QbD is not a single event but a series of events that constitute a planned journey from tactical and reactive science to strategic, information-driven science. The journey begins with the transition from a paper-based environment to digital with the required departmental standardization needs for harmonized data exchange across the enterprise. Through this process data can be effectively found and mined for QbD modeling. Modern informatics helps organizations better understand and describe the variables affecting the CQAs and ultimately optimize processes to achieve product and operational goals. This is the essence of QbD.

Over the last decade, large investments have been made in IT infrastructure in an attempt to improve life science manufacturing performance. This began with implementations of Distributed Control Systems (DCS) and Supervisory Control and Data Acquisition (SCADA) systems to measure, record, control and report on individual equipment skids, unit operations and plants. This has been followed by implementations of Laboratory Information Management Systems (LIMS), Enterprise Resource Planning (ERP), Manufacturing Execution Systems (MES), and Electronic Batch Record (EBR) and Electronic Notebook systems (ELN). These systems today represent "silos" of data and are rarely utilized for process and quality improvements on the scale needed to affect a QbD plan. The key to any "systems approach" is the ability to contextualize the "data-information-knowledge" transitions and use this data for operational excellence in R&D, pilot and manufacturing operations. The devil, of course, is in the data and what is needed is a scientifically aware informatics lifecycle management platform to capture, catalog, contextualize and define an informatics process for knowledge creation to affect improvements across the product development to commercialization continuum.

INTEGRATED PRODUCT DEVELOPMENT AND MANUFACTURING

Today, if we look at the journey of a product from lab to plant, we see that research informatics systems already deliver some level of custom electronic environments enabling scientists to document, explore and protect intellectual property. Likewise, manufacturing informatics is heavily reliant on ERP, LIMS, MES and other disparate silo-based systems to test quality into the product/production process. Rarely are these systems effectively linked other than for some trending reports. Development, on the other hand, has undertaken less informatics investment and is encumbered with many paper-based processes and data-management practices. Through an effective "platform data management strategy," information capture throughout the development to pilot plant to production plant processes will provide the foundation for long-term QbD operation (see Figure 1).

THE KEY TO ANY "SYSTEMS APPROACH" IS THE ABILITY TO CONTEXTUALIZE THE "DATA-INFORMATION-KNOWLEDGE" TRANSITIONS AND USE THIS DATA FOR OPERATIONAL EXCELLENCE.

The technology elements to facilitate this "platform strategy" are comprised of the following components (see Figure 2):

- R&D – a process and analytical electronic laboratory notebook (ELN)
- Pilot and Manufacturing (QC) – a Laboratory Execution system (LES) and Electronic Batch Records (EBR)
- Pilot, QC and Manufacturing – a next-generation Laboratory Information Management system (LIMS 2.0)
- IT/IS – a Process Informatics and Visualization system
- Instrumentation in all Groups – an Instrument Data Service (IDS) for real-time data capture and transfer

Through the effective integration of these technologies, the platform for capturing, mining, analyzing and correlating development, process and quality data sets can be realized.

For QbD to work, organizations must be able to capture all the data and transition the raw data into information that when analyzed can create the knowledge and wisdom to build quality into the process for next-generation operational excellence. The devil is indeed in the data.

Myth Busters: Egg-Based Vaccine Production

Despite continual advances in the technology, misconceptions remain about the validity and effectiveness of egg-based vaccine production

By Ken Christiansen, president of RAME-HART

VACCINES SERVE as a critical line of defense in disease prevention and control. As global communities interact more, there is a pronounced importance on rapidly delivering greater quantities of vaccine that reach more people as quickly as possible.

Health organizations are increasingly concerned about the potential of an influenza virus pandemic amidst a growing global population. This fear has been exacerbated by the 2009 H1N1 (swine flu) epidemic and more recently, the H7N9 (avian flu) outbreak in China[1]. The latter is a stark example of how this threat affects livestock and humans alike. Developers of both human and veterinary vaccines must address this challenge and deliver superior protection in shorter periods of time.

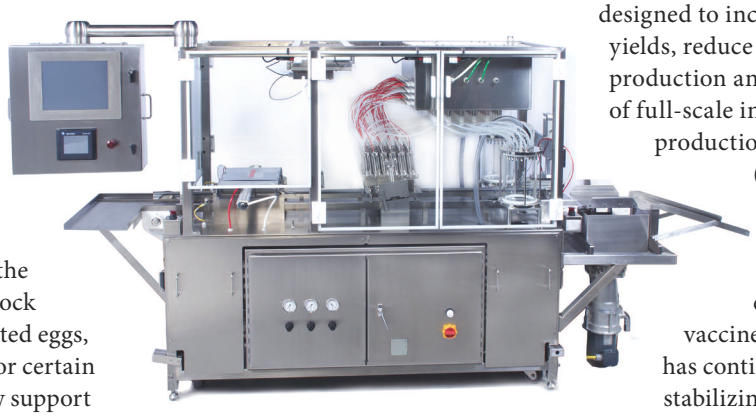
As new technologies are explored, health organizations stress the severity of an impending influenza epidemic. In 2005, the United Nations System Coordinator for Avian and Human Influenza outlined a global initiative designed to prevent the potentially devastating impact of an influenza virus, which could cause anywhere from five to 150 million deaths[2]. Alternatives such as cell-culture-based growth systems, recombinant protein expression systems and DNA-based vaccines face several limitations (e.g., tumorigenicity risks, ongoing clinical development, simply being cost-prohibitive) that would currently not make them viable options in the event of a pandemic[3].

Chicken-egg-based influenza vaccines, in contrast, remain the most effective manufacturing method available. As a part of its H7N9 preparedness strategy, the CDC is currently distributing viral samples grown in eggs to develop a vaccine. The H7N9 avian flu virus samples have been replicating well in eggs according to CDC reports[4]. The process is highly regulated, stable and predictable. Nonetheless, despite continual advances in the technology, misconceptions remain about the validity and effectiveness of egg-based vaccine production. In the following article, we discuss and evaluate the "myths" around this proven vaccine development process.

MYTH #1: "EGG-BASED INFLUENZA VACCINE PRODUCTION IS SLOW AND OUTDATED"

Egg-based vaccine production is on occasion characterized as outdated and old-fashioned. Originally developed in the 1950s, the technology has been used to produce seasonal influenza vaccines for more than 30 years. While long-standing, the process has evolved to address various challenges, including yield, automation, capacity, quality assurance and production speed. Improvements to egg supply variability have also been made, minimizing and often eliminating the periods of time that eggs were previously unavailable[5] for use.

One area where this mistaken perception arises is in the face of pandemic preparedness. Inadequate vaccine supply is an industry-wide challenge, but egg-based production comes under duress from the belief that livestock management is an erratic, un-evolved process. Vaccine manufacturer Sanofi Pasteur, however, recently developed new technologies to improve egg supply and increase availability in advance of vaccine production dates. With the advent of restructured flock management, embryonated eggs, previously unavailable for certain periods of time, can now support vaccine production year round[4].



In RAME-HART's automatic egg harvester, two infeed rails support the egg trays as they are pushed through the process by a conveyor chain equipped with pusher lugs.

Newer manufacturing methods such as cell-based production are predicated on improving areas like speed-to-market, risk of contamination and vaccine potency. But cell-based vaccines undergo many of the same critical processes as the egg-based method such as vaccine isolation, extraction and purification. Furthermore, in cell-based technologies, the use of animal cells in media is disadvantageous because of concerns over bio-burden potential and batch variability — two factors which compromise viral yield. Another shared concern is strain variability. Because of the influenza virus' propensity to change composition, trivalent vaccines that consist of different influenza strains must be formulated annually. While cell-based production is designed for faster response, it is still subject to the physical constraints of strain availability[4].

As a pioneer of inoculating and harvesting machines, RAME-HART has continuously developed advancements in egg-based vaccine production technologies. Thirty years ago, egg-based production was completely manual and very labor intensive. However, over time, RAME-HART has automated multiple steps in the manufacturing process including harvesting and inoculation, reducing the frequency of human error, bio-burden and the risk of contamination. Egg-based influenza vaccine production has gone from a manual operation to an almost completely automated process where eggs are loaded, inspected, inoculated, de-capped, harvested and unloaded without virtually any human interference.

Advances to the egg-based process like recombinant vector technologies are being explored to develop faster response times to an impending influenza pandemic. This method manipulates an adenovirus capable of infecting embryonated eggs to produce recombinant proteins. These egg recombinant technologies are designed to increase harvesting yields, reduce the cost of production and abridge the time of full-scale influenza vaccine production from 28 weeks (the standard timetable) to 20 weeks[6].

Overall, egg-based flu vaccine manufacturing has continually evolved, stabilizing egg supply variability, increasing vaccine yield, reducing human error, minimizing the incidence of bio-burden and raising production capacity.

MYTH #2: "EGG-BASED INFLUENZA VACCINE MANUFACTURING IS A MESSY, ERROR-FILLED MANUAL PROCESS"

As we have already seen, egg-based vaccine production has evolved beyond a completely manual process. Increased automation and advances in technology have now cut down on limitations caused by human involvement — physical manipulation, potential of increased bio-burden, damage to the egg supply and subjective evaluation of egg suitability. Nonetheless, egg-based production is often characterized as a primitive process marked by broken egg shells and spilled yolk.

In the past, manual operators trained extensively to recognize egg impurities and rejections before and after inoculation, but repetitive daily inspection innately led to increased error rates and longer inspection times. Another critical step inhibited by operator subjectivity was de-capping and egg-shell removal, an operation which repeatedly introduces bacterial contaminants into the egg harvest. Improper execution of these steps (e.g., incomplete de-capping, broken egg shells) can lead to loss of egg supply and deliver lower doses overall. However, new technologies in de-capping, candling and inspection systems (harvesting and inoculation) have increased automation while minimizing subjective operator assessments. As a result, these technologies enable egg-based vaccine

production to deliver high yields and ramp up production times. Operator handling has also been removed from the manufacturing equation and automation of the loading, transfer and delivery processes has reduced the incidence of broken eggs, spilled yolk and contamination.

For example, a recent project between RAME-HART and vaccine manufacturer MedImmune minimized human involvement from the vaccine manufacturing process, reducing the need for subjective operator decision-making from 100 percent to 10 percent[7]. The project resulted in a fully automated manufacturing line for egg-based vaccine production. Automating each operation from egg tray handling to candling reduced the facility's seasonal headcount by 25 percent. Instances of manual handling fell from 5,850 events per batch to four events per batch, and the facility increased production from 2,500 eggs per hour to 10,000 eggs per hour.

As egg-based vaccine technologies continue to advance, there will be fewer manual processes, less human errors and better harvest yields and production times.

BY INTEGRATING BIO-SECURE PROCESSES TO MINIMIZE THE RISK OF INTERNAL CONTAMINANTS AND PRECISE, AUTOMATED MANUFACTURING PROCESSES THAT MINIMIZE HUMAN INTERACTION, EGG-BASED TECHNOLOGIES ARE DELIVERING HIGHER VACCINE YIELDS.

MYTH #3: "THERE IS A GREATER INCIDENCE OF CONTAMINATION/BIO-BURDEN BY GROWING VACCINES IN EGGS"

Vaccine production carries distinct inherent elements of risk and safety. Development and production involves interaction with live viruses, pathogens and bacteria. In its final form, a vaccine must be proven safe for wide human application[8]. The egg-based method of vaccine production has had in place, for over 30 years, rigorous regulatory and compliance standards set forth by health organizations, but it continues to be mischaracterized as a "messy" process filled with greater incidences of bio-burden and contamination. Concerns over diminished vaccine yields stem from the health of livestock, the presence of trace-egg protein and bacterial contaminants (e.g., salmonella and campylobacter).

Advances to egg-based processes have become much more rigorous in recent years. Flocks associated with vaccine production are housed in air-filtered environments, kept under bio-secure regulations and examined using validated biological assays. Specific pathogen-free (SPF) eggs are sanitized and candled to remove infertile eggs and dead embryos, minimizing rejected candidates prior to incubation and manufacturing operations[9].

This challenge — directly managing the risk of virus and pathogen interaction while producing and ensuring a safe product — is not exclusive to the egg-based method. Cell-culture based vaccine technologies also encounter these obstacles. With cell-based vaccines, the cell substrates used to grow viruses possess tumorigenic and oncogenic potential, and it is this risk that has created regulatory limitations for wider cell-based vaccine application[6].

Egg manufacturing innovations have introduced greater efficiencies to the downstream process. RAME-HART's equipment has significantly reduced bio-burden and product contamination by automating key processes (e.g., inspection, inoculation, harvesting and cleaning), integrating these processes into an interconnected manufacturing line and minimizing operator involvement and assessment. These applications helped vaccine producer MedImmune increase harvest yield approximately 15 percent per egg harvested[7]. Furthermore, by integrating several automated processes into a single production line, operator interactions that previously led to contamination (e.g., de-capping, inoculation and harvesting) were virtually eliminated.

Behind long-standing regulatory safeguards, egg-based influenza vaccine production continues to progress. By integrating bio-secure processes to minimize the risk of internal contaminants and precise, automated manufacturing processes that minimize human interaction, egg-based technologies are delivering higher vaccine yields.

CONCLUSION

In the end, preserving global health in the face of seasonal or pandemic influenza outbreaks is not about the pursuit of one technology. Currently, egg-based influenza vaccine production is the strongest tool health organizations and nations can employ. Companies like RAME-HART are developing smarter technologies to improve the process and

give vaccine manufacturers a head start in rapidly delivering higher quality vaccines that keep the global population safe. In the event of a seasonal outbreak, or worse, a global pandemic, the egg-based platform is the preferred method of influenza vaccine production — in terms of scale, yield and safety — to provide communities adequate vaccine supply.

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Advanced Microscopy QbD Techniques Support Protein Therapeutics Manufacture

Microscopy techniques can be adapted to better understand protein aggregates and particles in protein formulations

By Vinod Jyothikumar,
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THERAPEUTIC PROTEINS have made an immense contribution to treatment of human diseases and represent an important part of the armamentarium available for this purpose. The life-saving benefits of products derived from recombinant protein technology, starting from the very first product insulin in 1982, have never been in dispute. Although this involves complex process than the traditional small molecule medications, proteins have the advantage of having a sustained half-life under physiological conditions; can be targeted to specific sites, and do not have the same concerns around metabolites generated during clearance in-vivo, resulting in fewer side effects. Initial protein therapeutics was hormones and growth factors that were designed, using the new tools of molecular biology, to replace the native proteins that were missing or nonfunctional in certain disease states.

MANY DEVELOPMENT CYCLES

Protein therapeutic products typically experience many development cycles, in which decisions are empirically derived concerning the identity, manufacturing process, final product presentation, and administration methods. To obtain a quality therapeutic product, significant resources are spent on the search for appropriate development parameters throughout a product's lifecycle. During the development cycle of protein therapeutics, it is critical to understand the physical integrity and other structural characteristics of the product. Once a protein drug candidate is selected, development is primarily focused on optimizing the parameters that effectively enable the manufacturing, packaging, storage and delivery of the final product. Before these parameters can be finalized for commercial processes, however, numerous analyses need to be performed to define the space and limitations of physical conditions that best fit the product.

Besides purification, the formulation development of protein therapeutics also requires a large number of experimental trials to select suitable conditions for final product presentation. The general aim is to find a formulation that will best retain the physical, chemical and biological properties of the product while meeting the desired shelf life requirements. More recently, patient convenience and comfort have become major factors that influence formulation development.

To derive suitable formulations, large arrays of factors are typically screened during the development phase for their ability to stabilize the drug product. Because it is well established that physical instability may negatively impact protein therapeutics, biophysical techniques offer relevant tools to monitor protein conformation in response to formulation and storage conditions. An important area of focus during

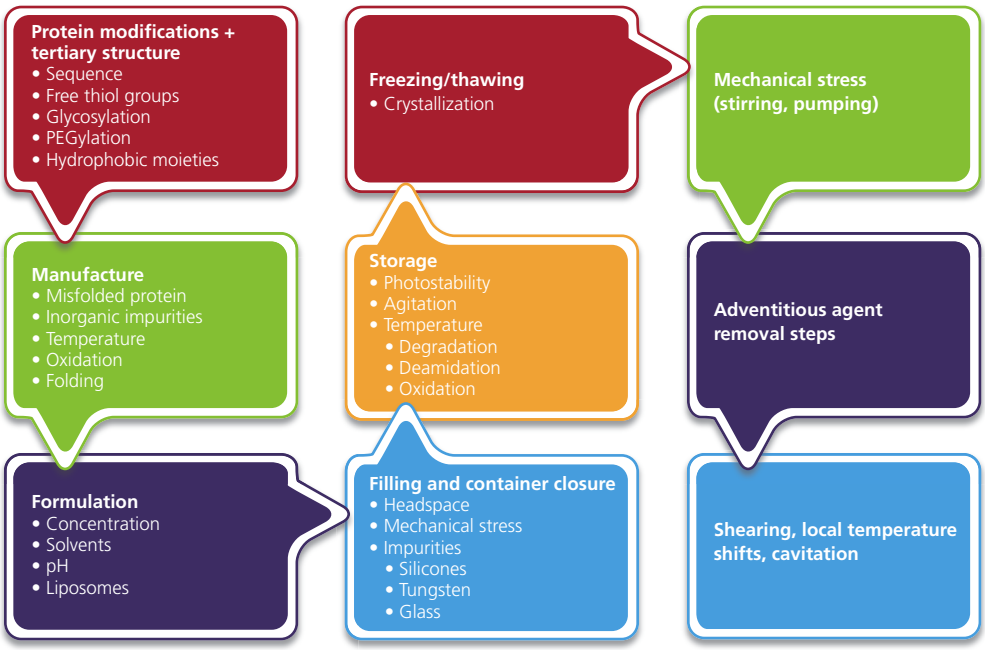

Figure 1: Factors contributing to aggregation during the manufacturing process and product development.

formulation development is the evaluation of protein aggregation propensity. Protein aggregates are thought to often impose detrimental effects on the therapeutic potency and side effect profile of the drug which may even lead to significant clinical safety concerns. As a result, protein aggregation is frequently used to differentiate formulation candidates.

Aggregation in biotherapeutic products is often discussed in conjunction with risk for immunogenicity, although a clear connection between the two for protein therapeutics has not been demonstrated. Nevertheless, this concern has led the industry and regulatory authorities to use aggregation as a critical quality attribute for biologics. Forming aggregates is to some extent an inherent property of a protein. While significant advances have been made in the understanding of the pathways of chemical degradation of proteins, the same does not completely hold for aggregation pathways or mechanisms. In light of this, judicious process and formulation development research is performed to control the development of aggregates during the production and storage of the product. The success of this effort is evident from the number of biotherapeutic products that have been commercialized and found to have favorable safety and efficacy profiles. It is quite reasonable to assume that these commercial products contain a range of aggregate levels and associated subvisible particulates. The term "aggregates" covers a large variety of heterogeneous species from reversible to irreversible, native and nonnative, and from dimers to multimers that range in size from a few nanometers to visible particles in the hundreds of microns. Protein aggregates can be classified as follows:

- Conformation: native or non-native,
- Linkage: covalent or non-covalent,
- Reversibility: reversible or irreversible, and
- Size: soluble or subvisible or visible.

Drug development begins with the discovery of molecules that have shown the biochemical potential to treat illnesses. Based on manufacturability and potential profitability, drug candidates are then selected for optimization and, eventually, for preclinical and clinical trials. To ensure that sufficient material is available for the different phases, manufacturing is concurrently scaled up during this stage in process development. Also throughout these stages, all the data regarding drug safety, efficacy and manufacture is reviewed for approval by the corresponding regulatory agencies. Approval requires that the drug product is produced consistently and that it is safe and efficacious for its indication. Pharmaceutical process development and approval is still extremely lengthy, highly expensive and uncertain.

Pharmaceutical QbD is a conceptual framework for the development and approval of pharmaceutical

manufacturing processes that aims to build quality into the product at every stage of process development. Application of QbD principles to pharmaceutical process development is outlined in the Process Analytical Technology (PAT) guideline "PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance" by the Federal Drug Administration and in the guidance documents "ICH Q8 Pharmaceutical Development", "ICH Q9 Quality Risk Management" and "ICH Q10 Pharmaceutical Quality Systems" from the International Conference on Harmonization (ICH), which is an association constituted by the USFDA, the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency of Japan (PMDA) and several experts from the pharmaceutical industry. Implementation of QbD to pharmaceutical manufacturing processes is an information-driven process where all available knowledge on the drug product including, but not limited to, its therapeutic mechanisms, its process of manufacture and potential sources of variability is used to define a range of manufacturing conditions that will ultimately ensure product safety and efficacy when administered to patients. More specifically, the ICH guidelines define the following requirements for the implementation of QbD to pharmaceutical processes:

- Defining of the quality target product profile (QTPP)
- Identification of the critical quality attributes (CQAs) of the drug product
- Identification of process inputs that affect product CQAs
- Selection of the appropriate manufacturing process
- Defining of a control strategy

Biophysical tools often play an important role in these efforts by providing a faster readout when the protein product is subjected to a range of experimental conditions. Two areas during protein therapeutic development frequently employing high throughput biophysical analyses is downstream and formulation development. The goal of downstream development is to find the most suitable purification process so that it can be properly scaled to deliver commercial product. Although the final optimization usually takes place at scales similar to the commercial settings, small- scale and high-throughput approaches are often utilized to predict protein behavior. Protein aggregates can be characterized by single-particle microscope-based approaches (nanoparticle tracking analysis) and classic microscopy-based techniques (atomic force microscopy, scanning electron microscopy, and transmission electron microscopy).

During light microscopy analysis, particles in solution are drawn through a grid-lined filter, dried, and either observed by a standard light microscope or subsequently stained with fluorescent or non-fluorescent dyes to enhance resolution. Particles can then be counted manually or by automated methods. Advantages of staining protein aggregates include enhanced detection of smaller particles and the selective binding of certain dyes to proteinaceous particles. Artifacts resulting from sample preparation, handling, and/or filtering are again the major pitfalls in using microscopy. In addition, particles <10 μm can be difficult to visualize and care should be taken to ensure amorphous or fibril shaped particles do not pass through the filter. Fluorescence microscopy can identify cells, cellular constituents, and particulate matter with a high degree of specificity and is rapidly expanding in use for pharmaceutical applications. The technique is used to study samples that can fluoresce either by themselves or after treating with fluorescent probes/dyes. Fluorescence microscopy can be very useful for the detection of subtle changes in the aggregation state of the proteins. Some of the dyes used to selectively monitor intermolecular β(beta)-sheet interactions often present among proteins that formβ(beta)-amyloid structures are Nile red, Congo red, and Thioflavin T. Covalent labeling of proteins with donor and acceptor fluorophores allows the use of total internal reflection fluorescence microscopy to image aggregated proteins.

NEWER INSTRUMENTS ARE NOW AVAILABLE THAT COULD PROVIDE AUTOMATED DETECTION OF PARTICLES THROUGH A MICROSCOPE IN A FLOW MODE.

Newer instruments are now available that could provide automated detection of particles through a microscope in a flow mode. Such a technique also referred to as micro-flow imaging (MFI), combines a flow-based cell with the microscope. As the sample slowly transverses the flow cell, bright-field images are illuminated by a 475 nm LED light source, magnified, captured by a digital camera, and then processed by the instrument software. Information about particle counts, size and morphological characteristics can all be obtained from MFI measurements. Since MFI does not rely on the blockage of light, translucent protein particles are more

readily detected and included by this analysis. Another advantage of MFI is that it can distinguish between silicone oil droplets, air bubbles and protein aggregates based on morphological characteristics. Nanoparticle tracking analysis [NTA] is a laser-illuminated-based microscopy technique that detects and sizes submicron particles in the range of ~50–1,000 nm moving under Brownian motion. With knowledge of the viscosity and temperature of the sample, the instrument calculates the diffusion coefficient that can then be used via the Stokes–Einstein equation to calculate the hydrodynamic size. Several groups to detect protein aggregates and particulates that have not been accurately analyzed previously are assessing this new analytical technique.

ATOMIC FORCE

An atomic force microscope (AFM) consists of a cantilever with an ultra-sharp tip (probe), a sample stage, and an optical deflection system. During AFM measurements, the cantilever is brought into close (atomic) contact with the sample and scanned across the surface (contact mode). The interaction between probe and sample, which can include mechanical contact, van der Waals, capillary, electrostatic, and/or magnetic forces, causes the bending of the cantilever which is precisely recorded by an optical deflection system. The scanning is done under feedback control so that the bending of the cantilever remains constant to maintain a constant force. The up and down motion of the sample is a record of the sample topography. In the tapping mode, which senses the oscillation amplitude of cantilever instead of bending, AFM generally causes less damage to sample. For analysis of biological materials such as protein aggregates, tapping mode AFM is preferred. One key limitation of AFM is it can only analyze a small fraction of the total sample volume at any one time.

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are standard tools used in biological research to examine a wide variety of samples due to their high resolution. Both SEM and TEM can also be used to characterize protein aggregates in the submicron size range. These techniques use an electron beam to bombard a specimen and generate various types of electron scattering. In the case of transmission electron microscope (TEM), electrons that go through a specimen (forward scattering) are collected and analyzed to provide image-based information on sample size and shape. The scanning electron microscope (SEM) collects the secondary and backscattered electrons to provide data not only on 2D sample size but also surface topology. Sample preparation remains a challenge for TEM and SEM in terms of ensuring the size and morphology of the sample do not change during preparation and analysis. Fortunately, recent advances in cryotechniques can minimize such problems by analyzing samples in the frozen liquid state. TEM and SEM analysis is also limited by sampling frequency, requiring acquisition of numerous images to provide a representative analysis of the sample to determine particle number and size.

By combining Fourier transform infrared (FTIR) detection with optical microscopy, compositional analysis of particles/aggregates down to 10 µm (micrometer) in size is possible. FTIR spectroscopy is also a powerful tool to analyze protein secondary structures and conformational dynamics. When combined with microscopy, this technique provides added information to analytical results that cannot be obtained by spectroscopy or microscopy alone. Another advantage of FTIR microscopy over conventional FTIR spectroscopy is that it permits the collection of an IR spectrum from a small sample area. FTIR microscopy is both a sensitive and potentially comprehensive method to help understand the nature, composition and morphology of the sample examined and has wide applications in the areas of forensic, biomedical and pharmaceutical sciences. One new application of FTIR microscopy is chemical mapping and imaging. The instrumentation required to obtain reliable IR chemical images has only recently become available. With this technology, multi-component systems can now be mapped and the location, nature, shape and size of each material present can be visualized through these chemical images.

The focus of this article is to bring out the various advance microscopy techniques that can be adapted to better understand the number, size range and composition of protein aggregates and particles in protein formulations. It is well recognized that no one analytical measurement can detect all types and sizes of protein aggregates. Utilizing better analytical methods along with an enhanced understanding of protein aggregation pathways should ultimately lead to important improvements in the impurity levels and long-term stability of protein formulations. Microscopy QbD may benefit protein therapeutics, because an increased understanding of product stability and enhanced product quality should enable the initial submission of less extensive stability data.

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e. Total Non-requested Distribution (Sum of 15d (1), (2), and (3))	6,219	6,229
f. Total Distribution (Sum of 15c. and e.)	19,786	19,729
g. Copies Not Distributed	959	841
h. Total (Sum of 15f and g)	20,745	20,570
i. Percent Paid and/or Requested Circulation (15c divided by f times 100)	68.57%	68.43%

16. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the November 2013 issue of this publication.
17. Signature and Title of Editor, Publisher, Business Manager, or Owner

Jeremy L. Clark, VP of Circulation Date 9/30/13
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).

PS Form 3526-R, September 2013

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