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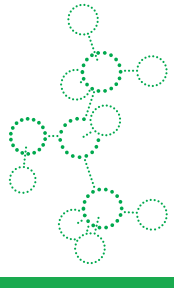

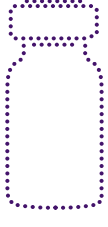

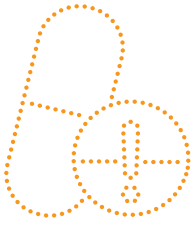

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An Injection a Day

Premature promises about cell therapies create expectations ripe for disappointment

THE PHRASE "an apple a day" has been referred to as everything from a proverb to a superstition to a Prohibition-era marketing slogan (if people can't drink apple whiskey, encourage them to eat apples).

While multiple theories about its origin exist, the prevailing one says the phrase dates back to 1866, when it appeared in an academic correspondence magazine as, "Eat an apple on going to bed, and you'll keep the doctor from earning his bread." Eventually, the phrase evolved to the more succinct version we are all familiar with: "An apple a day keeps the doctor away."

Whichever way you spin it, it's a pretty bold claim for 19th century medicine. While knowledge of the healthful properties of apples can be traced as far back as ancient Rome, there existed no clinical evidence in the 1860s (or now) that eating an apple could help a person completely avoid any and all medical issues.

Small fruit, big promises. Currently the same can be said for cell therapies. Around the world, there are clinics making dramatic claims about cure-all cell-based treatments, promising to heal everything from injured joints to multiple sclerosis to Alzheimer's. The problem is, the treatments they are using have not gone through regulated clinical trials. And as the unproven cell therapy market continues to grow, more and more patients are investing large amounts of money and the majority are walking away uncured.

Despite solid efforts from several industry groups, patients are still confused about the difference between unproven and proven cell therapies. If this confusion isn't addressed, it could become a problem that could ultimately stall research on legitimate cell therapy cures and discredit an entire industry on the brink of booming. As you'll read in this month's cover story, this is a fight worth waging, and pharma needs to join forces with those already invested in the battle and helping educate patients about what cell therapies can and cannot offer.

Over a century after the apple-a-day phrase was coined, there has been legitimate research applied to the theory. Actual scientific studies have linked the consumption of apples with reduced risk of some cancers, diabetes, high blood pressure and asthma. In a lab setting, apples have been found to have strong antioxidant activity, inhibit cancer cell reproduction and lower cholesterol. But even with all the proven benefits of apple consumption, an apple still does not guarantee anyone a doctor-free life.

Much to the relief of apple farmers and doctors alike, apples have seemingly survived a few overly enthusiast medical claims. But most promises made without regulated, scientific backing are likely to end in disappointment. And for emerging fields such as cell therapy, this disappointment can have dangerous and damaging consequences. It's more important than ever for the pharma industry to add its voice to the conversation, and make sure a few bad apples don't spoil the whole regenerative bunch.

BY KAREN LANGHAUSER, CHIEF CONTENT DIRECTOR
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Pharma Worlds Unite

Key trends highlighted at this year's CPhI Worldwide

AS THE most comprehensive event in the pharma world, CPhI Worldwide serves as a sort of barometer for understanding trends in the entire industry. This year's event, held in Madrid, was no exception.

As always, *Pharmaceutical Manufacturing* editors were in attendance to find out what pharma's top players had to say about the state of pharma and where the industry is headed next.

Here are some of the main points we gathered from lectures and meetings with CEOs and other leaders:

Softening the patent plummet: Companies haven't hit an innovation rock bottom just because their products fell off the patent cliff. There are still significant opportunities for innovation — including product development, process development, and new delivery mechanisms and devices. Proof of this progress was evident all throughout the show floors.

Pharma needs to be less conservative: Pharma frontrunners are looking to be bolder and more proactive in the way they embrace new technologies and processes, especially digitalization. This is going to be increasingly important as the biopharma sector explores new territories with gene and cell therapies.

Pharmaceutical Manufacturing editors, Karen Langhauser (left) and Meagan Parrish (right) along with publisher, Jim Baker, get dolled up for the CPhI Pharma Awards ceremony.

PHARMA COMPANY OF THE YEAR: NANOBIOTIX

THIS CPHI AWARD WAS GIVEN TO A COMPANY USING INNOVATING APPROACHES IN NANOMEDICINE-BASED CANCER TREATMENTS.

The ongoing image problem: The importance of the industry communicating its value and helping educate patients is still paramount.

Patient-centric manufacturing: Drugmakers are more frequently using patient feedback to aid drug development. Thus, pharma manufacturing is becoming a more personalized industry, where drugs are designed with the patient in mind from the start.

Integrating small and large molecules: This year's show brought with it the inaugural launch of bioLIVE, filling the large molecule gap that has existed in past events. Several speaker sessions highlighted the developments within the biologics supply chain, as well as the rise of biosimilars, and cell and gene therapies.

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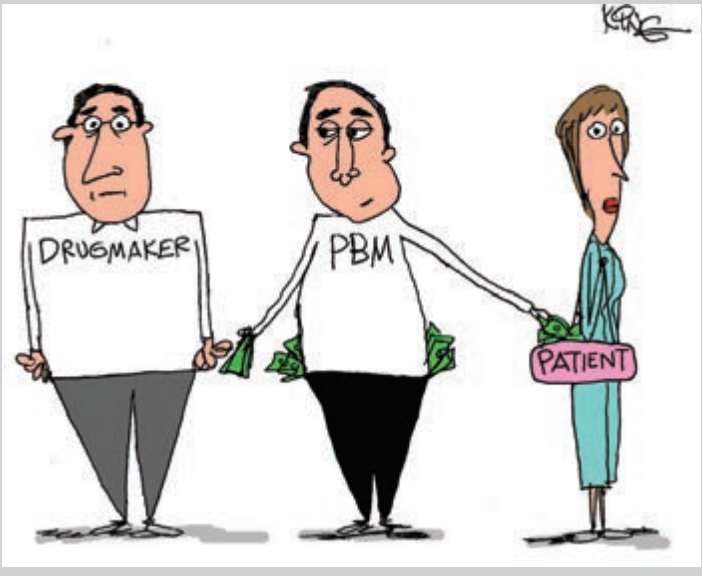
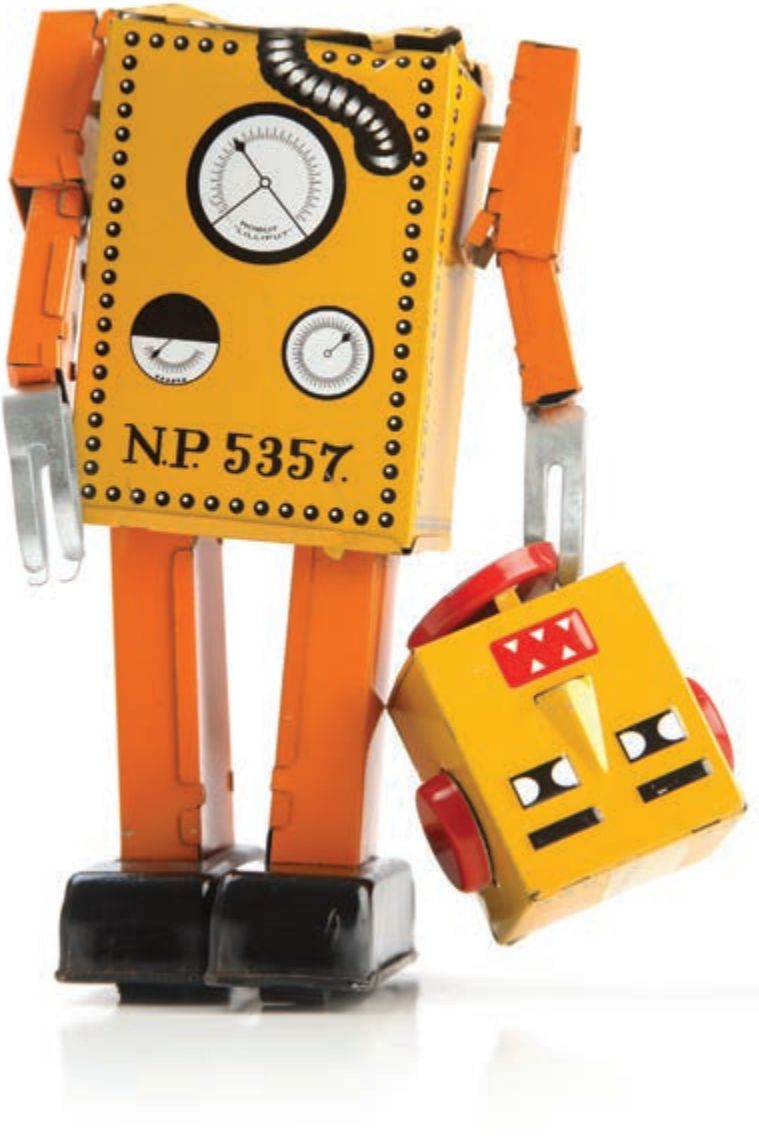


FUNNY PHARM

"It's a cash 22."
— Tim Feider

Funny Pharm comics, drawn by professional cartoonist Jerry King, appear on PharmaManufacturing.com. Readers submit suggested captions. To the left is October's cartoon and winning caption.



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BIOPHARMA MARKET: An Inside Look

Survey results reveal how slow-motion trends are driving biopharma growth

By Ronald A. Rader, Senior Director, Technical Research, BioPlan Associates and Eric S. Langer, President, BioPlan Associates

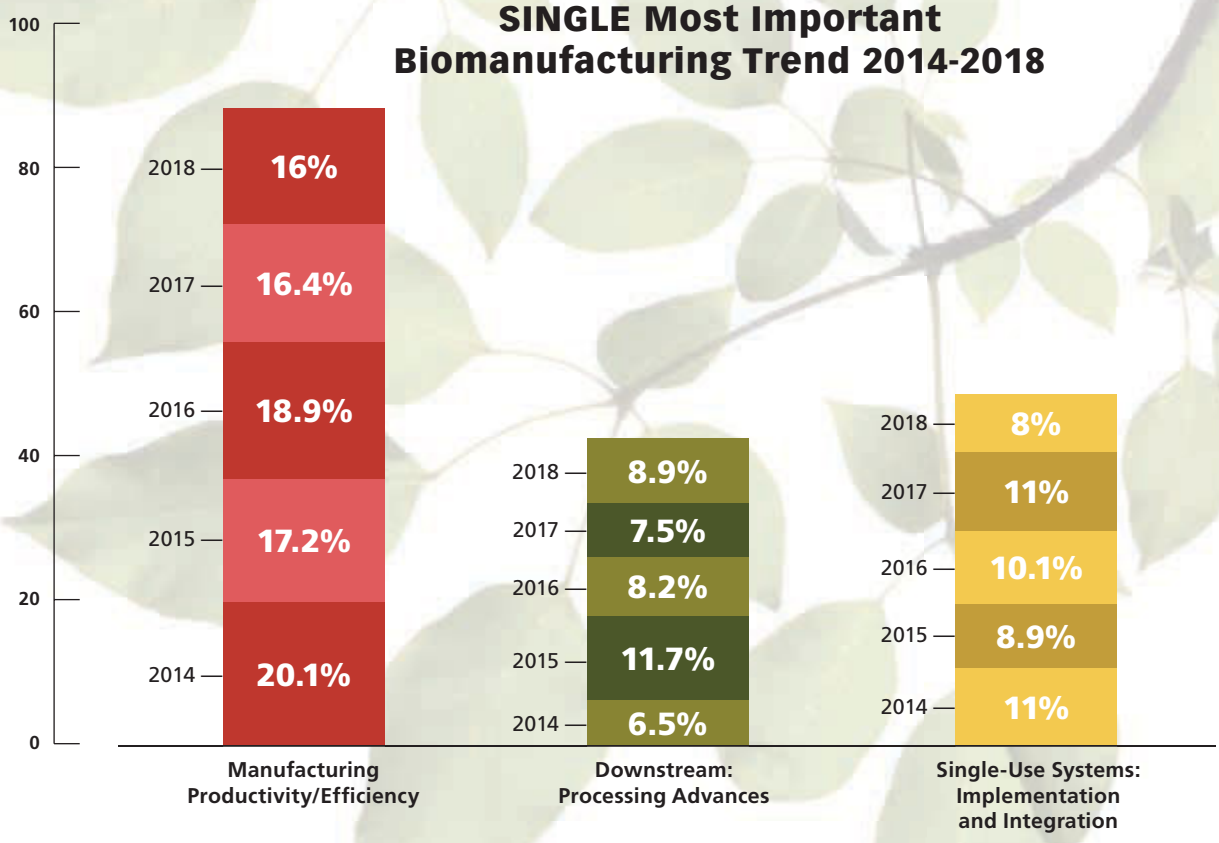
THE BIOPHARMA sector has seen incredible growth in recent decades, with growth the major long-term trend. Total annual revenue has increased from about $4.4 billion in 1990 to now about $275 billion, an increase of 6,250 percent, with biopharmaceuticals now more than 25 percent of the total pharmaceutical market.

For over two decades, the biopharmaceutical manufacturing industry has created a body of industrial knowledge and institutional experience. The sector can be considered mature, and the trends relatively stable. This can be good for future planning, and it can allow time for things like novel bioprocessing technologies to shake out glitches as they make it through the R&D and the regulatory pipeline. Of course, investors may not get nearly as excited about the molasses-speed of new product introduction, compared with other industries where inventions can make it to the market in months, rather than years. But the situation is much the same in the broader drugs (chemical substances as APIs) sector.

On the other hand, the bioprocessing market segment has grown remarkably consistently for the past 15 years we've been measuring supplier performance, at between 12-15 percent annually. Even when the data are broken out by growth in services, materials and equipment, the expansion shows notable stability; a good environment for risk-averse investors. This also matches the rate of growth in sales of biopharmaceuticals globally, as well. The upside of a highly regulated market that includes slow-motion trends is that its environment is relatively easy to track over time, and the data can be used to assess future movement more accurately.

This article presents trends and findings from BioPlan's 15th (2018) Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, and discusses the impact of some of our findings.[1] This survey and study provides a composite view and trends analysis from 222 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations in 22 countries, and includes over 130 direct suppliers of materials, services, and equipment. 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 major markets in the U.S. and Europe.

Exhibit 1



Source: 15th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity, April 2018

TOP TRENDS AND THEIR IMPACT

Despite the overall, slow-motion nature of the biopharma industry, the significance and impact of events most definitely affect decision-makers, strategy development and investments in new facilities and technologies. Because decision-makers are affected differently by diverse shifts and trends, there are no real "top trends," but rather, the trends have broad impact on the biopharma environment and how the industry responds.

The Importance of Manufacturing Efficiency and Productivity

This year when respondents were asked to choose the "single most important trend or operational area," the largest portion of respondents, 16 percent, cited "manufacturing productivity/efficiency," with this largely unchanged from last year (Exhibit 1). Over the past six years, we have consistently seen a high interest this area. This affects virtually all stake-holders. Suppliers need to gear their new technologies toward making biologics cheaper, better and faster. Biopharmas need to plan for the future now, and must decide if the facilities and equipment they own or specify will be future-proofed. Will what they do be efficient and still operating well enough a decade from now, using then likely legacy, inefficient technologies?

Bioprocessing Productivity Continues to Increase

This year, the average titer reported at both clinical and commercial scales was 3.20 g/L. Annual survey data and other sources confirm that bioprocessing efficiency and productivity, in terms of upstream titers and downstream yields, will continue to increase. BioPlan has reported rather steady increases in bioprocessing productivity, particularly upstream bioprocessing, over the past 30 plus years, since the first adoption of recombinant technologies.[2]

Biosimilars Bringing More Products and Players

Biosimilars/biogenerics are bringing many new bioprocessing players and facilities; and with these products facing considerable competition, cost-effective manufacturing is a basic requirement.[3] The Biosimilars/Biobetters Pipeline Database reports more than 1,000 biosimilars

(including biogenerics) in development or marketed worldwide.[4] There are now over 300 biogenerics marketed in lesser- and non-regulated commerce in developing countries, each of which could perhaps be upgraded for major market entry. Over 750 companies are involved in follow-on (biosimilar, biobetter and biogenerics) products, with many new entrants in both developed and developing regions.

Facility Constraints Create Bottlenecks

The factor most frequently cited (50 percent) as likely to cause capacity constraints at respondent facilities in five years (2023) was "facility constraints." This has remained the No. 1 cited factor since starting to ask this question in 2008.

"Develop better continuous bioprocessing — downstream technologies" was the area most commonly cited, by 42.2 percent as needing to be addressed to address (fix or avoid) future capacity constraints. Continuous downstream processing is also cited in responses to several other questions as needed and expected to resolve many of the current problems, with purification operations being the primary bottleneck in bioprocessing.

Lowering Manufacturing Costs

A majority of respondents continue to report efforts seeking to reduce bioprocessing costs, with 64 percent reporting that they have "implemented programs to reduce operating costs" at their facility within the past 12 months. Working to reduce bioprocessing costs has become a routine activity. This was the first year we surveyed about the cost/gram for recombinant protein manufacture. The average reported cost was $306.8/gram for respondents' primary recombinant protein product, usually a monoclonal antibody (Exhibit 2).

Supplier Growth

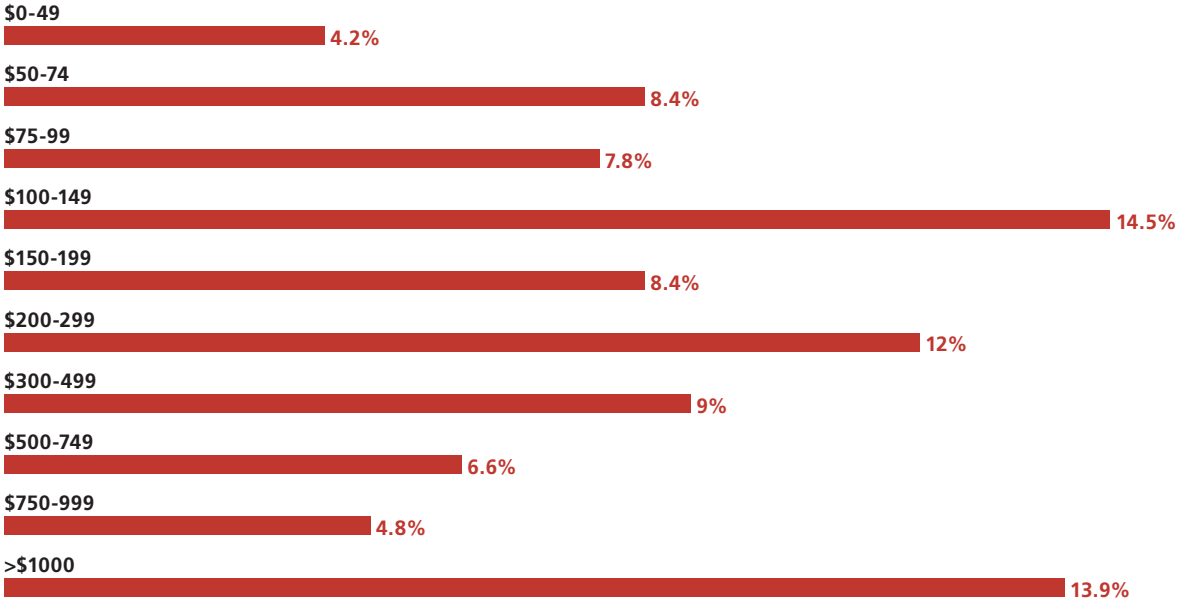
Besides overall annual growth in the industry generally being above 12 percent over the past 20-plus years, the equipment and supplies sector is reporting health and even better growth.[5] Surveyed supplier staff reported an average of 13.7 percent sales growth. "Equipment and instrumentation" took the top spot for growth with 16.8 percent average growth. Average growth reported in "raw materials and consumables" was 13.3 percent and "services (e.g., CMOs, CROs, consultants)" was 12.1 percent.

Bioprocessing Budgets are on the Rise

This year, no budget decreases were reported in any of the areas surveyed. Budgets for new capital equipment continued to be an area of significant growth, with respondents reporting an average increase of 8.2 percent in facility bioprocessing budgets for 2018. Much of this involves

Exhibit 2

DISTRIBUTION: Average Cost/Gram for Recombinant Protein Manufacture



Source: 15th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity, April 2018)

THE UPSIDE OF A HIGHLY REGULATED MARKET THAT INCLUDES SLOW-MOTION TRENDS IS THAT ITS ENVIRONMENT IS RELATIVELY EASY TO TRACK OVER TIME, AND THE DATA CAN BE USED TO ASSESS FUTURE MOVEMENT.

construction of new facilities, retrofitting, and the addition of capacity at existing facilities, (with an increasing number turning to single-use systems).

Single-Use Systems are Still the Rage

Again this year, over 90 percent of respondents reported currently using single-use equipment, with "tubing or disposable operations" alone cited the most, (90.6 percent), followed by "disposable filter cartridges," (86.2 percent) and "bags, empty," (81.8 percent). About 77 percent reported the use of single-use bioreactors. BioPlan estimates that more than 85 percent of pre-commercial product manufacturing now primarily involves single-use systems.

The Rise of Capacity in Asia

BioPlan's free database ranks the top 1,000-plus biomanufacturing facilities worldwide. The current breakdown of worldwide bioprocessing capacity includes:

- US/Canada: 6 million L (37 percent)
- W. Europe: 5.5 million L (33 percent)
- Asia Pacific: 4.7 million L (25 percent)
- China: 876,000 L
- India: 833,000 L

Overall, the fastest growth (from low baselines) is in Asia, particularly China.

China Becoming an Industry Leader

In a survey of 50 biopharma executives in China by BioPlan staff, the largest portion, 58 percent, cited a "more innovative biopharma pipeline" as what China must possess to expand globally. This was followed by 50 percent citing both need to develop an "overall quality image" and "capacity, commercial scale."

China has recently moved ahead of India in terms of bioprocessing capacity. Also, BioPlan's directory of the top 60 biopharma manufacturing facilities in China portrays an embryonic industry working to expand its GMP-quality manufacturing capacity to supply domestic needs while also aiming to becoming a major global player in innovative and follow-on biopharmaceuticals.[6]

IMPACTS OF TRENDS

Collectively looking at its past, current status and trends, the biopharmaceutical industry is very healthy, and continues to grow at its usual rather steady pace, with most growth-related parameters, such as industry revenue, generally annually increasing by about 12 percent or more. In fact, there are hardly any significant negative trends. Despite any industry-related growth rates below the norm considered by some in the industry to be negative growth or contraction (with about 12 percent growth so long the norm, it's considered the baseline), the roughly 12 percent annual biopharma industry growth rates are considerably higher than for most other established industries and the growth rates of developed countries. In the meantime, biopharmaceutical industry-related growth rates are even higher in the rest-of-the-world, particularly in the major Asian bioprocessing markets, although growth has only recently started from much lower or even near zero baselines.

The trends show that biopharma manufacturing is continuously growing, evolving, demanding and adopting (albeit slowly) new and improved technologies to reduce costs, increase efficiencies, improve product quality, and improve development pipelines. Ongoing industry trends support an optimistic vision of the future that includes more:

- Biopharma facilities worldwide, in both major markets and Asia
- Biopharma products
- Revenue and added-value for patients from innovations in products and processes
- Diversity in products in development and marketed, e.g., cellular and gene therapies

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- Efficient bioprocessing — titers and yields will continue to increase
- Use of continuous processing, including for downstream processing
- Automation, monitoring and process control
- Use of bioprocess modeling, data mining, PAT, QbD
- Use of high-tech expression systems and other genetic engineering advances
- Modular facilities, including cloned facilities in developing countries and for regional cellular/gene therapies manufacturing
- Complex regulations which drive many other specific needs, advances and trends

WHAT THE FUTURE HOLDS

The current situation in the biopharmaceutical industry is exciting, with new technologies and markets, such as continuous processing, biosimilars, cellular and gene therapies, and many new opportunities in emerging markets causing constant changes that must be adapted to.

Overall, the primary impetus for trends in bioprocessing is innovation. Innovation opens new opportunities and makes existing ones more attainable. It also speeds discovery, increases choices/options, and can drive down costs and improve productivity. The industry will see some (relatively) rapid changes in the coming years, including the rise of new classes of products, notably cellular and gene therapies; and expanded adoption of new(er) technologies, such as continuous bioprocessing. There will also be regulatory changes, such as more in-depth risk assessments related to leachates/extractables and other potential bioprocessing-associated risks to patients and staff.

However, changes in the bioprocessing sector, particularly any major advances and shifts in bioprocessing, take a long time. For example, it has taken over a decade for single-use systems to fully dominate pre-commercial biomanufacturing, despite the cost savings over stainless steel. Because new technologies are generally only adopted for new products, major changes in bioprocessing are inherently slow, generally take a decade or more. In the meantime, incremental innovation in improved manufacturing productivity continues. This ongoing adoption of new technologies, not dramatic paradigm shifts, is the general rule; and is the primary driver for many biopharmaceutical trends.

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SURVEY METHODOLOGY

THE 2018 FIFTEENTH ANNUAL REPORT AND SURVEY of Biopharmaceutical Manufacturing Capacity and Production yields a composite view and trend analysis from 222 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 22 countries. The methodology also included over 130 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 major markets in the U.S. and Europe.

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Bio's Bad Apples

Can unproven therapies spoil the sector's sweet success?

By Karen Langhauser, Chief Content Director

FEW WILL dispute the enormous potential of cellular therapy — and for patients suffering from vision loss, leukemia or lymphoma who have had life-changing experiences with these new treatments, cell-based therapies are nothing short of a miracle.

Although they lack a globally harmonized classification system, cell therapies fall under the broad umbrella of regenerative medicine. There are several types of cells that can be used for cell therapy and the type of cells administered depends on the treatment. Collectively, these therapies are heralded for their ability to promote the repair of diseased, dysfunctional or injured tissue. What this ultimately means is that cellular therapies offer the potential to treat conditions for which few, if any, treatments exist.

Around the world, there are clinics making dramatic claims about cure-all cell-based treatments that have not gone through regulated clinical trials — which means their safety and efficacy has not been proven to regulatory bodies. If this confusion surrounding cell therapies isn't addressed, it could become a problem that ultimately discredits a whole industry on the brink of booming.

It is estimated that the unproven cell therapy market is currently worth $2.4 billion and treats approximately 60,000 patients annually.[1] While it's difficult to identify exactly how many clinics exist, a 2016 analysis of online direct-to-consumer marketing activity in the U.S. found 351 distinct businesses offering interventions at 570 physical locations — and this number has undoubtedly grown.[2]

But when it comes to cell therapy, "potential" is still the key word in the discussion. Currently, the only stem cell-based products approved by the U.S. Food & Drug Administration consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood — and there are fewer than 10 of these products on the market.[3] Kite Pharma, Novartis and Dendreon hold the only immune cell therapy approvals in the U.S. This is likely to change in the future, however. According to the FDA, there are nearly 800 active cell therapy Investigational New Drugs (INDs) on file with the agency.[4]

The potential for miracle cures also brings with it the potential for large financial gain, which has sparked the growing private interest in the cell therapy space. While the pharmaceutical industry might be quick to dismiss these bogus cell therapy clinics, the unfortunate reality is that the general public is still confused. And in that confusion arises a genuine concern that the popularity of unproven cell-based therapies will have a negative impact on the future of legitimate, science-based cellular therapies — which is an issue the industry should not dismiss.

FDA DOING ITS PART

The FDA is not ignoring the rise of unproven cell therapy clinics and has acknowledged the role that regulatory gaps have played in the proliferation of direct-to-consumer cell therapy treatments.

In August 2017, the agency stepped up its efforts to enforce regulations and oversight of stem cell clinics. When this was announced, FDA Commissioner Scott Gottlieb acknowledged that new, complex therapies are challenging the traditional approach to regulations.

"The field of regenerative medicine, because of the very nature of the science and the rapidly evolving clinical developments, not infrequently lends itself to often close calls between what constitutes an individualized treatment being performed by a doctor within the scope of his medical practice on the one hand, and what constitutes a medical product that is currently subject to the authorities Congress has already charged the FDA with exercising," said Gottlieb.[5]

Part of the allure of unproven cell therapy clinics is that they promise to solve unmet medical needs. When a potential cure to an ailment is tied up in the FDA approval process, patients are more

likely to seek help elsewhere. In order to find a balance between safety concerns and innovation, the FDA made a major move in November 2017 to modernize product licensing pathways by introducing an additional expedited program in which a product could be designated as a regenerative medicine advanced therapy (RMAT). The expedited RMAT program — like the fast-track designation, priority review, accelerated approval, and breakthrough therapy designation that were introduced a year prior with the 21st Century Cures Act — is now helping to speed the development of new regenerative therapies, particularly those aimed at life-threatening conditions.

Last May, the FDA stayed true to its promise to increase oversight and enforcement to "protect people from dishonest and unscrupulous stem cell clinics"[6] and sought permanent injunctions against clinics in Florida and California after they failed to address violations outlined in FDA warning letters, including serious cGMP violations.

GOOD GUYS DON'T ALWAYS WEAR WHITE HATS

Unfortunately, the pharmaceutical industry continues to struggle with its image problem. Many patients still perceive the pharma industry as impersonal and rapacious. Unproven cell therapy clinics are capitalizing on this stigma, and creating environments that appear to be warm, welcoming and highly personalized.

"Providers of unproven cell are seen as entities which are really taking care of patients versus pharma, which is perceived as unconcerned with personal needs. Pharma is seen from the patient perspective as more concerned about business, while unproven cell therapy clinics seem to be the good guys — which, in reality, is the opposite of the truth," says Massimo Dominici, M.D., associate professor of medical oncology and head of the Laboratory of Cellular Therapies at University/Hospital of Modena, Italy.

Formerly serving as the president of the International Society for Cellular Therapy (ISCT), Dominici is now chairing the ISCT Presidential Task Force on the Use of Unproven and/or Unethical Cell and Gene Therapies. Established in 1992, ISCT is a growing global organization of clinicians, regulators, researchers, technologists and industry partners dedicated to translating cell and gene therapies for the benefit of patients worldwide. Its unproven cell therapy task force is a major player in the fight to characterize unproven and unethical cell and gene interventions, and promote safe and effective practices worldwide.

What it comes down to is that unproven clinics are doing a much better job of branding themselves. One Connecticut-based clinic's website, for example, features personalized testimonials as well as the Buddhist quote, "When love meets pain it becomes compassion."

"The marketing around unproven clinics is quite similar to that of five-star hotels. Essentially this is what people are looking for and how they want to be treated," says Dominici. "But at the end of the day…it's fake."

THE DANGERS ARE REAL

The most obvious danger linked to unproven cell therapy treatments and clinics is patient safety. Without a detailed evaluation of the manufacturing facility and process, there's no way to assess the general safety and risk factors of a specific cell therapy product. And without going through the proper channels outlined by registered clinical trials, there's no standard for logging, reporting or following up adverse events — and plenty have occurred already.

So far, there has been several cases of poor outcomes linked to unproven cell therapy treatments performed in clinics including documented deaths, a patient who became blind due to an injection of stem cells into the eye and another patient who grew a spinal tumor after receiving a spinal cord injection.

There is also a certain degree of psychological harm that can come from unproven treatments related to side effects, possible financial loss (treatments can cost up to $40,000),

WHAT IS AN UNPROVEN CELLULAR THERAPY?

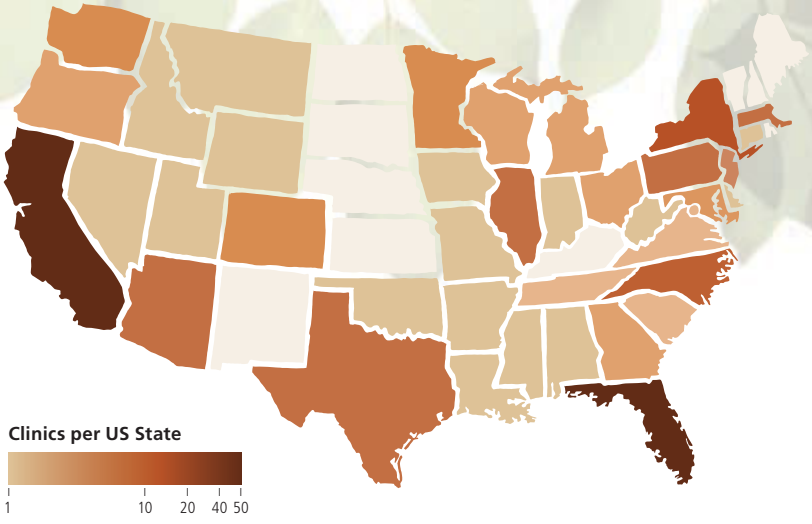
- Unclear scientific rationale to suggest potential efficacy
- Lack of understanding of the mechanism of action and/or the biological function to support clinical use
- Insufficient data from in vitro assays, animal models and clinical studies regarding the safety profile to support the use in patients
- Lack of a standardized approach to confirm product quality and ensure consistency in cell manufacturing
- Inadequate information disclosed to patients to enable proper informed consent
- Use within non-standardized or non-validated administration methods
- Uncontrolled experimental procedures in humans

Positioning a Scientific Community on Unproven Cellular Therapies: The 2015 International Society for Cellular Therapy Perspective

and unrealistic expectations that do not yield tangible results.

Not only do safety and ethical issues negatively impact patients — they also affect the future of the entire cell therapy community. Negative experiences with unproven cellular therapy can erode financial confidence, which could restrict investment decisions.

"Unproven cellular therapies, which are marketed as safe and effective, can have a destabilizing influence on financial sector confidence that emerging cell therapies are well-founded and ready for development," stated ISCT in its latest reference guide.[7]



Top five states: CA (49), FL (35), NY (15), PA (11), and AZ (10). (No sites were recorded in HI or Alaska)

Courtesy of Stem Cell Reports, ISSCR

WHAT CAN PHARMA DO?

When it comes to the fight against unproven cell therapy treatments, pharma's voice is somewhat missing from the battlefield — and this might actually be a wise approach.

For pharma, part of the solution involves a cultural shift. The industry has already begun to realize that in this new era of personalized medicines, it is necessary to interface with patients much earlier in the drug development process and continue that relationship all the way through commercialization. This approach will invariably generate higher levels of patient trust, which in turn will help improve pharma's "bad guy" image.

But cultural shifts don't happen overnight, and the issue of unproven cell therapies is immediate. So why are the drugmakers who are investing millions of dollars in the development of legitimate cell therapies not fighting back?

Because the issue is a delicate one, and has to be dealt with carefully, explains Dominici. In a situation where patients don't entirely trust the pharma industry, fueling the fire may just make things worse.

"Yes, I would call for bigger commitment from pharma, but not alone. If they stand up by themselves, they risk fire-back. This is why the involvement of organizations like ISCT is so important," says Dominici.

Third parties, such as ISCT, are already hard at work raising awareness of the dangers of unproven therapies. Pharma's collaboration with such organizations is crucial, and will allow drugmakers to add their voices to a trusted, unified front against unproven therapies. Partnerships that include academia, industry, regulatory bodies and patient advocates will enhance credibility and minimize potential concerns about an industry-biased conflict of interest.

The ISCT Presidential Task Force on Unproven Cell and Gene Therapy is working towards a series of initiatives, including establishing a global, publicly-accessible, cell therapy patient safety registry and providing additional tools to patients that can be used as guidance in evaluating a potential treatment.

"Teaching and communication — not policing — are key," says Dominici.

Around the world, drugmakers are expanding cellular therapy portfolios, putting their faith in the future potential of this emerging class of therapies. A collaborative, concerted effort from all parties is needed to ensure that the true potential of cellular therapies is not lost in the shadows of unproven treatments.

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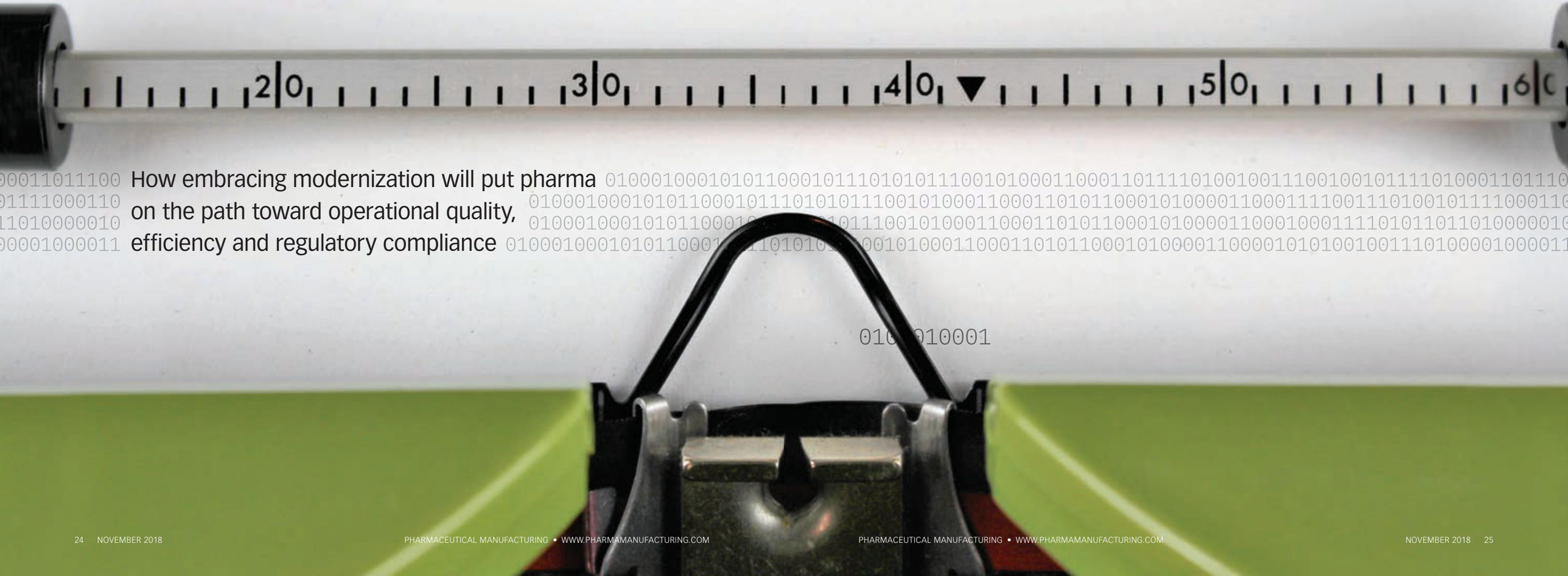
Disrupting the Status Quo of **Legacy Systems**

By Tim Gellner, Senior Consultant,
MAVERICK Technologies

How embracing modernization will put pharma on the path toward operational quality, efficiency and regulatory compliance



TO KEEP pace with the ever-changing world of regulatory compliance, pharmaceutical manufacturers are faced with modernizing their legacy control systems to optimize performance. Emerging technological advancements, such as data collection and analysis tools, are helping facilities make more informed data-driven decisions and meet regulatory requirements.

Many facilities, however, have yet to take advantage of the latest tools and techniques available, relying instead on traditional methods that continue to run on legacy computing power. Change is hard. There are many unanswered questions that arise when facing the daunting prospect of modernization. Uncertainty and doubt can stop forward progress, creating risk as processes run on aging platforms or equipment.

For those in the uncertain category, let's look at modernization from a different perspective: Why should you upgrade or enhance legacy process control systems and data collection equipment at all? What gains will be made? Your existing system works, so why mess with it given the combined expense of the equipment, engineering, installation and validation? Many facilities have been running their production processes for years, creating and storing printed reports, paper strip charts, etc., then dragging it all out when a compliance audit occurs. It works … mostly.

So, what has changed that requires us to change?

DRIVERS OF CHANGE

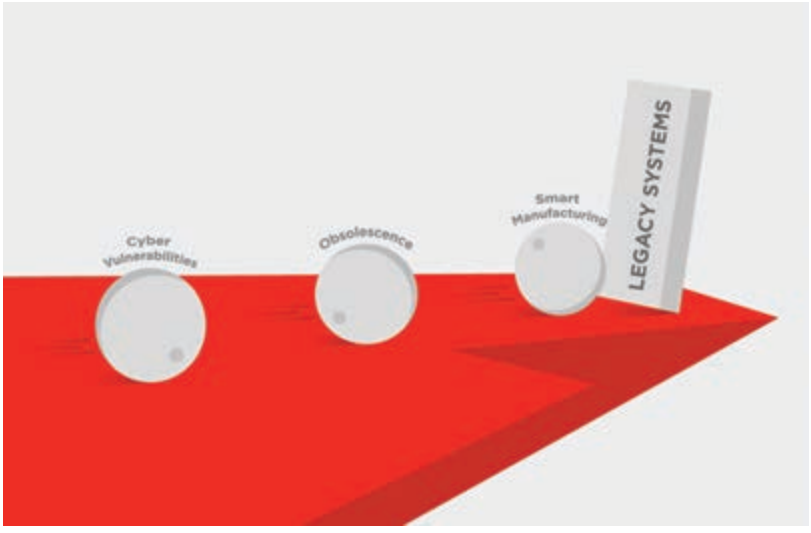
With respect to modernization, there are typically three primary areas that drive change:

- Cyber vulnerabilities
- Smart manufacturing
- Obsolescence

Cyber Vulnerabilities

Many in the life sciences industry have enrolled in the United States Computer Emergency Readiness Team (US-CERT) program, and receive regular alerts detailing the latest identified vulnerabilities in industrial control system (ICS) components and software. A large percentage of the alerts contain this disconcerting statement: "ATTENTION: Exploitable remotely/low skill level to exploit." This kind of vulnerability presents a seemingly good argument for not having modernized and connected control systems. After all, you can't hack a filing cabinet, remotely anyway.

One flaw in this argument, however, is that legacy systems are connected, typically residing on flat network architectures. Legacy process control networks were originally reasonably secure, because they served a very limited purpose: They provided inter-processor communications where needed, gave operators the ability to monitor and interact with the control system, and served data to the process historian. Basically, if left to themselves (isolated from the outside world), this works. Over the years, however, some very ingenious tools and techniques have been devised to expose process data to the business layer, and this is where the vulnerability problem lies. In the new connected enterprise world view, some very comprehensive technology is available that provides centralized tools for securing, managing, versioning, tracking and reporting automation-related asset information. This automated asset management software enhances visibility into all aspects of the network and control systems hardware and software. It provides real-time information that can impact uptime, productivity, quality and regulatory compliance.



Smart Manufacturing

Smart manufacturing is not as much a revolution as it is the realization of the benefits provided by the advent of the connected enterprise and big data. From the control system perspective, smart manufacturing had its beginnings with the first distributed control systems (DCSs) and programmable logic controllers (PLCs) in the 1980s. In many instances, these control systems (dating mostly from the mid to late 1990s) are still in use today. Unfortunately, these systems generally lack the interoperability, capacity and structured data that is needed as a foundational piece of the smart manufacturing construct. Additionally, these systems are not designed with the degree of security required in today's cyber landscape.

Whether or not pharmaceutical manufacturers embrace the entirety of smart manufacturing, there is ever increasing pressure from the business side of the fence for more data from the manufacturing layer. They want access to data that can be delivered in real-time, is actionable, and complete to facilitate collaboration among employees, suppliers and customers. This information ensures the right products can be delivered at the right time: safely, profitably and in the correct quantities.

With the arrival of big data and advanced analytics, we now have process data, maintenance data, logistics data and product data (a company's intellectual property) making up the constellation of interesting information about industrial assets. This data is sensitive by nature, containing information that could, if maliciously obtained, be very damaging to a company. This new data paradigm requires building in more thorough security at every level to address the sensitive nature of industrial data. To accomplish this, we are forced to revisit the network architecture and infrastructure of our facilities and enhance or, more likely, upgrade the control systems to support the cyber security and data model requirements. If we take a wait-and-see approach, we are faced with outdated systems and the potential for catastrophic consequences.

Obsolescence

In today's digital world, the speed at which technology changes increases exponentially. Just look at the computing power in our handheld

devices. How often do we find ourselves upgrading to the latest operating system or buying a new device just to accommodate more mobile apps, gaming and entertainment capability and other bells and whistles? When we don't upgrade, we experience slow data connections, compatibility issues and communication challenges.

The life sciences industry is facing similar pressure to upgrade and modernize. Customer demand and new innovative technologies, such as the Industrial Internet of Things (IIoT), cloud and mobile computing, open architecture, and advanced data analytics, are driving change. Without compatible systems to run these technologies, your facility will be hard-pressed to improve quality and efficiency to meet compliance regulations and stay competitive. You may believe maintaining the status quo is the best option. As your systems age, however, you run an increased risk of unplanned downtime as components fail. Sourcing spares for these systems becomes difficult as OEM support comes to an end. The cost of maintaining legacy systems can approach the cost of an upgrade or full modernization, without realizing any of the benefits gained from upgrading.

Add to this issue the specialized operational knowledge required to monitor and maintain these legacy systems. What happens when long-term experienced engineers leave or retire? Without a way to efficiently capture and transfer this knowledge to new employees and the next generation, this undocumented tribal knowledge may be lost and can lead to operational challenges and therefore significant cost. You will need to attract and retain new talent who relate better to a modern workplace. To this end, you will need to use smart, flexible and open systems, running new technology, to move forward.

TECHNOLOGY FOR COMPLIANCE SAKE

The primary areas that drive change also compel us to embrace it. For pharmaceutical manufacturers who have been working within regulatory constraints for years, it is hard to change validated processes and shed regulatory uncertainty. Process analytical technology (PAT) practices have made improvements easier

to implement but changes are still complex. Those who rise to meet these challenges and take advantage of new standard requirements (e.g., 21 CFR Part 11), smart manufacturing technologies, data tools and techniques, and new platforms will benefit, especially in meeting compliance requirements.

Compliance with FDA regulations and current good manufacturing practice (CGMP) standards depends on smart instruments to extract data that is, again: accurate, actionable, timely and complete. This is particularly important when considering product/process geology records. If modernization is implemented properly, you can know everything that happens when executing a batch, order and the like, depending on the facility. This includes everything that goes into the product, what equipment is used, who is involved, how long it takes, whether there are any deviations, whether a clean in place (CIP) is required and whether it was executed, who did it, did it conform to the required specifications, were the necessary lab tests run, what are the results and on and on. Also, just as important, can I access this information quickly? Can I provide compliance reports to auditors with everything they need when they need it? These questions and others concerning product and process genealogy can be easily answered in a timely fashion with the thoughtful implementation of both upgraded control systems and data analytics infrastructure.

FORWARD PROGRESS

Modernization is inevitable and necessary to stay competitive. To start the journey, you need a clear path forward to help get past the fear of disrupting the status quo. Of course, many factors must be weighed and considered when upgrading legacy systems and technology, such as standard requirements, equipment inspection, validated processes, quality documentation, supply chain traceability and more.

Embracing technological change gives you a real competitive advantage and can start you on the right path toward operational quality, efficiency and regulatory compliance.

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RISK MANAGEMENT FOR REGENERATIVE MEDICINE DISTRIBUTION

By Mark Sawicki, Chief Commercial Officer, Cryoport

Pharma faces an urgent need for new clinical product distribution and logistics standards

REGENERATIVE MEDICINE will soon be the standard of care for replacing tissue/organ systems in the human body, according to the United States Department of Health and Human Services Report, "2020: A New Vision—A Future for Regenerative Medicine." The impact of this shift will be huge. For instance, a definitive cure for heart-valve disease in the U.S. alone would provide an annual cost savings of $23.4 billion.[1]

Reaching that potential has been anything but a simple task. Manufacturing cell-based therapies is expensive, and companies have faced considerable challenges to achieve standardized quality using methods that are scalable and sustainable.[2]

Still, all of that expense and effort will be for nothing if the product is damaged or destroyed while in transit. Protecting the product in the last mile is every bit as important as how it is protected during every other step.

THE NEED FOR UPDATING

The emergence of regenerative medicine as a viable therapy class has amplified the focus on current clinical product distribution standards and the need for enhanced requirements that parallel current manufacturing standards in the industry. The regenerative medicines market generated $17.03 billion in revenue in 2016 and is expected to reach $50.55 billion by 2025.[3]

The fragility of RMAT products is not what past supply chains were built for. The industry is seeing accelerating clinical progression for personalized therapies for diseases from hemophilia to cancer in as little as four years. This timeline compression has placed enormous pressure on existing supply chains, which were never set up to effectively manage risk for a drug product that is modified for a single individual — and in most cases does not have back-up doses if something goes wrong during transport or storage.

Clearly, the industry faces an urgent need for new clinical product distribution and logistics standards as robust as the standards for manufacturing.

One common observation is that current cold-chain container qualification and management processes are insufficient in effectively managing risk during personalized medicine distribution. Basic requirements outlined in 21 CFR 210 and 21 CFR 211 for traceability of equipment utilized in the manufacture and storage of drug substance and drug product must be implemented and utilized in the drug distribution space.

To that end, both the Alliance for Regenerative Medicine (ARM) and the Foundation for the Accreditation for Cellular Therapy (FACT) have instituted review bodies to look at all aspects of the collection, manufacture, transportation, and administration of regenerative medicines.

Moreover, emerging Chain of Compliance requirements for regenerative medicine distribution are rapidly becoming the standard for ensuring product integrity.

THE CHAIN OF COMPLIANCE

Early on, the industry correctly understood traceability as links in a chain:

- Chain of Custody: Traceability of the custody of each client's or patient's therapy
- Chain of Condition: Traceability of the condition of each client's or patient's therapy
- Chain of Identity: Traceability of the identity of each client's or patient's therapy

But the fragility of RMAT products — and the urgent need for standardization — means that a fourth chain is now required: the Chain of Compliance.

This traceability can be addressed using Chain of Compliance processes which effectively manage this traceability. Chain of Compliance is establishing full traceability of the equipment and processes used in managing the environmental control of the commodity. This includes container performance and requalification history, commodity history, courier handling and performance history, calibration history, and correlation competencies that can link in field events to equipment performance. A review of these requirements are as follows:

1. *Container performance history:* All transportation equipment has a validated hold-time standard that can change over time for multi-use equipment. Data supporting an accurate calculation of the hold-time of a cold chain container might include the nitrogen evaporation rate, liquid nitrogen capacity, vacuum integrity, dynamic hold time, as well as the actual in field temperature, humidity, shock and orientation data.

2. *Commodity history:* In addition to the performance of the equipment utilized for a given shipment, a complete historical ledger of the contents shipped in any given container should be tracked so that one has the ability to determine if a given piece of equipment has only ever been used for the distribution of non-infectious human materials and can certify this history.

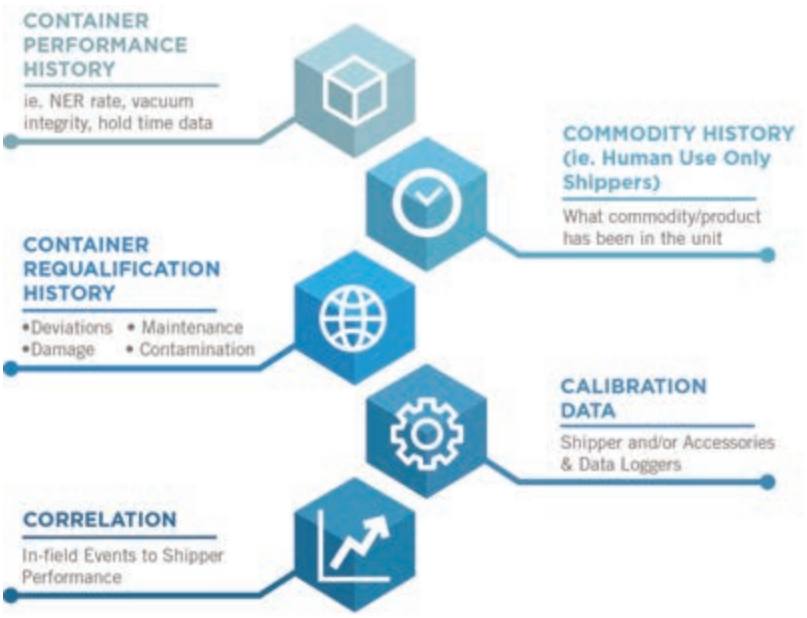
3. *Container (re)qualification history:* Additionally, one needs to have accurate records as to the requalification or testing of the performance of the equipment to be utilized. These records should also include any repairs or maintenance done to the equipment, any deviations or damage during use, as well as any contamination or sterility issues over the entire historical usage of the equipment in question.

4. *Calibration history:* All calibration data for any electronic components of a given package must also be traceable back to such equipment. This would include thermocouple calibration or validation data, battery performance, software or firmware updates by date and version, and serialized accessories that are archived by part number.

5. *Correlation:* Lastly, the ability to cross reference field handling events including shock, damage, delays, orientation and anti-tamper competencies to the impact on the commodity shipped is a key requirement. Additionally, one should be able to cross reference the historical custody of the tank as well. This would include all locations receiving the tank, as well as the courier for freight partners who were responsible for the delivery of the tank from origin to destination.

COMPLETE DATA

The reason that the FDA and other regulatory bodies are interested in Chain of Compliance is that it provides the ability to collect, interpret, and leverage comprehensive data, enabling a significantly more intelligent supply chain. Rather than reactively



trying to determine what has gone wrong after multiple failures, it becomes possible to take a proactive approach.[4] Moreover, effective implementation provides historical traceability of logistics processes, equipment and third party support entities, enabling one to critically assess its complete supply chain and minimize failures and risk.

What's more, having complete data gives you the ability to significantly reduce the risk of product failure. Robust data reveals patterns you can leverage year after year.

With a complete picture of every element and a data-rich understanding of how those work in the real world, you can apply Quality by Design risk management processes to your supply chain strategy. QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound sciences and quality risk management. Put simply, QbD yields better results than "Quality by Hindsight."

A STRONG RMAT SUPPLY CHAIN IN ACTION

What should companies demand from a modernized, RMAT-ready supply chain?

Obviously, there will be individual company-level differences but at a baseline level the following are necessary.

Unit Level Performance

This approach includes:

- Serialized packaging that tracks the performance of each unit.
- All equipment managed by a QbD process that incorporates risk due to transit related events.

Intelligent unit level tracking prevents commissioning of equipment that does not have requisite specification for the lane/commodity selected.

"Fuzzy Logic" Risk Management

A robust informatics package should provide:

- Proactive alerts (it's no good to open the dewar on arrival only to discoverer it has not been maintained at the correct temperature). Also, when alerts occur there should be clear, standardized SOPs for escalation: People need to know what to do when there's a problem.
- A method for correlating transit-related events to product integrity.
- Constant monitoring for deviations, exceptions and other handling events.
- A method to maintain historical carrier performance by lane and packaging.

Reporting

All reporting should:

- Be 21 CFR Part 11 compliant.
- Have a database that retains all transit and packaging records.
- Be capable of providing certification and performance reporting at the unit level.

REGULATION IS RACING TO CATCH UP

The pace of change in regenerative medicine can seem daunting. It demands a balance of speed and proactive management while carefully guarding against downside risk. Yet the promise to dramatically improve patient outcomes and create important new lines of business means there has never been a more exciting time to be part of this industry.

It's likely that regulations from the FDA will be established in the next 12 months. Not all companies will be ready to respond, but those that do will be positioned to leapfrog past competitors who take a wait-and-see approach.

Regenerative medicine is already revolutionizing the treatment of diseases, and promises to rapidly scale in the coming quarters, putting additional stress on supply chains used to distribute therapies that have no tolerance to excursions. Reconsidering or completely re-engineering your cold supply chain to support future regulation is entirely necessary — and worth the effort.

FIVE ESSENTIALS FOR EFFECTIVE CHAIN OF COMPLIANCE IMPLEMENTATION

1. Continuously track individual equipment performance.
2. Track and archive what's being put into your equipment and who is moving it.
3. Ensure you have comprehensive (re)qualification and maintenance records for your equipment.
4. Integrate all four chains — custody, condition, identity, and compliance — into a single data stream for cross-referencing and accountability.
5. Insist on world-class informatics, and real-time integrity measurements.

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PHARMA TRAVEL LOG:

Holland Highlights

Top five sights from our Netherlands biopharma industry tour

By Meagan Parrish, Senior Editor

MAYBE IT'S the small land area and dense population. Maybe it's the long history of meeting global challenges with major innovations. Or maybe it's all the good cheese. Whatever the case, the Netherlands has, for decades, been one of the top countries for big ideas and scientific collaboration — and the same holds true for pharma.

Although the Netherlands is roughly the size of Maryland, its biopharma scene packs a big punch in the industry. According to the Netherlands Foreign Investment Agency, the country is home to about 2,500 life sciences or medical technology companies and research organizations.

This fall, *Pharmaceutical Manufacturing* was invited on a whirlwind press tour of the country's biopharma industry that included meetings with dozens of innovative startups and established pharma companies, as well as tours of world-class R&D institutes. All told, the tour covered six cities in three days and demonstrated how the country is a leader in the R&D, manufacturing and regulatory sectors of the pharma. Here are some of the most memorable stops and sights along the way.

JANSSEN BIOLOGICS — LEIDEN

Although Janssen, the pharmaceutical arm of Johnson & Johnson, develops treatments for a range of therapeutic areas, its Leiden facility is focused on vaccines for some of the world's most vexing viruses.

Now the largest foreign R&D investor in the Netherlands, Janssen inaugurated its Leiden facility this fall. Commissioned in 2014 to help combat the Ebola outbreak, the new, single-use biomanufacturing facility will allow the company to scale up its full pipeline of vaccines for influenza, Zika, Ebola and more. Janssen is one of several companies — including Merck and GlaxoSmithKline — in the race to bring an Ebola vaccine to market. And the efforts are intensifying as new cases continue to be reported in the Democratic Republic of Congo.

Janssen's Leiden facility is also focused on developing an HIV vaccine, which company representatives refer to as the "holy grail" of combating the disease. To aid its vaccine development, the company will utilize its proprietary viral vector vaccines technology and PER.C6 manufacturing platform.

IN THE NETHERLANDS, ABOUT 360 LIFE SCIENCES COMPANIES ARE PACKED INTO A 120-MILE RADIUS.

PIVOT PARK (THE BIRTHPLACE OF KEYTRUDA) — OSS

This bustling life sciences campus has quite the claim to fame: Years ago, it became the headquarters for a team of Dutch scientists who made the initial (and accidental) discovery that led to the development of Keytruda. The immuno-oncology drug, which was commercially developed by Merck, has since become one of the biggest blockbusters to hit the pharma scene this decade.

Today, Pivot Park is home to dozens of companies and organizations working busily in the field of pharma R&D.

The Pivot Park Screening Centre uses cutting-edge robotics and automation to provide assay development for drug discovery. Acerta Pharma, which is partially owned by AstraZeneca, is also stationed in Pivot Park. Launched in 2013, the company is one of the industry's leaders in the field of using covalent binding technology to develop novel cancer therapies.

LUMC LABS — LEIDEN

Kidneys are the most commonly transplanted organ (from living donors), and rates of kidney failure are becoming more prevalent around the world. But what if there was a way to regenerate a failing kidney instead of hunting for a donor?

Inside a lab at the Leiden University Medical Center (LUMC), which brings together academic and private sector R&D, a team of researchers have set their microscopes on developing a range of innovative treatments for renal disorders, such as using stem cells to restore organs to their original function. The research is also advancing the field of bioengineering organs, which could pave the way toward artificial kidney replacements.

If successful, the findings in regenerative medicine could be used to treat a range of chronic diseases, and revolutionize the field of organ transplants.

KITE PHARMA — AMSTERDAM

Shortly into his presentation, Markwin Velders, VP of operations and managing director at Kite Pharma's EU Amsterdam facility, declared that the company is on the cusp of curing cancer.

Kite, which Gilead purchased for $12 billion last year, has indeed developed one of the most promising oncology immunotherapies in the class of CAR-T therapies. In October of 2017, Kite's Yescarta became the first CAR-T cell therapy approved by the FDA for use in adult patients. Its highly personalized therapy takes a

The Pivot Park Screening Centre in OSS uses cutting-edge robotics, automation and a collection of 300,000 compounds to aid drug discovery.

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patient's cells, reengineers them and reintroduces them back into the patient to attack cancer cells.

Handling patient's cells, however, creates logistical challenges. Which is why the California-based company announced this year that it is opening a 117,000-square-foot facility in Amsterdam. The new plant will allow Kite to more easily and efficiently engineer and deliver cell therapies to patients in the EU. The company said that the Amsterdam facility will create about 300 jobs by 2020.

THE NEW EUROPEAN MEDICINES AGENCY HEADQUARTERS — AMSTERDAM

A visit to the new European Medicines Agency building, which is under construction, wasn't officially on the tour, but we caught a glimpse of it on the way into Amsterdam. It was also clear from our meetings that becoming the new seat of the EU's drug regulations agency has generated a lot of excitement in the Netherlands' pharma industry.

After the UK voted to leave the EU in 2017, the search was on for a new home for the EMA, which was stationed in London. Along with technical requirements and easy access, the EMA was especially concerned about staff retention for its roughly 900 employees. The agency eventually settled on Amsterdam, which narrowly beat out Milan. It's a victory that could draw more attention to the industry in the Netherlands, and help boost its reputation as a flourishing hub for pharma.

A pig kidney being used inside LUMC Labs where research is taking place to advance the field of bioengineered organs and regenerative medicine.

Clever Cleanroom Supplies

From minor updates to high-tech changes, vendors are helping pharma meet strict cleanroom standards

By Meagan Parrish, Senior Editor

THERE ARE few parts of the manufacturing facility as complicated to manage as the cleanroom. The requirements to meet cleanroom standards are stringent and every aspect of the space — from airflow and what workers are wearing to which direction the doors swing — has to be carefully considered.

The stakes are also high, as manufacturers use cleanroom environments to handle delicate materials that could be easily ruined by contamination. And the rise of personalized medicines is putting more manufacturing work into the cleanroom space.

"The increased demand for oncological and immunosuppressant therapies in the pharmaceutical market paired with the 'biotech boom' has brought unique manufacturing challenges to the industry," says Michael Avraam, the global product manager at ChargePoint Technology for PharmaSafe products. "On the one side, the market is experiencing a surge in drug manufacturing using high potency active pharmaceutical ingredients and on the other, the requirements for sterile and aseptic processing have reached an all-time high."

Designed specifically for critical environments, LabSox products by DuctSox combine airflow design with specialized permeable fabrics and precisely shaped panels.

With more time spent in sterile environments, manufacturers are looking for ways to make life in the cleanroom easier, while further reducing risks of contamination. With those goals in mind, vendors are continuing to rise to the challenge with innovative products.

CLEAN HIGH FIVES

It's a simple change to a standard cleanroom product. But the innovation behind STERIS' new aerosol alcohol dispenser has still made a big impact for operators.

Traditionally, when workers in a cleanroom want to sterilize their hands they have to locate and fumble with a can of aerosol spray before returning to work. Now, STERIS' new dispenser allows operators to decontaminate their hands using a foot pedal or an elbow/forearm actuator.

"It's not complicated at all, but was designed with that cleanroom environment in mind," says Michael Gietl, the senior product manager of Process Cleaners at STERIS. "It offers robust cleanroom features including stainless steel, and can reduce some of the variability in hand sanitization procedures."

Gietl says the new dispenser shows how a simple update — such as the hands-free design — can go a long way in improving efficiency for manufacturers.

AIR IT OUT

Airflow is one of the most critical considerations of designing a cleanroom space. The higher the

grade of cleanroom, the more air flow is needed to keep the air free from contaminants.

Although much of the equipment in a cleanroom is stainless steel, which can be easier to decontaminate, DuctSox Corporation, a Rite-Hite subsidiary, has innovated an air duct and dispersion system that instead uses fabric.

Designed with critical environments in mind, the company says that unlike metal, the fabric DuctSox system diffuses air evenly across the entire length of the ductwork system while offering 360 degrees of draft-free air dispersion.

"One of the major challenges when designing airflow for critical facilities is achieving the correct amount of air at a low enough velocity to not interfere with air sensitive equipment such as fume hoods," the company says.

DuctSox says the fabric system is able to enhance sanitation in critical environments because it reduces the threat of condensation commonly generated by metal diffusers. And because the fabric system can be removed and laundered, it is easier to clean and more cost effective than traditional metal duct work.

The STERIS aerosol alcohol dispenser features a foot-activated dispenser for hands-free use, stainless steel and flexible installation.

SMART MONITORING

Of course, there are plenty of high-tech solutions aiding cleanroom manufacturing as well. Just like other parts of the facility, automation is becoming an increasingly prevalent tool for improving operations.

ChargePoint Technology recently launched its VERIFI smart-monitoring hub — a wireless technology that fits directly onto a split butterfly valve (SBV) installation and provides operators with vital usage data while also generating an easily accessible audit trail. Avraam says that targeting the SBV allows companies to more efficiently and flexibly protect workers and products from contamination exposure.

"By recording how many times the valve has been used and monitoring its temperature, VERIFI generates data that allows operators, and health and safety teams to proactively manage the maintenance of their containment solution with very little human intervention," Avraam says.

THE COMPLETE SOLUTION

Because the cost of square footage in a cleanroom is high, manufacturers have also been increasingly looking for ways to save space in sterile environments.

"There is a desire for fewer walls and more connectivity, but the necessity for protecting the integrity of the cleanroom itself remains," Peter Levison, executive director of business development at Pall Biotech, says. "Though it can be challenging to achieve these goals, the growing adoption, and development of single-use technologies has enabled the introduction of closed, bioburden free cleanrooms that require less infrastructure."

Recently, Pall Biotech, which provides a full suite of single-use systems, announced a new partnership with G-Con Manufacturers, who provide self-contained, ready-to-use manufacturing PODS. Under the deal, G-Con PODS will be customized with Pall bioprocessing equipment, including automation and utility supplies. The new partnership will allow the companies to offer a sort of one-stop shopping solution by providing a complete, scalable facility that is modular and easy to clean. The companies say the turnkey solutions are available for continuous bioprocessing and viral vector production.

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ROSS Custom Multi-Shaft Mixer

ROSS recently designed a custom 150-gallon Triple Shaft Mixer with elaborate automation and safety functions (ROSS VersaMix Model VMC-150). Notable among the special added features are six (6) pneumatic clamps rated for 4000 lbs. each for remote locking of the mix vessel to the mixer cover designed for 29.5"Hg vacuum and 5 psi internal pressure. The clamps likewise function as redundant limit switches, allowing for operation only when secured. The VMC-150 also includes automated valves for powder feed and CIP liquids, RTD multi-point temperature sensor, built-in vacuum pump assembly, load cell system and centralized HMI.

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Pharma's OpEx Mission

What Special Operations Forces can teach pharma about digital transformation

BY CHAD STORLIE, RETIRED US ARMY SPECIAL FORCES OFFICER, AUTHOR, ADJUNCT LECTURER

HIGHLY SKILLED soldiers lurking through the pitch dark of night and a manufacturer using digital tools to create better products for patients appear to be completely unrelated. When we look closer at the skills that Special Operations Forces (SOF) personnel use to create mission success, we discover techniques that can drive and inspire digital business innovation.

Although the come from across the U.S., SOFs are extensively trained to deploy worldwide at a moment's notice. They comprise just 3 percent of the overall military, but SOF teams are deployed in hundreds of countries to train foreign military forces, conduct reconnaissance on enemy targets, attack terrorist cells, and rescue downed military aircraft crews.

Business digital innovation teams can learn and capitalize on the planning and operational excellence that SOF teams embody.

Hire for personal character, train critical skills: SOF organizations have a highly specialized and demanding candidate selection process. During "selection," candidates are stressed with fatigue, physical challenges, mental challenges, and leadership problems all designed to make the SOF candidates reveal their true character. It is only after a candidate's character has been validated that they begin the unique and specialized training. Business can learn and understand that personal character, unique experiences, and diverse backgrounds are what generate true innovation. Unique skills can be taught, but character can rarely be developed.

Deeply understand the needs of your patient: Before a SOF team conducts a mission, they undergo a detailed and isolated mission planning process. The purpose is to deeply understand the needs of the military commander ordering the mission and all the possible options the team can create. Pharma manufacturers must learn that understanding the patient, their current needs, and anticipating their future needs are the true bedrock of innovation. Great technology matched with an intimate understanding of patient needs are what fuels tangible innovation.

Identify and build success from data: SOF teams use data and analytics to support decisions on how to best accomplish a mission. SOF teams evaluate their own skill sets and those of fellow team members. The primary data that SOF teams use are the results of mission rehearsals. Rehearsals are full up experiments, in business terms, that prove or disprove if they can accomplish the mission. Following a rehearsal, SOF teams do extensive reviews of their performance to improve shortcomings and maintain actions that performed well. Organizations can use rehearsals, lesson-learned sessions, and iterations of experiments to test their ideas.

GOING FROM SUGGESTION-DRIVEN TO MISSION-DRIVEN IS CRITICAL TO SUCCESS

Share information and build external ideas: Internally, SOF teams share as much as they can on intelligence, operations, out-of-the-box ideas, and contingency plans. SOF teams also create extensive idea sets and different ways to accomplish the mission in case conditions change. Teams believe in extensive equality regardless of rank, experience, and skill sets so they constantly share, update and listen to new information. How SOF teams share information is an invaluable teaching point for non-military organizations that focus too heavily on position, roles, and hierarchy. Information needs to be set free to inspire and guide innovation.

Go all-in on your plan: SOF teams disagree during planning, rehearsals and mission preparation. During these stages, SOF team members know everyone is expected to provide input, suggestions, and ideas to improve the outcome of the mission. However, once a mission is decided, all new ideas end and the entire team is "all in" to make the mission a success. This characteristic of SOF teams — to go from suggestion-driven to mission-driven — is critical to the success of SOF. Non-military organizations need to have vibrant discussions to allow full input on ideas. Then, they need to fully support each other for the hard tasks of mission execution.

When it comes to digital transformation, the pharma industry can find inspiration from unique sources like SOF teams to learn how to create, test, and execute innovative business plans.

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