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Globalization of Single Use

We track the rapid rise of single use systems – and explore their role in the biomanufacturing facility of the future

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Going Global

No longer the new kid on the block, single-use systems are an established part of the biopharmaceutical industry. We ask – what comes next?

Single-use systems have enjoyed a meteoric rise in recent years. No longer limited to niche applications or clinical manufacturing, single-use systems are fast becoming the go-to option for all but the biggest batches. The appeal is obvious: disposable systems save time, money and effort during drug manufacture and dovetail neatly with broader industry trends around smaller batch sizes and flexible manufacturing.

However, the initial entry for single use hasn't been easy, particularly in light of the industry's conservative nature. There have been many questions around how best to deploy the technology, but collaborative groups are now close to finalizing standards on extractables and leachables (E&L), particulates and integrity assurance (page 18), clearing the way for single-use systems to go global. Advances in technology are also expanding the reach of single use. The performance gap between single use and stainless steel systems is rapidly narrowing and the single-use bioreactor (now available in capacities up to around 2,000 liters) is often the first choice for manufacturers working at small scale. There have also been advances in high-tech connectors, which allow connections, disconnections and reconnections of flow paths, while maintaining a closed, sterile system.

All in all, as our experts point out on page 10, single use is well established and now entering the "age of optimization". More than 90 percent of biopharma facilities use at least some single-use components, and the market for single-use bioprocessing is estimated to reach US$ 5.9 billion by 2024 (page 9). So what comes next? It's a safe bet that the adoption of single use will continue to grow, particularly for the manufacture of cell and gene therapies. We can also predict more clarity in quality and regulation, more advances in technology, greater understanding of E&Ls, and more facilities that rely on single use almost exclusively.

One interesting side effect of single use systems has been a strengthening of the relationships between suppliers and manufacturers. Single-use components effectively shift responsibility for quality and compliance from the manufacturer to the supplier. Consequently, the relationship goes beyond transactional, with suppliers expected to provide a greater level of documentation and support. Suppliers have always played a central role in the industry, and their contribution will only increase in years to come.

Ready or not, the era of single use is well and truly here. In the following pages, expert contributors will discuss the past, present and future of single use systems.

Charlotte Barker
Editor

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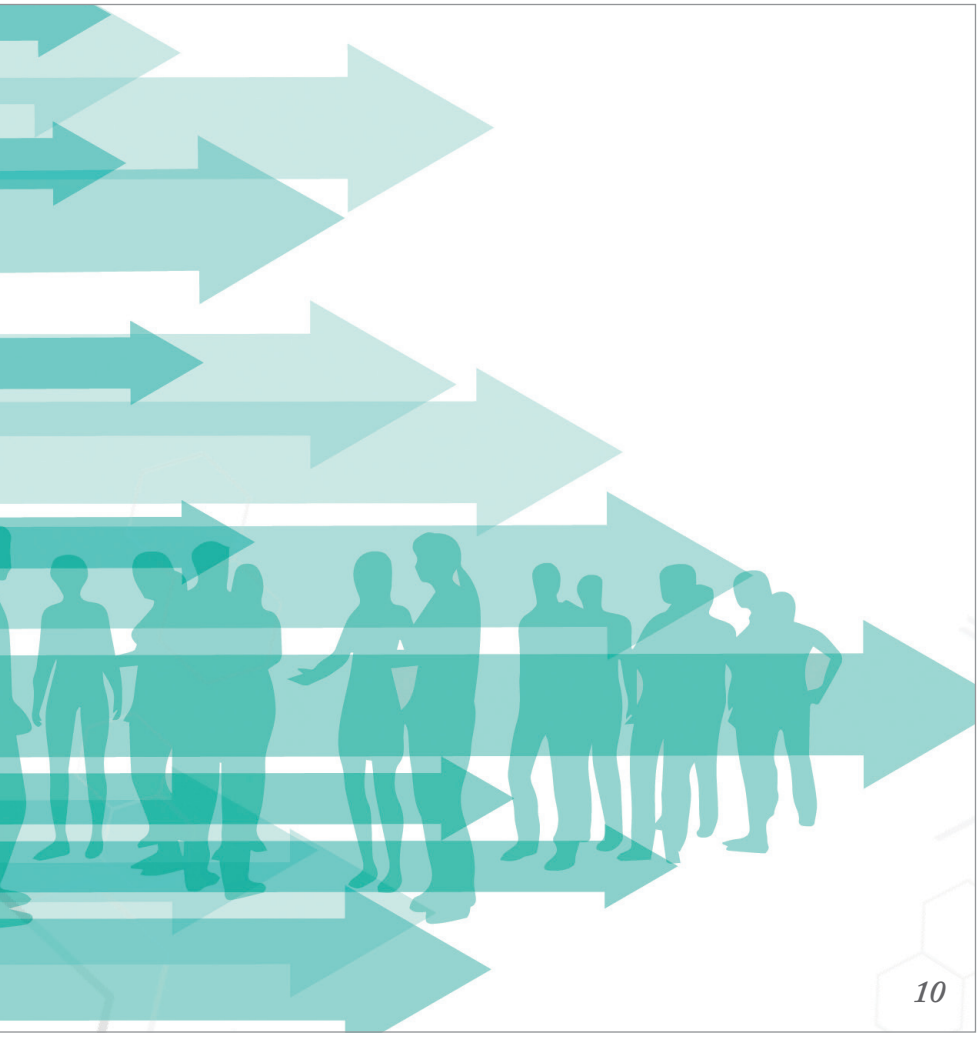

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Don't Think Twice

Single use technology is fast becoming the norm in biopharma, despite being relatively new technology. How can you get the best out of single use?

By George Adams, MilliporeSigma.

Vaccine manufacturers were early adopters of single use technology for two good reasons: to protect the vaccine from contamination and to protect operators from the vaccine. Moreover, the relatively small process volumes involved in vaccine manufacture nicely matched the scale of single use technology available at the time (around 250 liters) – the 2,000-liter single use bags we have today simply weren't available.

As the technology improved and the scale increased, we began to see single use appearing in more applications in the pharmaceutical industry for two primary reasons:

- Flexibility. You can more easily change bag sizes rather than having to buy and install a new stainless steel vessel.
- Cleaning. Sanitization of stainless steel vessels is time consuming and costly. The process must be developed and validated, operators must be trained, and then there is the is utility consumption. For many processes, it is simply more economical to use plastic disposable technology, much like we use plastic containers for food storage.

Flexibility and the reduced total cost of ownership make single-use systems an attractive prospect for many biopharma manufacturers. Even emerging markets, such as China and India, are getting on board, albeit at a much slower rate than the West.

That said, single use isn't always the answer; stainless steel will still be the go-to solution for certain applications, and there is also fear of change; we've found that many customers still have concerns about single use.

Throwaway fears?

Supply chain security is a critical issue for pharmaceutical manufacturers, from raw materials for the drugs themselves to the resins used to make the single use components for final filling. When a pharmaceutical company buys a stainless steel vessel, they have full control of it once it is delivered and installed. In the case of single use, it's a case of buying boxes of bags over and over again – and everything about those bags is the responsibility of the vendors in the supply chain. The pharmaceutical industry is famously conservative, and is reluctant to give up control of critical process technology.

Validation is another major issue. Pharmaceutical companies are concerned about whether chemicals released from the polymers in single use products might contaminate the drug. It's not an issue unique to single use. Even in traditional facilities, residual cleaning chemicals or degradation of the stainless steel/glass components can cause contamination issues. That said, plastics are known to release extractables and leachables, and drug manufacturers are obliged to identify any effects on patient toxicity,

"Flexibility and the reduced total cost of ownership make single-use systems an attractive prospect."

efficacy of the drug, or the manufacturing process. All three potential effects are being widely discussed in the industry today.

How can pharma companies address those concerns? Firstly, it's crucial to think about manufacturing early in drug development – even in Phase I when clinical materials are first being produced. Process developers can rely on suppliers to provide information about the single use products to help them understand how the technology will or will not affect their drug and their patients. Even in these early stages, when the precise drug formulation and dosage regime are uncertain, it is still possible to make conscientious choices that can be scaled up in later stages of development.

Later in the drug development process, toxicologists require advanced analytical data to be aware of the chemical compounds being extracted, so they can make a thorough patient safety assessment. This data can be expensive and time consuming to acquire, and the regulatory guidance for process technology is not black and white. We sometimes find it challenging to convince customers at companies who

"How can pharma companies address those concerns? Firstly, it's crucial to think about manufacturing early in drug development."

One World

With our increasing awareness of the impact of human activities on our planet, the environmental sustainability of manufacturing processes is ever-more important. At first glance, adding disposable plastic components may seem like a retrograde step, but traditional manufacturing has many hidden environmental costs. To clean and sterilize a stainless steel bioreactor requires huge amounts of water, cleaning products and energy, so most analyses conclude that single use in in fact the "greener" option.

While plastic is far from fantastic for the environment, the amount involved is small in comparison with the mountain of plastic waste generated by other industries. Research suggests that the most efficient way of dealing with plastic waste from biopharma production is to incinerate it, with the potential to generate energy from combustion (1).

Single Use Swap

In a case study (1), swapping to single use gave one manufacturer annual savings of:

1 million
liters of water

28,812 kwh
electrical power

Over 20 metric tons
of CO_2 from their carbon footprint

In The Balance

Stainless steel

Cons
Huge water usage
Much higher demand for energy and detergents

Pros
No disposal of plastics required

Single use systems

Cons
Plastics used in biopharma typically cannot be recycled, generating solid waste

Pros
Water usage 87 percent less than in a stainless steel system (2)
Less energy used, minimal detergents

References

1. *W Flaherty, P Perrone, "Environmental and financial benefits of single-use technology", ISPE Knowledge Brief (2012), Available at: http://bit.ly/2hjmlG7. Accessed December 19, 2016.*
2. *A Sinclair et al, "The Environmental Impact of Disposable Technologies", BioPharm International (2008), Available at: http://bit.ly/2h2Rno0. Accessed December 19, 2016.*

About Provantage® Services

- 40 years of experience validating process technology for the pharmaceuctical industry.
- A global network of laboratories and staff governed by a common Quality Management system
- Access to MilliporeSigma's extensive scientific and regulatory network of subject matter experts.

may be working with tighter budgets, or have a higher risk tolerance, that their toxicologists need this data. We help them by assessing their risk and proposing a validation strategy and study plan that will ensure they have the data they need as economically as possible.

Gain the advantage

Regulatory guidelines around the globe oblige the drug manufacturer to ensure that a given drug manufacturing process does not contribute harmful contaminants to a drug. Such statements can be broad and without specific guidance, and industry and regulators are now talking about how to apply more definitive standards to process technology.

Our Provantage® validation services answer a lot of the questions that customers have about performance, reliability and regulatory compliance. We work with drug manufacturers worldwide to understand their drug formulation, how it is going to be used by patients, and what process technology they want to implement. Taking all of that into account, we conduct a risk assessment and develop a validation strategy so that they will have the information they need to be confident in their process, and the scientific data to substantiate their decisions with the regulatory authorities.

"We work with dozens of drug manufacturers in a wide range of applications, so our experience is comprehensive."

Much like our Development Engineers and Applications Specialists, Provantage Validation Coordinators work with many drug manufacturers on a wide range of applications. We apply our experience and the lessons we learn to solve challenging issues for future customers who come to us with similar needs.

Cycle of innovation

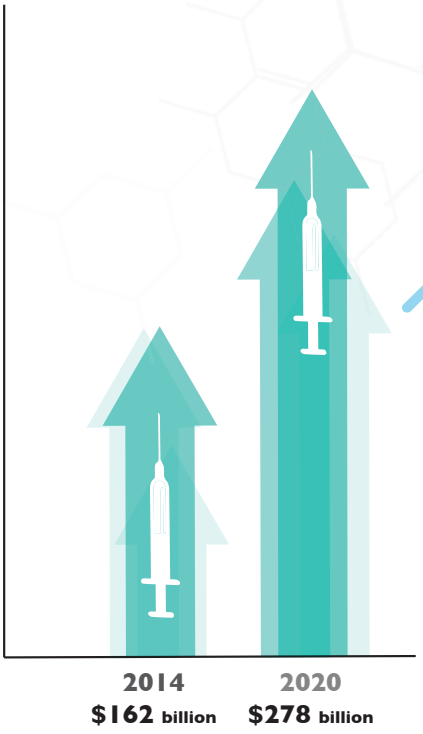
How the industry uses single use technology is also changing; for example, many companies are developing antibody–drug conjugates (ADCs) – monoclonal antibodies connected to cytotoxic small molecules. The conjugation process can involve harsh solvents and conditions, some of which are not going to be immediately compatible with single use technology.

Our customers are thoughtful, they are challenging, and they are pushing us in directions that we may not have considered otherwise. Single use technology is only 10 years old and has room to evolve as new challenges arise – and collaborating closely with our customers is part of that process.

We are all in a positive cycle of innovation; as the industry evolves, it identifies new opportunities and issues – and suppliers respond with new products, which open up further possibilities. We're excited to be part of that cycle, and we hope you are too.

George Adams has been with MilliporeSigma for almost 40 years. He was at the forefront of the company's decision to pursue single use technology for biomanufacturing. For the past two years he has been responsible for validation services, including Provantage®.

Strong growth in the global biopharmaceutical market

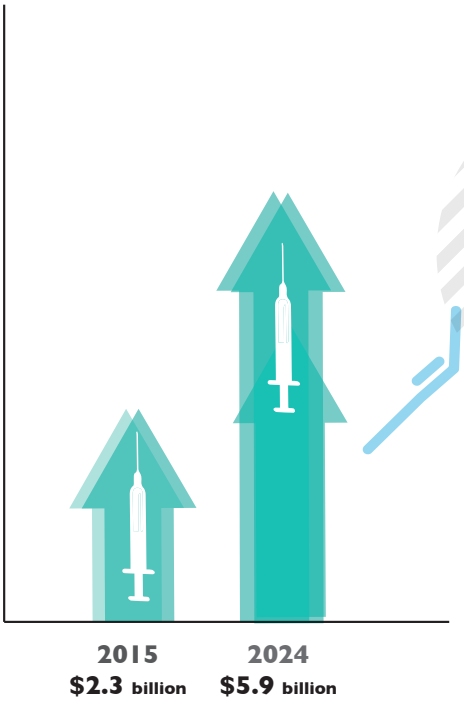


Source: *Persistence Market Research, http://bit.ly/2gAlPmb (2016)*

More than 90% of facilities use single use/disposable technologies

Source: *Bioplan Associates, http://bit.ly/2kwtfss*

Growing market for single use bioprocessing



Source: *Transparency Market Research, http://bit.ly/2hlg8N2 (2016).*

All for One

Single use systems have taken biopharma by storm. Following rapid growth over the past 15 years, disposable systems are now making the leap from clinical to commercial scale biomanufacturing. But the story doesn't end there – many believe there is a lot of untapped potential. Three experts give us their take on the past, present and future of single use technology.

Take us back to the birth of single use for biopharma...

Mike Felo (MF): As an end user, my first exposure to single use systems came in the early 2000s, when we first started to use disposable bags and tubing sets for buffer management. It was an easy way to transport small volumes (up to around 50 liters) of buffers around the facility without the need to clean the transport container. I viewed it simply as a convenient, time-saving device – at that time we had no idea it would morph into such a huge market.

Karen Green (KG): From there, suppliers started to transition filter cartridges from stainless steel to disposable capsules. As people saw the benefits – no cleaning and no cross-contamination – they started to become more comfortable with the single use format. More and more steps in the process were converted from stainless steel to single use – just as they were in food management processes.

What were some of the milestones?

KG: The first truly game-changing technology was the advent of the single use bioreactor – GE's WAVE rocking bioreactor was first onto the market, in the late 1990s. In the 2000s, a big advance was the launch of aseptic connectors, like the Millipore Lynx connector, which allowed various single use components to be linked together into sterile assemblies.

MF: I agree with Karen's picks, and I would also throw in single use mixing. There were two early entrants into that area in the 2000s – Sartorius LevMixer and Millipore Mobius® Mix – which massively increased turnover in the buffer prep suite. The benefits of these products to the user were so obvious that it really accelerated adoption of the technology, and mixing remains a common entry point for customers into single use technology. It's seen as an area to "test the waters", before adopting the technology throughout their processes.

Meet the Experts

Karen Green
is a Senior Product Manager for Mobius® single use assemblies. She's been with MilliporeSigma for two years, and has more than 20 years' experience in bioprocessing and biopharma.

Mike Felo
is MilliporeSigma's Director for Single Use Product Management. His background is in chemical engineering – working at both start-up biotechs and big pharma companies, before moving to MilliporeSigma nine years ago.

Michael Scanlon
manages a group of MilliporeSigma sales development specialists worldwide, who support design and implementation of single use technologies. He has been with the company for 14 years.

More recently, one of the big drivers for adoption has been the introduction of the 2,000-liter bioreactor. Given the dramatic increase in yields over the past seven years, from less than 1g/liter to 5–8g/liter, the 2,000-liter single use bioreactor can supply the entire patient requirement for a lot of the small-volume biotech drugs now being produced.

KG: Traditionally, when drugs were produced in stainless steel, a standard batch size would be 10,000 liters. But with more patient-specific and specialized medicines, the batch sizes for many products have come down to 2,000 liters or below – hitting the sweet spot for single use.

Single use is simple to connect up and run, and the time savings are impressive. As Mike mentioned, you don't have to wait for equipment to come back online after cleaning. You can just pull it out of the box, set it up and go.

Michael Scanlon (MS): As well as the technological breakthroughs that Karen and Mike have summarized, there was a period between 2005 and 2008 during which single use systems were economically evaluated in great detail. As the industry moved towards more flexible manufacturing, with smaller batch volumes, and fewer "blockbuster" drugs, there was a clear market agreement that the flexibility and cost savings of disposable technologies were significant. More recently, adoption of single use has spread to all corners of the world, including some of the less developed emerging markets of South America, the Middle East, Asia and Africa.

Where is the market now?

MF: Adoption has been rapid, certainly above the general market growth for pharmaceutical adoption. Until quite recently, the technology was largely used for clinical or pre-commercial production, but it's exciting to see how quickly it has moved into the commercial stage. Now that companies like Amgen are pushing hard to move as many of their processes to single use as possible, I think we'll continue to see rapid adoption for commercial production.

KG: I agree - now that some of the key opinion leaders have latched on, the rest will follow. We're in growth mode, and it's an exciting time for the field.

MS: The projected benefits of single use systems have been largely realized, and we're already at a stage where almost all

unit operations have a fully single use or supported single use capability. Now, we're in an age of optimization. As companies have transferred accountability for validation and other process guarantees to their suppliers, there is intense scrutiny of supply chain transparency. There is a strong economic focus on security of supply, as some of the largest players in pharma production and biotechnology standardize their processes across the globe. They are looking for a greater level of reliance and trust, with sole suppliers to multiple sites around the world. As a supplier, that is very exciting.

Is everyone switching to single use?

MS: There are hold-outs. Even with 2,000 liter bioreactors and yields being maximized, the highest volume products are still more economical to manufacture at very large batch sizes. Those plants are still operating, and will continue to operate, using stainless steel. Even in facilities that aspire to be all-single-use, such as Amgen's "facility of the future" in Singapore, there are still some unit operations driven by stainless steel. Optimizing these hybrid operations is the next challenge.

KG: It depends to some extent on the legacy at the company. As Mike mentioned, some customers are going all-in for single use. Other are still debating whether to switch or stick with traditional stainless steel. Companies are embarking on something new, and our job is to mitigate any risks that concern them, so that they feel confident to make the switch. I think change is good; you always have to be evolving. But ultimately, what matters is that the customer gets a positive result.

How will single use technology evolve?

KG: We're still in adoption mode – every year there are more single use systems coming online in drug manufacturing, whether it's at clinical or commercial stage.

MS: I think adoption will continue to grow at the current rate for some time to come. The early adopters amongst the largest pharma and biotech companies are ramping up, and you'll see others doing the same. Innovative modalities, like cell and gene therapies, will make use of single use technology from the start, in clinical, process development, and commercial manufacturing suites.

MF: There's still plenty of room for innovation. As single use moves into commercial production processes, we're matching the performance of current systems. One aspect is achieving the same level of control and data management that customers have right now with stainless steel. We're optimizing sensors for the bioreactor and downstream system, as well as automation, data capture, and integration with existing control platforms.

"We're in growth mode, and it's an exciting time for the field."

MS: Things will continue to evolve from a quality and regulatory standpoint too. There has been a lot of attention on extractables and leachables in recent years. The regulatory guidance is not black and white in this area but there has been a lot of work in the past two years on developing clear standards across the industry. All suppliers recognize that while they want to differentiate themselves, they must meet the needs of the market place, and that means standardization. It's incumbent upon us as suppliers to help the industry advance in this area.

What new MilliporeSigma products are you most excited about?

MF: We have a lot of fun stuff that has recently launched or is coming soon. One of the most interesting technologies we've launched this year is our Lynx® CDR (connect, disconnect and reconnect) product, which is the first sterile connector on the market that can be used multiple times for multiple connections between sterile single use systems. That is something that isn't possible in stainless steel systems without steaming and sterilizing the connection in place, so it's pretty cool. We're also just about to launch a new set of single use mixers, with performance that rivals their stainless steel counterparts. The performance gap between stainless steel and single use is steadily being erased.

KG: Our end users are global, they have multiple sites, and they are partnering with and acquiring other companies – not

everything is done in one plant any more. Bulk manufacture might be done in one plant, before the product is shipped to another plant for fill and finish. Or the drug might be dispatched after manufacture into various geographical regions for packaging and distribution. We're increasingly seeing not just the company but the drug itself being globalized. With that in mind, we just launched a line of single use bags and carriers for transport of large liquid volumes like bulk drug substance.

MS: One area we haven't mentioned yet is the continually growing fill/finish market. The stakes are raised the further down the value chain you go. The scrutiny and transfer of accountability to suppliers that we mentioned earlier is maximized at fill/finish, and we take great pride in training, implementation and validation of single use in fill/finish. We work with all the major filling system manufacturers to make sure this critical step is problem-free for clients.

What will the biomanufacturing facility of the future look like?

MF: I believe the next big jump forward is building full facilities around single use technology. Certainly, we're already in discussions around mobile cleanrooms, and we expect to see these modular units being set up in emerging economies in South America, Asia, and Africa in the near future. These units could produce vaccines or antibody products in months rather than years, by bypassing the need to build and validate infrastructure. Instead, a pre-validated system is delivered on-site. The technology and the market aren't quite there yet, but for me the cost and time savings are irresistible, and I believe that it is just over the horizon.

MS: Like Mike, I'm excited by the potential of mobile manufacturing. The concept of cleanroom pods and modular facilities has been around for some time, but it has never been effectively implemented, hampered by a lack of technical know-how and skilled operators. Our aspiration is to be a problem-solver to the life science industry, and this is a great example of where we can make a difference. As a supplier, we're a few steps away from the patient, but I'm enthusiastic about a future where we can play even a small part in bringing healthcare closer to patients.

KG: I would also envisage more patient-specific therapies, like gene editing and cell therapies, which will require micro-scale manufacturing.

MS: I've spoken to cellular therapy developers, and they caution that these personalized products may not fit into the standard CMO template – there will be steps that need to be customized, and most people are expecting cell therapy manufacturing to be largely based on single use systems. Another big jump in technology will be enabling perfusion and continuous processing with single use technologies.

"Ten years ago, anyone could build and supply a single use system, but we've moved beyond that."

What is your advice for companies who want to do more with single use?

MS: First and foremost, consider facility design. Taking a hard look at the design of the facility will allow you to keep your footprint small and optimize usage of the technology. It's vital to build quality into the design of your facility, just as you do for your products.

MF: Ten years ago, anyone could build and supply a single use system, but we've moved beyond that. As single use products have become widespread, the expectations both at a practical and regulatory level have increased significantly. Now customers need security of supply, and regulatory documentation to support the use of single use systems for GMP manufacturing or commercial supply. With that in mind, there should be a lot more thought put into the selection of a supplier than just price or location. Making the proper choice of supplier will be fundamental to the success of your manufacturing facility and your process as a whole.

KG: Use your supplier as a partner – this is especially true for smaller companies, who may not have the experience and resource of large-scale manufacturers in terms of supply needs and regulatory documentation. The supplier–user relationship is much more intimate than it was 10 years ago. The customer relies on the supplier – it becomes more of a partnership and collaboration when you are supplying a single use assembly, as opposed to simply fulfilling an order for stainless steel.

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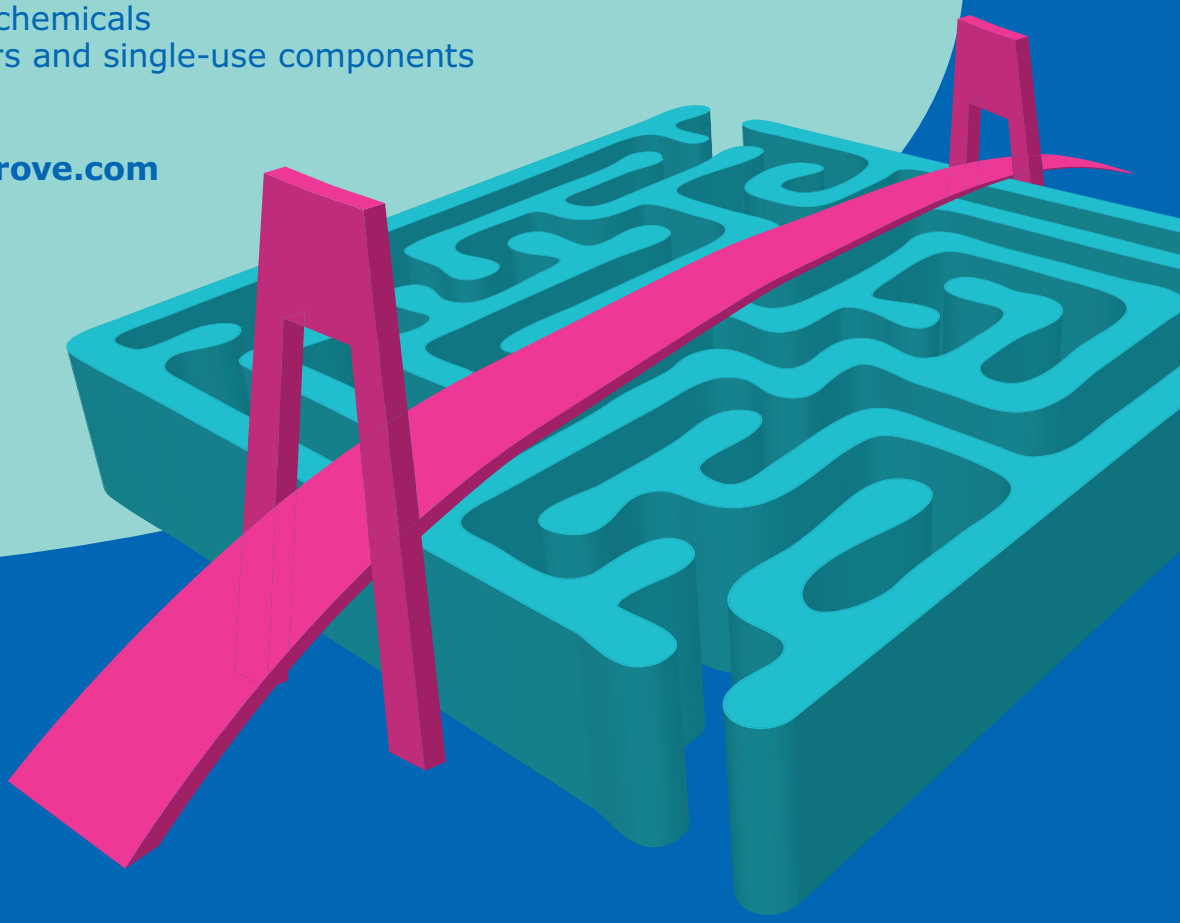

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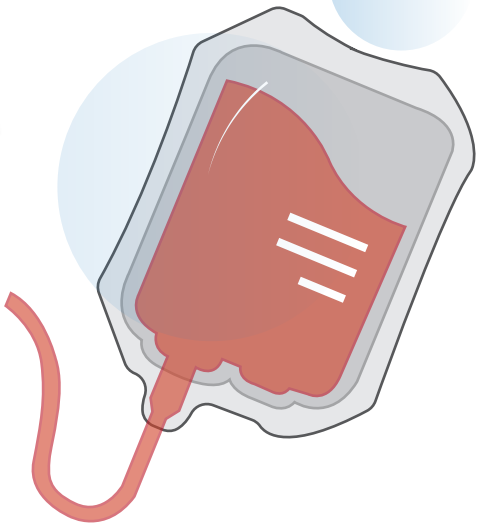
The Evolution of Single Use

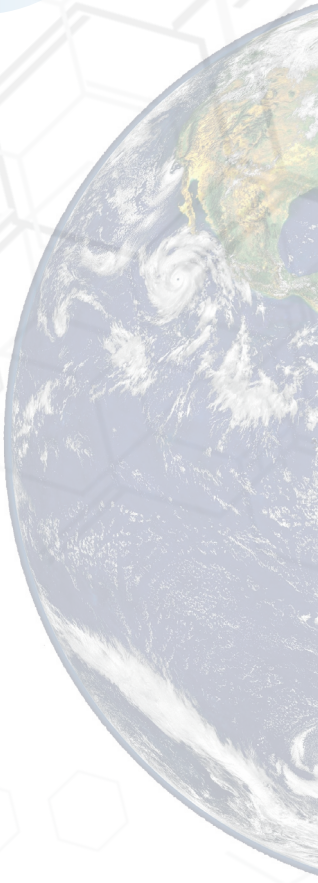


1980s

- Small filter capsules produced to replace stainless steel filter housings
- First disposable biocontainers (for large-volume parenterals and blood)
- Late 1980s: 10-inch capsules introduced

1900s

- Early 2D bag development, starting with 50-liter and by end of the 1990s 3,000-liter 3D bags
- WAVE bioreactor (1996)



- Large-scale tube welders and sterile connectors enable connection of two sterile fluid paths
- BioProcess International's first supplement on disposables (2004)
- Stirred Tank SUB (Hyclone, 2004)
- Expansion of single use into final fill

2000s

2010s

- First single use systems launched in the market (2012)
- Increased use of bags for bulk drug transport and freeze/thaw applications

How to Ensure a Trouble Free Countdown to One

Regulators see single use systems as a way to boost safety in biomanufacturing. However, novel technology can introduce new risks. Where are regulators focusing their attention – and how is the industry responding?

As you've already read in this supplement, single use technology has been one catalyst for a shift in the supplier–customer relationship in pharma. With single use, the responsibility for ensuring safety and regulatory compliance falls squarely on the shoulders of suppliers. "It means that even though we're not inspected by regulatory bodies, we have to be aligned for validation," says Janmeet Anant, Global Product Manager at MilliporeSigma. Of course, end users must still conduct some tests, but they also need to trust that their supplier has performed due diligence and supplied a quality product.

Relinquishing control can be difficult, but there is a clear advantage: pharmaceutical companies can focus on the core mission of bringing drugs to patients. "If we do our job right, our customers can concentrate on getting that final drug product to clinical trials and onto the market," says Anant.

Supply of equipment is only half the story. Customers also need training and technical support; poorly-trained operators opening a box of single use bags with a knife or over-tightening an O-ring could spell disaster. Once again, a solid customer–supplier relationship is key.

In short, to meet current regulatory guidelines and pre-empt future requirements, manufacturers need the full support – and guidance – of their suppliers.

Single use rules

"Regulators are enthusiastic about single use, particularly as there are obvious benefits for safety," says Heike Michaelis, Director of the Emprove® program at MilliporeSigma (see page 22). For example, with new developments in connectors, it's possible to create and maintain a closed system, even after multiple connections and disconnections. However, there are few detailed guidelines from regulators and, until recently, few industry standards that specifically cover single use.

But broad guidelines don't necessarily have to spell bad news. "Regulations are vague and rightfully so," says Anant. "I don't think a regulatory body should be prescriptive as it would limit innovation in the industry. From a technical point of view, we as an industry can propose best practices. And those can be ever-changing as we move forward."

With that in mind, the industry has taken matters into its own hands and started to develop recommendations, according to Michaelis. Efforts so far have concentrated on three key issues: extractables and leachables, particulate contamination and integrity assurance.

Extracting problems

A big focus for customers, regulators and suppliers alike in recent years has been extractables and leachables. Regulators are focusing on the risk of patient toxicity, but manufacturers must also consider how extracted or leached chemicals could affect cell growth or purification processes. "We're understanding more and more in terms of the quality of the plastics, but how does that affect a drug formerly made in a different system? There are no standards at this point," says Anant. "But the industry is working on it."

Organizations like the BioPhorum Operations Group (BPOG), which comprises more than 25 of the top multinational biologics manufacturers, are proposing standard approaches. And BPOG's offshoot Supply Partner Phorum is also getting involved by bringing together drug companies and suppliers to tackle key issues in the biomanufacturing supply chain. Michaelis draws attention to a 2014 white paper by BPOG, which set out recommendations to suppliers on how to perform extractable tests (1). These recommendations are now being widely implemented.

Though standards are emerging for biopharmaceuticals, the increasing number of cell therapies in development (most of which are manufactured in single use systems) add a new dimension to extractables and leachables testing. "How will extractables and leachables affect very sensitive cells?" asks Anant. "For example, if the cell therapy is designed to produce beta cells in the pancreas to produce insulin in diabetics, will the plastics affect the differentiation or insulin-producing ability of the cells?" The cells may stay in the body for years, or even decades, so even subtle changes could have a cumulative effect.

"The industry has taken matters into its own hands and started to develop recommendations."

A particular issue

Extractable and leachables aren't the only major concern for biomanufacturing. "Regulators tell us that the presence of particles causes over 20 percent of all pharmaceutical recalls," says Anant. It's of little surprise then that regulators are making the elimination of such particles a top priority.

Particles can be introduced into single use systems when plastic tubing is cut, welded or melted, from cardboard packaging, lint or fibers from operator's clothing, and so on. With single use assemblies, the supplier takes on responsibility for validation and quality, including inspecting and testing for particulate contamination. The debate currently centers on exactly what monitoring is necessary. As with extractables, there are no fixed standards for manufacturing systems. However, there are standards for final drug product containers, and industry groups are translating these into guidance on particulate monitoring in single use systems. "The BioProcess Systems Alliance has written a white paper on the topic, which lays out some good practices," says Anant (2).

If particles are discovered in a single use system, it's important that the supplier has a robust process to investigate the root cause, correct any problems identified and prevent them happening again.

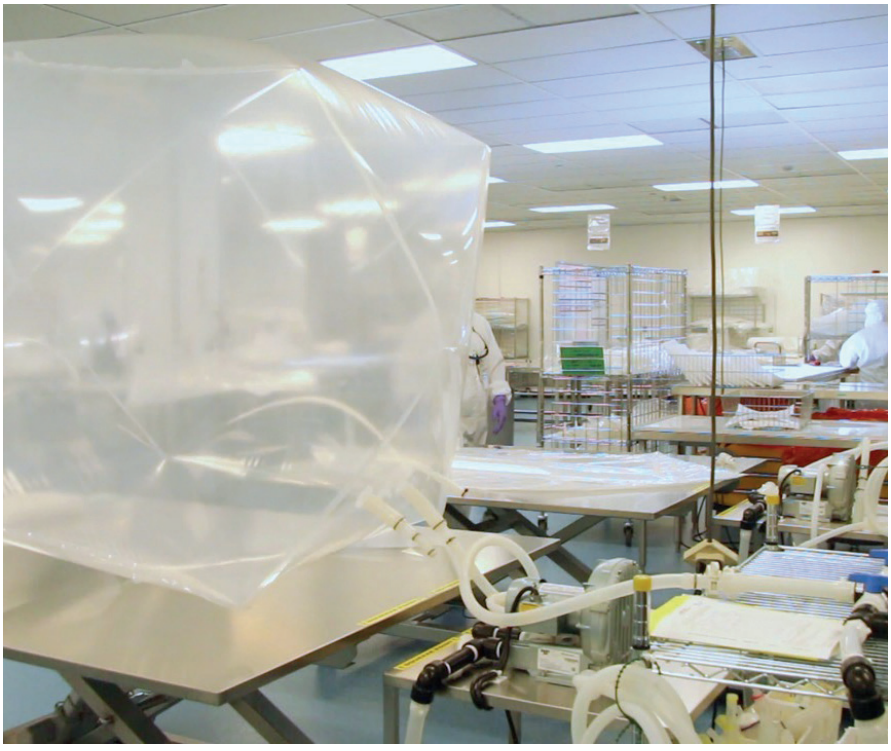
Building a fortress

It's crucial for aseptic systems to remain closed, so that bacteria and other contaminants cannot enter and jeopardize quality. Some biopharmaceuticals pose a real risk to operators, so as well as making sure contaminants don't get in, it's important that the drug product can't get out. "Making sure the system remains closed – integrity assurance – is another crucial issue for manufacturers and users of single use technology," says Anant.

There are a number of different approaches to verifying the integrity of manufacturing systems. The American Society of Testing and Materials has a method based on pressure, with and without restraining plates. The single use system under scrutiny is sealed and pressurized, while very sensitive detectors measure any pressure drop over time. An alternative method uses helium as a tracing gas. The system is filled with helium and any helium detected outside the system indicates a problem. Gas and pressure systems have one flaw – the smallest "holes" they can detect in the system are still larger than some microbes. However, the results can be validated. Bacteria can be introduced via aerosol to the air around the system, followed by a test for contamination, which makes intuitive sense, as microbes are likely to come from the surrounding environment. An even more stringent approach is to immerse the system in a liquid spiked with bacteria, but it has met with controversy. "Some people say that immersion is too harsh – that it's never going to happen in reality. Others argue that we should apply the toughest test available, to provide another layer of safety," says Anant, adding that the optimal testing interval is also up for debate. "If every time we do the test it shows that there's no issue, do we do the test every three months, or is once a year enough?"

Regulators encourage the use of closed systems, and have started to relax cleanroom requirements for facilities making use of the technology. If nothing can get in or out, the environment around

"Coming together to agree standards across the industry will help to advance the field."



the system is theoretically irrelevant. In practice, regulators aren't ready to give up all environmental controls, but a drop in cleanroom classification can save companies millions of dollars per year.

Keeping risk in perspective

Anant believes that as companies carry out more testing, they are likely to find that the risks of single use technology are limited. "Right now, I think we are overdoing it a bit. That's understandable – it's better to be safe than to run into an unpleasant surprise later on. But as we do more tests, and more drug products reach the market, manufacturers and regulators will gain confidence in single use systems – and apply a more balanced risk assessment."

Michaelis agrees: "Although single use technology has been around for approximately 30 years, I still consider it a young industry. Very few customers have trialed full single use suites. The famous Amgen facility in Singapore is the flagship, and there are more to follow. As it's adopted more and more, we will learn more, and be able to make improvements."

One improvement that is needed, says Anant, is shoring up the supply chain. Pharmaceuticals make up a tiny proportion of the market for plastics, so it's crucial for single use suppliers to have solid relationships with plastics manufacturers. "Even a small change in the chemical composition of a plastic could have serious knock-on effects, so we choose to work with suppliers with a dedicated medical or food division, who understand the issues."

Further down the supply chain, the relationship between single use suppliers and pharmaceutical companies is strengthening, with increasing collaboration between the groups in setting standards and assessing quality. "Over the past two or three years, collaborations have started across the board, with many different industry associations around the world. Before that, everyone was checking their own agenda and focusing on their own needs. I think coming together to agree standards across the industry will help to advance the field," says Anant.

Michaelis believes the future is bright for single use systems: "Single use has yet to reach its potential, especially in the direction of personalized medicine. The pharma industry used to focus on large-volume drugs to treat millions of patients. Now, they are going after more complex personalized medicines, treating far fewer patients. Lower volumes mean that manufacturers need to be much more flexible with their production capabilities – a big plus for single use.

"Stainless steel won't die out, so I don't see a totally plastic future. But I do think single use systems will have a huge impact," concludes Michaelis.

References

1. *BPOG, "Extractables Protocol", (2016). Available at: http://bit.ly/2gZq2TN. Accessed December 19, 2016.*
2. *BPSA, "Recommendations for testing, evaluation and control of particulates from single use process equipment", (2014). Available at: http://bit.ly/2gPdVoS. Accessed December 19, 2016.*

Learn More...

Get the latest on single-use technology, validation and regulation with these useful resources.

Particularly Relevant

The Bio-Process Systems Alliance (BPSA), a consortium suppliers to biomanufacturing, has produced a detailed white paper on particulate in single use systems. The document provides helpful and realistic guidance on classifying and reducing particulate contamination – a major focus for regulators.

http://bit.ly/2gPdVoS

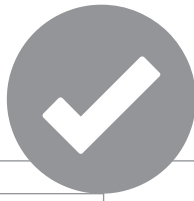
Testing, Testing

Application of single use technology now spans from cell culture to final fill, making it more challenging to determine what to test, when to test and what to do with the resulting data. In this webinar, MilliporeSigma extractables and leachable experts will review industry guidance and advances in best practices in the context of a case study.

http://bit.ly/2hhPlJe

Setting the Standard

The 28-member BioPhorum Operations Group (BFOG) formed a Disposables Working Group in 2012 to produce standardized protocols for extractables for single use systems. BFOG published protocols in November 2014, and members are in the process of phasing in new extractables testing requirements for 2017. The group also makes all the required information available on their website to encourage non-members to use the protocols.



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New Lynx® in the Chain

Current disposable connector technology only allows a single, dry sterile-to-sterile connection per device and often requires complex assemblies in situations where multiple connections are needed. The Lynx® CDR Connector offers users the ability to connect, disconnect and reconnect, while maintaining a sterile flow path for up to six connection/disconnect cycles. Additionally, connections and/or disconnections can be made wet and with the flow path under pressure. This webinar explains how the device works and what testing has been done to validate it.

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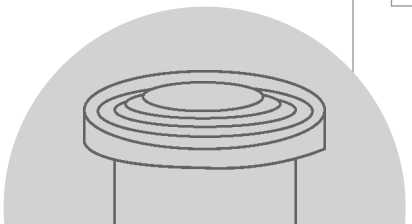
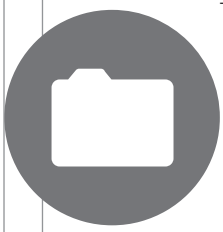
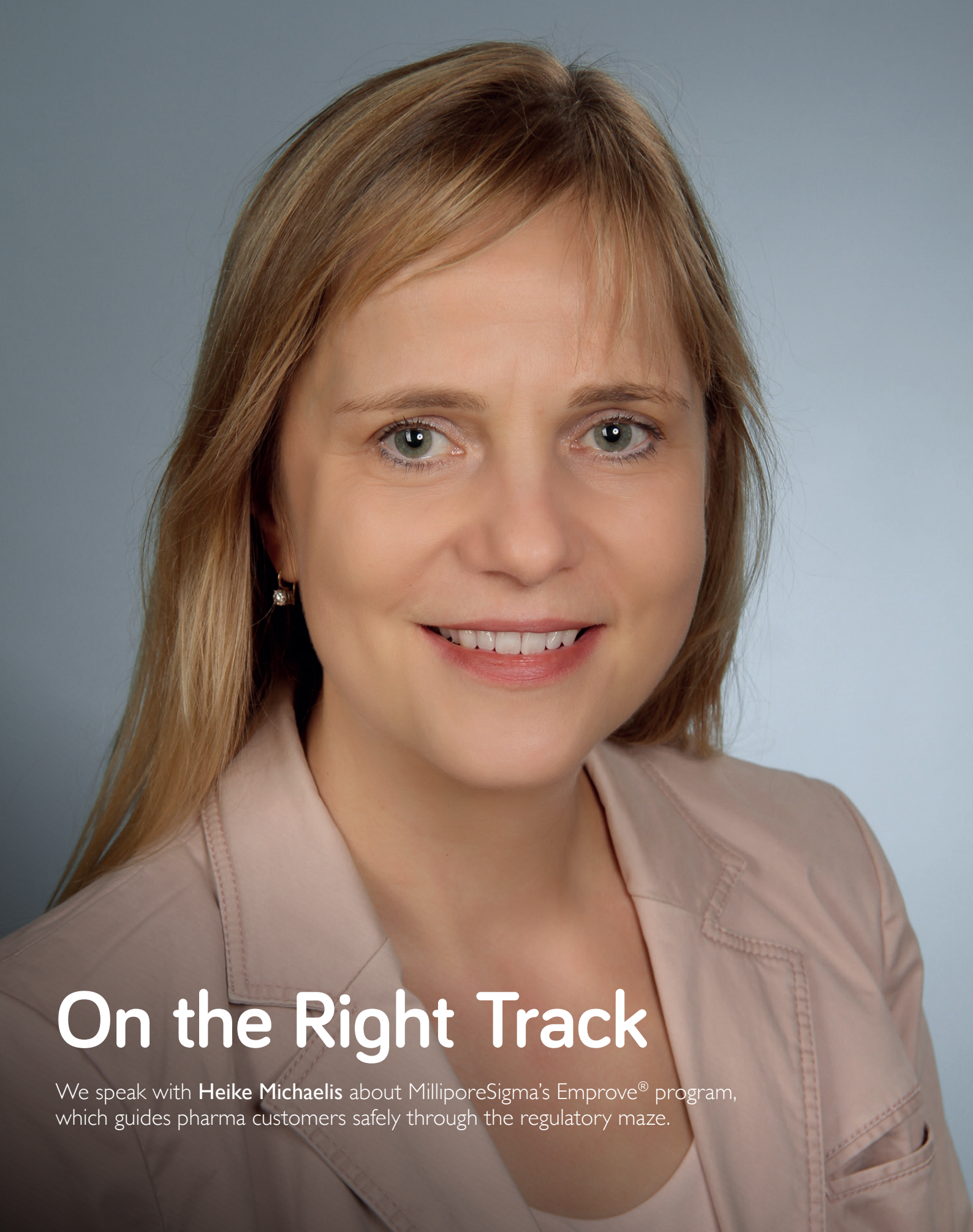


Through the Regulatory Maze



The Emprove® program makes it easy for MilliporeSigma customers to find all the information they need for regulatory compliance, with a series of comprehensive dossiers covering materials, quality management, and operational excellence. Watch a short video interview with Program Director Heike Michaelis, to find out more.

http://bit.ly/2hYW5F8



On the Right Track

We speak with **Heike Michaelis** about MilliporeSigma's Emprove® program, which guides pharma customers safely through the regulatory maze.

What is the Emprove® program?

The Emprove® program makes our wealth of in-house expertise on quality and regulatory topics available to our customers. Already established for our chemicals, we are now expanding the program to include filters and single use components.

Based on thorough internal qualification, a comprehensive set of information around our products and the quality systems applied is made accessible to our customers in three dossiers. Strict procedures are in place to manage the lifecycle of the information.

Our goal is to anticipate and answer the customer's questions before they ask them. Consequently, in the Material Qualification Dossier, we address typical questions customers have during qualification – whether that's for a material, a single use component or another product. The Quality Management Dossier supports our customer's risk assessment. It talks mostly about us – how we manage our quality systems and suppliers, changes, and so on.

Our Operational Excellence Dossier helps customers to optimize their processes. It contains technical data to help customers meet regulatory requirements. For example, the dossiers for filters and single use components include extractable profiles according to the recommendations made by the BioPhorum Operations Group two years ago (1).

All dossiers are available through our Emprove suite – an online library, enabling customers to access the information 24/7.

Why did you decide to expand the program to single use?

The regulatory landscape that covers single use equipment is not yet well developed. Drug manufacturers want to be compliant; if there are no regulations they can refer to, they feel insecure.

When we prepare the Emprove® qualification for a new product group, we put a lot of thought into exactly what the industry needs and expects – above and beyond regulation. We implement product qualification and quality management procedures to ensure that we can answer all those questions for every product in that class. As far as we are aware, no other supplier offers such a mature program or supplies such clear structure and comprehensive coverage of regulatory concerns.

Can you give an example of how Emprove® dossiers are helping companies?

When a customer wants to qualify or re-qualify a material (whether a chemical, filter, or single use component), they need to know technical data of our components and how we validate them. Having all of that product information controlled and consolidated significantly decreases the time and resources needed by our customers to use a product within their processes. We already have examples of customers decreasing the time to enter a new product into their system by two-thirds! Another scenario is when a customer wants to evaluate batch-to-batch consistency during a risk assessment; we provide a product quality report with our chemicals that includes critical parameters (for example, pH value) from all the released batches from the previous year. Opening up this data to our customers allows a high degree of transparency and really helps build trust.

For single use components, what other data do customers need?

As well as providing statements on materials of concern like latex, we include data on how we determine the stability and shelf life of our products. These days, there is also a lot of concern around data integrity, a consequence of our increasing ability to handle large amounts of data. A growing number of FDA audits and warning letters indicate that data integrity is not always at the expected level. Though the systems can handle the data, the industry's processes have not always grown with the systems.

How can we improve data integrity?

Many people talk about supplier relationship management – I think we need to go further. We need to integrate our supply chain, and especially our information systems. We need interfacing systems which are validated from the ERP to the final dossier. But ideally we also need to find a way to connect our system with our customer's systems.

What are the key regulatory questions going forward?

Extractables will continue to be a hot topic. Though standards are being proposed and are certainly useful, the procedure can be optimized for the whole industry. We believe we can make this smarter and leaner.

Another big issue, as noted, is particulates. Specifically, alignment between manufacturers and end users on what amount of particulate is acceptable and how it is tested, because there are no zero-particle processes.

With the Emprove® program we don't just want to cover existing regulations, we also want to address unregulated needs. The industry is always evolving; once you've covered one uncertainty, another will emerge. Transparency along the supply chain and proactive dialogue is the right way for the industry to handle those challenges.

Reference

1. *BPOG, "Extractables Protocol", (2016). Available at: http://bit.ly/2gZq2TN. Accessed December 19, 2016.*

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