BioProcess Insights

A collection of articles examining the trends and challenges of bioprocessing

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The world's first biopharmaceutical was launched in the early 1980s and since then biological products have come to dominate industry pipelines. Today, bioprocessing is commonplace, but it remains a complex and costly activity that can also, at times, be unpredictable. Good decision making is key when setting up a new bioprocess as you'll be faced with many questions. Can a new specialized facility be built from scratch? If not, how can an existing facility be enhanced? Do I use stainless steel or single-use technologies? Which is the most effective? And which is the most cost effective? What will give me a competitive edge in the future? Which industry and market trends must I watch out for?

These questions are being asked by the entire biopharma industry and to reach the best answers I believe that collaboration and the sharing of insight is key. A number of industry groups and organizations, such as the Bio-Process Systems Alliance, are trying to encourage this but equipment suppliers have a role to play too in terms of developing cutting edge solutions and helping companies to deploy them effectively in order to modernize their bioprocess operations.

The Medicine Maker is delighted to co-present this Bioprocess Insight series with GE Healthcare, where Jeffrey Carter, Mats Lundgren, Madhu Raghunathan, Peggy Lio and Jinghui Xu all share their own insight and personal expertise on a different topic of bioprocessing – with the aim of helping you to understand the opportunities for enhancing your operations and to give you the information you need to make the right decisions.

Stephanie Sutton
Editor, The Medicine Maker

Rational human beings make sound decisions based on what they have learned in the past. What could seem like an irrational choice from the outside can make perfect sense if you understand the underlying reasons that led to it. But how do we ensure that we have access to the most appropriate information so that our decisions are not just rational, but the best we could possibly make?

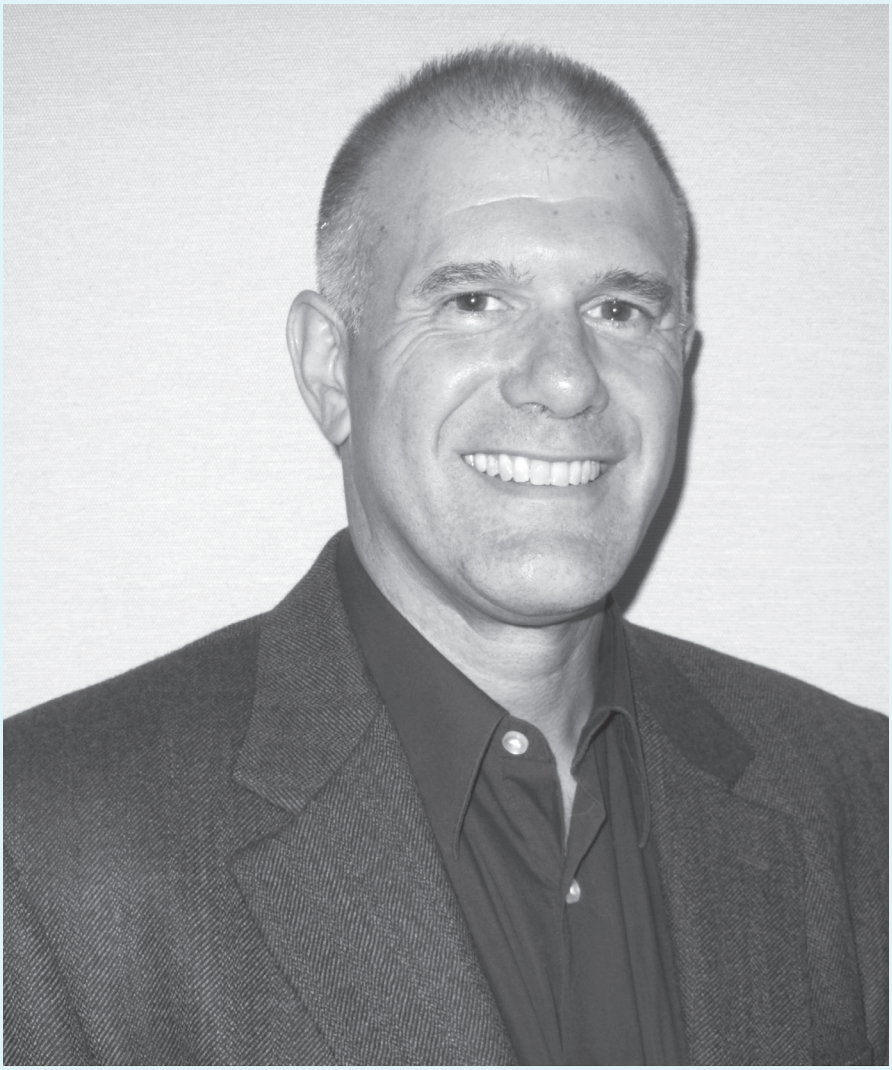
Unfortunately, there is no simple answer. Hard work spiced with a good portion of luck has always been important. However, to increase our ability to make great decisions we need to avoid past mistakes and access thoughts and perspectives from those driving future innovation. It is invaluable to interact with, and learn from, experienced individuals who are willing to share their knowledge and insights gained from solving many different and complex problems in a variety of situations.

This Bioprocess Insight collaborative content series aims to bring you thoughts and perspectives, knowledge and information. The five highly experienced individuals featured here each represent different aspects of modern bioprocessing. They will move through single-use leachables and extractables, modern vaccine processing, innovative downstream operations, clever cell culture strategies, and Asia, one of the most dynamic bioprocess markets today. You will learn about current opportunities and challenges, suitable strategies, and future perspectives. We believe that these insights will help make your future decisions successful, accelerating your bioprocessing journey.

Brandon Pence
Global Marketing Leader, BioProcess

Getting Under the Skin of Extractables and Leachables

There are key benefits to having an industry standard for E&L studies – but a standard is only the beginning. The bigger question is what comes next and how do we dig even deeper into single-use systems?



As Strategic Projects Leader at GE Healthcare, and first Vice Chair on the executive board of the Bio-Process Systems Alliance (BPSA), Jeffrey Carter focuses on the world of single-use manufacturing. He facilitates collaboration, engages with industry stakeholders and fires up discussions to help solve the most critical problems facing users and suppliers of single-use systems. One issue he has focused on recently is the industry's growing uptake of single-use systems and what effect this will have on the way extractables and leachables (E&L) studies are performed.

What is your role at GE Healthcare?

I spend my time trying to identify and understand the most pressing global issues in adopting single-use systems in biomanufacturing – and then investigating how we can help resolve those problems, either within our company or as part of a broader, external industry collaboration.

Single-use technologies are certainly becoming better established, but there are still some issues that users and suppliers must consider, such as addressing particle presence, leak rates, change notifications, and managing the supply chain. One of the most talked about issues is the potential for leachables from single-use material. These leachables could end up as contaminants in drugs and lead to unwanted effects.

What global trends do you see in today's biopharma industry?

Despite the relative youth of the biopharma industry, certain (sometimes inefficient) practices have become engrained. Making drugs, especially specialty biopharmaceuticals, is a notoriously expensive business, and success in today's fast-paced industry often involves bringing down your cost of goods, getting to market more quickly, and managing various forms of risk. To that end, people are trying to figure out how to move away from the 'standard' manufacturing practices (batch unit operations, stainless steel, glass...) and attempting to make their processes more efficient. Two important goals for the industry are to increase the speed and flexibility of manufacturing. Single-use technologies can help in both regards; they are not a silver bullet, but they are very effective at increasing flexibility and can be deployed very rapidly. Conversely, meeting changing needs with a hard-plumbed, stainless steel infrastructure can be difficult.

What does an increase in single-use technology mean in terms of E&L?

E&L is a well-known topic in the industry, as they are a staple tool to evaluate safety aspects to surfaces that are in contact with process fluids or final drug products. People have been talking about E&L for years – and they have been successful in managing it for the most part. That said, E&L have not always been managed in the most efficient way, particularly when it comes to creating datasets.

Today, we're seeing greater uptake of single-use technologies, which means the amount of plastic in the manufacturing line is increasing. Historically in manufacturing, you perhaps had a sterilizing filter that needed E&L testing, which was relatively straightforward. Now, you might need E&L data for the sterilizing filter, in addition to a process bag, a tube set, connectors, and buffer bags. There is also the issue that material changes trigger a new extractables study, which adds to the volume of studies to be managed by both users and suppliers. When you double or quadruple volumes, inefficiencies in the current way of working quickly become apparent. One problem that is significantly adding to the burden is the lack of industry norms when it comes to extractables study designs.

At the moment, end users obtain extractables data from multiple suppliers. But each supplier has their own approach and analytics, so end-users end up with myriad data sets and consequently spend a lot of time, resources and money trying to draw conclusions. From their perspective, it is a frustrating exercise akin to comparing apples to oranges.

Is there enough knowledge in the industry about the importance of E&Ls?

Some people are fully engaged with E&L at a quality level; they understand that E&L study results have intrinsic value in assessing the quality of single-use equipment. Others see it as more of a compliance issue; the work must be done because it is a regulatory expectation, but they are not interested in the gritty details of study design. Others are even more tentative with E&L studies. Indeed, companies sometimes ask for our opinion on how to manage extractables and whether they should be conducting a leachables study. We can help these people by orienting them on how one might design a risk assessment and by providing technical information. Ultimately though, the conclusions and decisions that ensue must be owned by the end-user.

"People have been talking about E&L for years – and they have been successful in managing it for the most part."

How is the industry moving towards standardized E&L studies?

An industry standard for E&L testing, which is being discussed by stakeholders at the moment, would allow everyone to at least read from the same instruction book. We would all know what the study design should look like, and how it's supposed to be executed, meaning that the reports at the end should consequently look very similar. The data would be easier to manage and process, saving time and resources. In reality, a standard would not be a panacea, but it would be a very good start.

And you've been involved in the discussions?

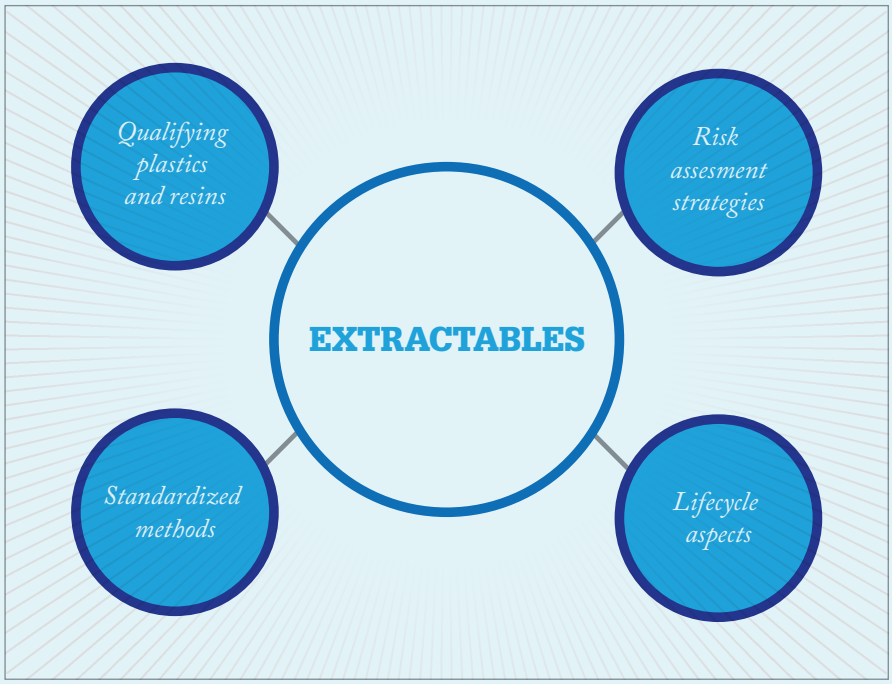
I'm one of the voting members for ASTM's Committee E55 on the Manufacture of Pharmaceutical Products. ASTM is a standards-setting organization, and though it's not the only organization of its type, they do have a very rigorous process for developing and approving international consensus standards. I was on the original committee that was working between the BioPhorum Operations Group and the BPSA to work out a proposal that would be submitted to ASTM. Some of the questions being addressed are:

- what is the correct test article?
- what solvents should be used for the extractables test?
- how long should the extraction be conducted?
- what time points should be used?
- what should the analytics look like?

The big question: what comes after the standard?

It's not clear if or when a standard will appear, but regardless, the standard is just one step. Other topics need to be discussed too. One concern for me is that whenever we test something, there is an element of "testing quality in". In other words, we're assessing whether or not the plastics being used are adequate for the task, but only after the plastic components have already been made. As an industry, we should also be looking to solidify standards that we use to qualify the plastic resins and additives in the first place. In my opinion, this is a good place to practice quality-by-design principles.

We also need to talk about how we use data. Once we have standard datasets, what do we do with them? Those that already know the answer to that question are fully primed to make best use of data. Other companies are not so prepared. When they receive extractables data, they will ask if this is all they need, or if they need to take the next step



and execute a leachables study that is process-specific, rather than relying solely on the supplier's intrinsically generic extractables study. The answer to this question is rooted in process- and product-specific risk assessments. To date, we have seen generalized industry guidance stating that various unit operations are typically seen as high, medium or low risk; however, I wonder if it would be beneficial for the industry to convene a working group to add detail and discuss how risk assessments are conducted.

Finally, we should talk about extractables studies in a lifecycle context. For example, when we consider changes to single-use products, under what circumstances does it make sense to re-do an extractables study? Some argue that in the absence of a change, there is no reason to arbitrarily re-do the study; others argue that processes drift over time and that it would be good practice to re-do the studies at some to-be-determined frequency. These questions are best addressed as an industry collaboration.

"It is interesting to turn the question around and ask how the industry will affect single-use technology."

How else do you think single-use technology will affect the industry?

Clearly, technology is always evolving as suppliers improve the products they offer, but change management practices often prevent users from adopting intrinsically better, more robust, solutions. I am hopeful that we can strike a new balance that can open the change pathway. The concept of "functional equivalence" is one that the industry should explore. At GE, we don't want to "force" changes on our customers; rather we want to share information about what options exist and by doing that help them to make well-informed decisions. The more insights we have and can share, the better the final outcome.

Single-use technology will also mean changes for the supply chain. Adopting single-use manufacturing means that the end-user will relinquish direct control over some quality attributes of their manufacturing equipment and become more dependent on the supply chain. This in turn leads to a need for more information flow from both up and down the supply chain, which will only happen when there is mutual trust. To this point, I think end-users are starting to grapple with the natural tension that exists between wanting to play suppliers off on each other to foster competition, and wanting to develop these more seamless partnerships that are key to managing quality in a single-use equipment environment. It is instructive to ask the following question as we all work our way through our new relationships with our suppliers: are we buying commodity items that can be replaced without skipping a beat, or are we developing security of supply?

The speed and flexibility advantages of single-use equipment are likely to continue to play out, and we will see how the industry adopts this technology on a more wholesale basis in commercial manufacturing, as opposed to process development and clinical batch production. The technology advances are likely to proceed more quickly than the strategies for managing the quality of the technologies and the control of the technologies to assure predictable and reliable performance. From this perspective, it is interesting to turn the question around and ask how the industry will affect single-use technology. I think the more advanced end-users will have a marked influence on not only the technologies that we develop, but also the control strategies that we adopt to support the technologies from a quality perspective.

Bringing Vaccines into the 21st Century

Medicine manufacturing has benefited from countless advances in technology over the last few decades, and yet many vaccines are still being produced with decade-old processes. Change is never easy, but is falling behind really an option?

Mats Lundgren has an intense interest in the field of vaccines, with an academic and professional background to match. Dr. Lundgren's passion is understandable; vaccines have helped conquer numerous healthcare challenges and no doubt have a great deal to offer in the future. Despite their value, many vaccines are still being manufactured using legacy technology such as eggs or animal tissues. Today, Lundgren works as Customer Applications Director at GE Healthcare, where he helps companies with implementing modern processes. The end goal? More efficient production and higher vaccine quality.

What was your route into GE Healthcare?

I've worked for several biotech companies over the years, but the reason I joined GE Healthcare in 2008 was because I wanted to be more applications-focused and to work more on the technologies used in the biomanufacture of monoclonal antibodies and vaccines. Vaccines are a really interesting area for me. Not only do they have a major impact on health worldwide (it is thanks to vaccines that we were able to eradicate smallpox) but they are also interesting from a technology point of view. We have seen lots of advances in this area, particularly in terms of single-use technology. At GE, I support our customers with application knowledge, such as how to use innovative products and how to implement new processes.

What are the global trends in the vaccine industry?

Consolidation is one big trend right now. It's being seen across the developed pharma and biopharma industries because of cost pressures and the need to be more efficient. In the vaccines area, we've seen major deals such as GlaxoSmithKline's acquisition of Novartis' global vaccines business, which took place earlier this year. Large vaccine manufacturers based in Europe and North America are also seeing increased competition from developing markets. More and more companies, mainly in Asia but also in Latin America, are setting up their own domestic vaccine production. In some cases, this is for their own market, but many companies are starting to export. For example, The Serum Institute of India is a huge exporter of vaccines to UNICEF.

Importantly, I think we're also seeing a greater appreciation of the value of

vaccines. In the 70s to 90s, vaccines were to some extent considered low-profit products, but now decades of research is starting to come to fruition with the development of more advanced vaccines. Some vaccines could have the potential to even treat disease, such as cancer vaccines. I believe these advances have renewed interest in the vaccine field.

What are the main problems with traditional vaccine production methods?

Some vaccines on the market are produced using egg-based processes and technologies that were developed decades ago. Egg-based vaccine manufacturing is a lengthy process and companies have to predict demand ahead of time. Production can't be accelerated or ramped up in case of a pandemic, and sometimes there may even be situations where eggs cannot be secured in the correct numbers, such as during an avian flu outbreak. Other processes may include a lot of manual handling (for example, with open flasks during expansion of adherent cells), which can be a quality risk. Moreover, the demand for human resources makes production costs high. And it's not only the technology that is behind the times; the industry still uses a lot of animal-derived raw materials, which can carry the risk of contamination.

These drawbacks are being increasingly recognized by the vaccine industry, particularly in light of increased competition in the field. Vaccine manufacture needs to be faster and more efficient – subsequently, companies are starting to look at how they can bring processes into the 21st century. If you're wondering why it's taken so long to come to this realization, you need to consider that vaccines haven't traditionally turned big profits, which didn't match the fact that modernization requires investment. In addition, vaccines tend to be used in healthy individuals (and many children) and must not give rise to unwanted side effects. Thus, there was a mentality that if the old processes work then why should they be changed? And what if changing a process brought about a new side effect? Costly clinical trials might be required to show that the new processes indeed can produce safe and efficacious vaccines. In my experience, updating processes improves product quality, especially as that usually means using the most modern systems, which have been specifically designed to improve manufacturing. Change, of course, always involves an expense, but this can be balanced by a better process economy (and lower production costs) in the long term.

"These drawbacks are being increasingly recognized by the vaccine industry, particularly in light of increased competition in the field."

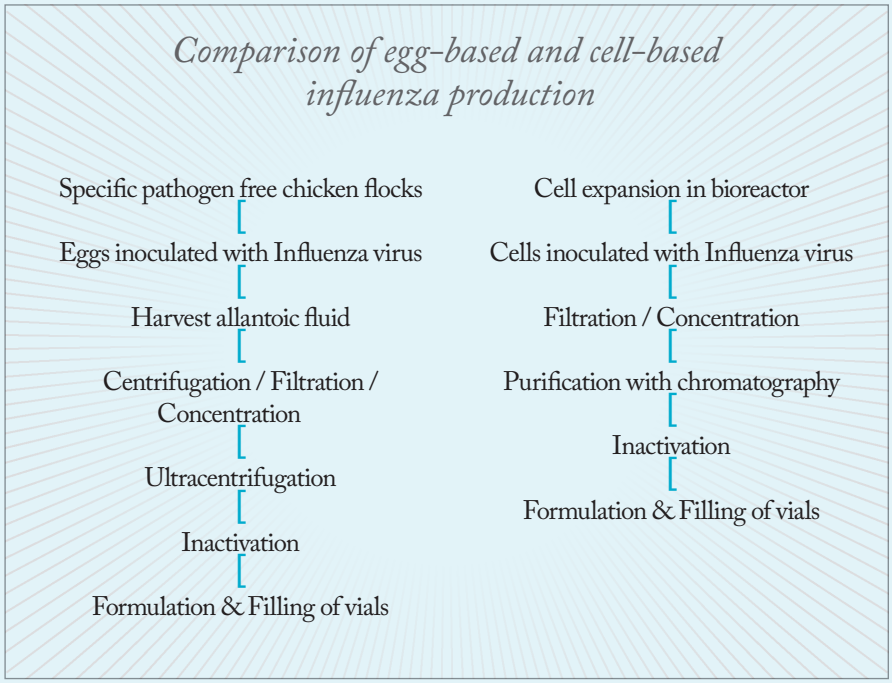
What changes are being made?

We are seeing a shift away from egg-based to cell-based production, which is a very well-defined process. Changes are also being seen in technology; instead of centrifuges, you can use chromatography to purify vaccines; instead of stainless steel bioreactors that are difficult to clean, you can use single-use bioreactors; instead of growing cells on the surface of (many) flasks you can grow the cells on microcarriers, which are tiny beads inside a stirred bioreactor. There are also newer cell culture products available that help to more efficiently propagate the viruses and bacteria, as well as analytical tools that can control and track what is happening throughout the whole vaccine production process. The key benefits of all of these new technologies is that they are faster, more efficient and take up less space. Most new technologies have also been designed to accommodate the industry's need for more flexible manufacture by being modular and disposable.

How do attitudes to new technology vary among companies?

Overall, I believe that most companies are really keen to use the latest systems available to them, but at the same time they are also cautious. Many established companies have been using the same processes for 50 years or so. Their facilities are well established and often built around these old plumbed-in processes so it's challenging to accommodate changes – both from an infrastructure point of view and a regulatory point of view given that they are working with long-approved products. But this doesn't mean that updating is impossible. I don't think it's very useful to tamper with an established process just because of cost, but if it benefits vaccine quality or purity then the change will be appreciated by regulators because it will result in a better, safer product overall. A complete retrofit of a plant may be difficult but smaller steps can be taken; for example, getting rid of tissue culture flasks and moving to disposable bioreactors. This change can easily be justified because of the quality benefits.

The big opportunity for change for established manufacturers comes when they are developing a process for a new vaccine, expanding production or building a new plant. There is an opportunity here to employ modern



technologies, gaining the benefits right from the outset. I see a lot of companies – even large, experienced ones – that try to work with processes that were originally developed for lab-scale work rather than commercial manufacturing. Scale up in this instance can be a frustrating experience. Working with modular, scalable technologies right at the beginning saves a lot of time.

Companies new to vaccine manufacturing are perhaps more able to implement the latest technologies because they are designing their processes and plants from scratch, so there is a real opportunity to get a competitive edge on established companies by employing modern, efficient manufacturing technologies. Some of these new manufacturers are located in areas where the regulatory framework might not be as well developed as perhaps Europe and the US. However, these countries are catching up very rapidly and, as mentioned earlier, companies in developing markets are keen to export and will be looking at technologies that can facilitate the consistent production of products in line with global quality requirements. Not all companies are aware of the complexities of establishing a new vaccine plant, particularly one that aims to export. And this isn't just a problem in developing countries – any company anywhere in the world can encounter production difficulties and trouble with scale up, but this is where we come in with our advice and support. It's not just about selling technology – it's important to offer support and knowledge too. And this increases trust between the vendor and customer – and means that our products are used in the best possible way.

How can companies overcome the challenges of change?

Knowledge is crucial. First of all, you need to have a solid understanding of your processes and product to understand where the opportunities for change and an increase in product quality and production efficiency lie. Next, you need a good grounding in the latest production equipment and single-use systems so that you can see how these will fit into your processes – or how they can be used to create a new process from scratch. Finally, you need regulatory knowledge so that you can understand current requirements.

At GE, we've tried to raise awareness of the problems facing vaccine manufacture and of the benefits of new technology. We speak with our customers frequently to understand their problems, we speak at conferences and we are also starting to work with industry organizations, such as DCVMN – the Developing Countries Vaccine Manufacturers Network. This is a powerful organization where manufacturers in developing countries can share their knowledge of new production technologies, as well as regulatory and quality aspects.

What are the real risks of being left behind?

A big part of my role is to visit companies and to talk about the different technologies and how they can be implemented in different processes. I always propose changes that will impact the final vaccine product in a positive way. Companies that don't embrace the potential benefits of modernization could become obsolete. More and more companies are keen to enter the industry and this growing competition means you can easily become outdated. That may sound a bit dramatic, and I don't expect to see companies immediately dropping out of the market, but to secure a long-term future, I think you need to examine the benefits of updating your production processes. It's very tempting in the pharma business to stay with the same old technology that you know and trust, but it's an attitude that can come back to bite you sooner or later. We are firmly in the 21st century. Do we really want to be producing life-saving products with legacy systems?

Breaking the Bioprocessing Bottleneck

Battling logjams in downstream processing is a constant challenge, but even when it feels like there's no room for maneuver, small yet clever steps can help gain efficiency. And sometimes a fresh pair of eyes can find new and surprising solutions.

Originally aiming for a career in traditional manufacturing, Madhu Raghunathan obtained an advanced degree in engineering, but later found a passion for the application of innovative technologies. Today, Madhu is Product Strategy Leader at GE Healthcare Life Sciences, where he is tasked with scrutinizing the latest advances in downstream processing operations to help companies identify opportunities for greater efficiency. But the quest for efficient downstream operations is not easy, particularly when you must balance solutions against existing constraints. Fortunately, such problem solving is exactly what Madhu enjoys.

How do you get involved with downstream-processing challenges in your role at GE Healthcare Life Sciences?

My role is to specifically focus on downstream processing. I analyze the market, and study the trends, challenges and constraints facing our customers. From there, I look at how we should evolve our portfolio to ensure that we can address these problems and help make downstream bioprocessing operations more efficient. It's a fascinating area because the solutions and technology applications vary depending on the situation – there is no 'one-size-fits-all' approach. I must look at how innovative technology and a combination of approaches and knowledge can be pieced together to solve real-life problems in a practical way. I'm very interested in process analytical technology, continuous processing, automated unit operations and real-time product release because there are a lot of innovations being seen in those areas. But across the board, whenever GE gets involved with downstream processing, I am happy to join the team to examine areas that can potentially be improved.

Could you provide some examples of technological innovation?

I'm seeing a lot of interest in automating unit operations as recent developments in automation platforms facilitate efficiency and scalability. A lot of companies are also looking at the potential of continuous chromatography and continuous processing; some companies are starting to experiment with continuous chromatography for one purification step, while others are rolling out continuous processing for their entire chromatography operations – or even looking at an end-to-end continuous downstream processing operation. That said, I think that mainstream adoption of these techniques is still a few years away, as they are still novel and the industry is still figuring out how best to implement and use them.

One technology that is becoming

more mainstream, however, is single-use systems. Companies are definitely more aware of – and more at ease with – the challenges and benefits of single-use technology. I've seen a lot of 'hybrid' processing operations that use single-use technology for certain steps, and then traditional stainless steel for other steps, resulting in more economical and functional processes.

What are today's most common downstream bottlenecks?

Historically, resin capacity constraints and column footprint were perceived as the main bioprocessing bottlenecks, but these aren't really a problem in today's industry where binding capacity and downstream productivity tends to be high. This is in part thanks to new developments in downstream processing equipment and materials. However, this doesn't mean that bottlenecks no longer exist; on the contrary, I believe that most bioprocessing companies today face some form of bottleneck in their production processes. This is especially true for companies that have legacy production facilities.

One common bottleneck is inefficient process handling during scale up, such as moving from pilot- to full-scale manufacturing. Many different steps make up downstream processing and all of these need to be scaled up, which can involve hold times for buffers and necessitate new controls to manage things effectively. In addition, once you start scaling up in volume you start to see increased preparation times and higher footprint requirements. If your processes aren't efficient, then delays can occur, which can cause buffers to be held for too long or affect time-critical steps.

Another common bottleneck is column packing. While traditional column packing is a very slow and manual process that requires testing activities, it is still used by many companies.

Single-use technology is a third potential bottleneck that companies are not always prepared for. The vision behind the technology is that you 'plug and play' a new component and then move on with your processing. Single-use technology certainly offers many advantages but the implementation can also include challenges. Such challenges are often related to the infrastructure that is already in place. In addition, single-use technology will require additional qualification activity, such as extractables and leachables studies.

Another common bottleneck is cleaning and its validation, which affects many areas of pharma and biopharma manufacturing (interestingly this bottleneck can be mitigated through strategically employing single-use technologies).

"I'm sure we all wish we had a magic wand that could transform everything to a lean, productive process stream – but transformation is never easy."

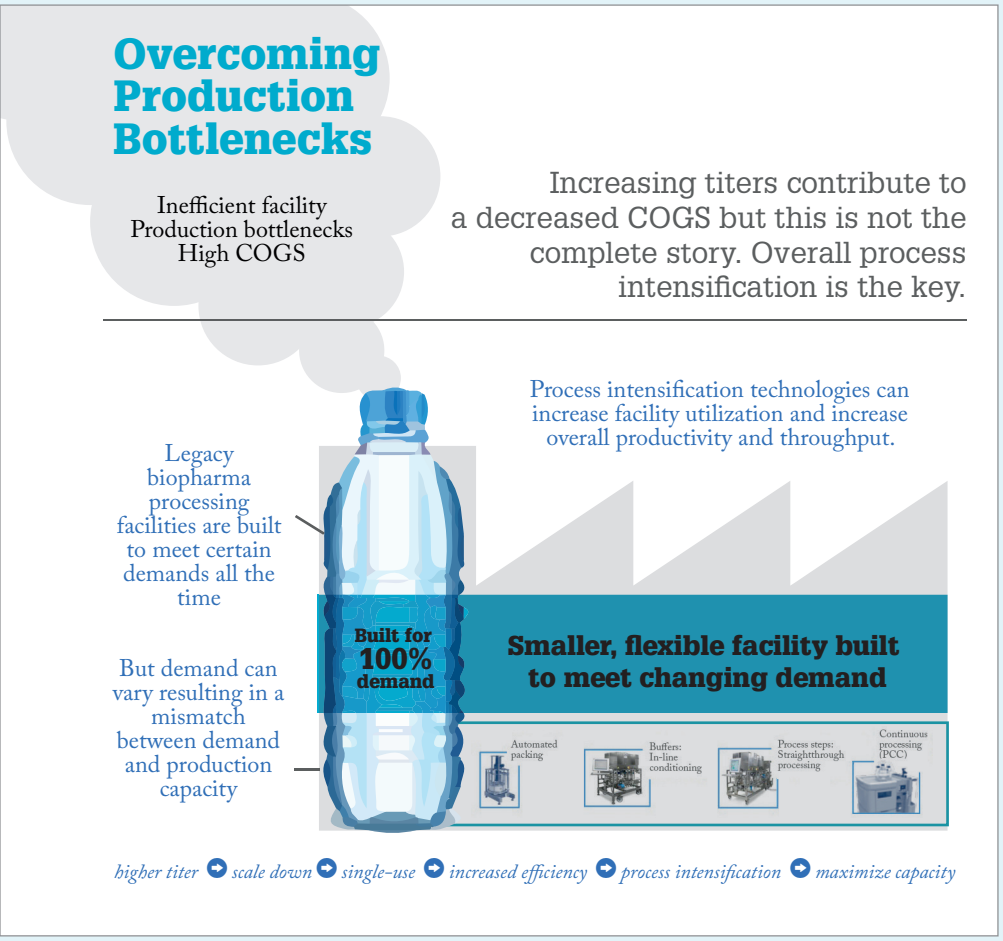
And do you have any solutions?

When it comes to proper buffer preparation and buffer handling, there are a couple of approaches. One effective solution is to formulate your buffer using concentrated stock solutions at the right point just in time – this is known as in-line conditioning and is really helpful in driving down preparation times, as well as the area and volume required for hold vessels. It makes the process of buffer preparation a lot more efficient by diluting concentrated buffers as and when required in the downstream process.

With regards to column packing, technology can lend a helping hand. Pack in and place technology uses nozzles that somewhat automate the column packing process. Or, even better, there are now columns that employ axial compression technology, and columns that utilize intelligent packing methodology to simplify the packing workflow and help prevent column packs from falling outside of specifications on a consistent basis. Companies can also consider utilizing pre-packed, pre-sanitized, and ready to use columns for pilot scale operations or for campaign use as a means of intensifying their purification process. With the right systems and ancillary products, it's possible to consistently automate most of the operations around column packing.

As for single-use technologies, I recommend that you have an upfront discussion with a vendor to see what can be done to facilitate the implementation. You need to introduce the technology in a way that is comfortable for you – and you'll also need to ensure that there is a framework in place for submitting a change control notification in a timely manner. I think that users and vendors should share some of the burden when it comes to rolling out single-use technologies. At GE, we have done a lot of work in ensuring security of supply and building knowledge around integrity testing and single-use qualification. This is essential to allow the industry to reap the benefits.

As for cleaning (and validation) bottlenecks, there are several solutions. As mentioned previously, single-use technology is one. Another approach



is to design your bio-burden control strategy in a very effective way and to leverage recommendations made by the manufacturers with regards to how you clean and validate your equipment. In this instance, the documentation that you get from equipment vendors is useful.

Do you think there is a solution for every bottleneck?

I'm sure we all wish we had a magic wand that could transform everything to a lean, productive process stream – but transformation is never easy. Sometimes companies fail to address bottlenecks because they are constrained to doing things a certain way. Biopharma is very regulated and many facilities were built up years ago with legacy infrastructure that can make the incorporation of new technology challenging. It's tricky to balance your constraints with the need to be more efficient, but there are always at least a few steps that you can take.

For example, one area of concern for all companies is resin and slurry wastage. How do you ensure that your resin is effectively transferred from the container into the column – in an aseptic or a near aseptic manner – whilst ensuring minimum or even zero wastage and, at the same time, ensuring that your slurry has been homogenized properly and that the slurry concentration has been measured accurately? There are solutions that help to improve and automate this process to make it more effective – and these solutions can be implemented irrespective of how the facility is set up. As I mentioned earlier, column packing is another common bottleneck and again you can implement new technologies here to bump up efficiency, regardless of facility constraints you may be facing.

There are a wide variety of solutions in the downstream toolbox, from resins, to columns and systems, to consumables – and our toolbox is constantly expanding. When I'm looking at problems, I pick and choose the right tools and solutions depending on the specific situation (and constraints) that I'm dealing with. There is always something. I strongly advise working closely with a vendor because they will have worked on many different projects in many different facilities, which gives them a huge amount of process experience – you may be surprised by the innovative ideas that they can propose.

How can biopharmaceutical companies prepare for future requirements?

Whenever you are looking to build a new facility or revamp an old one, it is crucial to have a good understanding of not only your current requirements, but your future requirements too. Historically, companies have built a large facility and made a huge investment upfront, with the expectation that the demand would come later. But it could take several years to build up a reliable cash flow, which is clearly not the most effective way of building a business. It is far better and more cost effective to keep capacity in line with demand. By designing a facility to be modular, you can meet current demand and build up when necessary.

Part of my role is to make sure that companies have this in mind and I recommend that you think carefully about the scale of operations, throughput and type of facility infrastructure that you may need in place. Are you going to have a controlled environment? What is grade-space? What are your future expectations? Are you going to manufacture a single drug or are you going to manufacture multiple products? Answers to these questions and others all play a big hand in the way a facility is built up. Remember that one size does not fit all! Just because something worked in a specific scenario at a specific scale does not mean that it will work work at any scale or in any production paradigm. We must think carefully and make the right choices. After all, selecting the correct solution is a critical factor in making your operations as efficient as possible.

Making Media Better Than Average

Cell culture media developers used to focus on maximizing protein yield. But yields are yesterday's problem, and some might ask if it's worth continuing to tweak culture media – isn't what we have today good enough? No, because your cell culture medium can improve biomanufacturing output above and beyond mere titer.

Peggy Lio is Global Leader of Cell Culture and Process Sciences at GE Healthcare. She originally started her career in big pharma working on Intron A, one of the first biotherapeutics to receive FDA approval. After seeing the bioprocessing industry evolve from the early days through to its current complexity, Peggy is curious to see what the next developments will be. Here, she discusses how she applies her experience from both sides of the fence – as an end user and as a supplier – to help improve cell culture process performance.

What is your role at GE Healthcare?

I lead a team of senior process scientists and our remit is to help people with their cell culture process development issues. And this is a great opportunity for me because I am able to use my experience from large pharma to help customers with the same problems that I myself have faced and overcome. So we collaborate with customers and offer solutions to issues they may have and make recommendations for how the process can be improved based on our experience. There's also a lot of connectivity to experts in related bioprocessing areas – both upstream and downstream. For example, cell culture media is intimately linked to mixing technology to ensure the right preparation for large-scale use. Or if a customer has an issue at the bioreactor stage, I can link our process development expertise to the know-how we have in bioreactors. At the end of the day, it is all about providing holistic, integrated solutions that provide performance and efficiency gains.

What general trends are you seeing in cell culture media?

About 10 to 15 years ago, the focus was on optimizing monoclonal antibody titers in CHO processes to support the manufacturing of blockbuster biotherapeutics. The main driver was to increase titers to decrease COGS. Years of effort went into that and now there are many excellent cell culture media available that can support the production of high titers of antibodies – 3-5 g/liter or more – from CHO cell lines. So today, titer is no longer the main issue and the current focus is instead on product quality and reducing variability. Biosimilars have influenced this shift because developing a biosimilar is not as straightforward as developing a small molecule generic. If you think about a biosimilar compared to the innovator product, starting from a cell all the way to a final therapeutic, nothing in the production process will be exactly the same; the cell line is going to be different, your process is going to be different and your medium is going to be different. The medium that was originally used for the innovator process is probably a decade or more old (and quite likely proprietary to the innovator) and may not include some of the recent advances in cell culture media design. For example, the original medium may contain hydrolysates. Hydrolysates have been associated with quality issues so the industry is now aiming to move away from them entirely. We often work with both innovators and biosimilar developers on how we can improve media formulations to take advantage of all the lessons learned in the manufacture of large molecule biotherapeutics.

Looking at other product areas, the trends are a little different. Vaccines, for instance, are still evolving; many companies still use legacy processes with different cell types and media, including non-chemically defined, serum-containing media. While it's difficult (and costly) to change traditional vaccine production processes, I think we need more modern media designs, especially for new vaccines. Historically, vaccines were to some extent seen as a commodity, but this is changing rapidly now and the vaccine area is getting

‘Titer – yesterday’s problem?’

Year	*Protein titer*
1982-85	5-50 mg/L
1985-2005	50-1,000 mg/L
2005-2010	1,000 – 5,000 mg/L
2010-present	>5,000 mg/L

Other numbers

Number of components in classical RPMI 1640 medium:

42

60-80

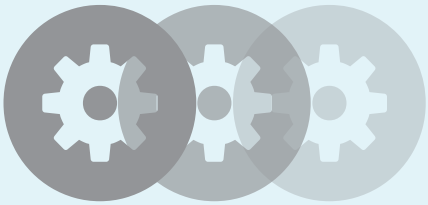
Average number of components in a modern, chemically defined medium:

Comparing batch and fed-batch

A 20 L *fed-batch process takes typically 14 days and consumes 20 L medium in total.*

A 714 mL **perfusion process, perfused with 2 reactor volumes per day in 14 days consumes** **20 L** medium in total

Now that difficulties with product yield have largely been resolved, process design can focus on optimization of culture media to address other issues in protein manufacture. In particular, close attention to media choice, with due reference to its impact on each step in an integrated biomanufacturing process, will enable yields to be maintained while product quality is enhanced.



A modern process:

In a bioreactor with a volume of:

1000 L **You can grow:**

20 000 000 000 000 cells

That can produce:

5 kg antibody

If your annual batch production is: 20

This process will generate 100 kg of antibodies

a lot more attention. A recent example is the Ebola breakout and the need for an Ebola vaccine.

Another area receiving increased attention in the industry is continuous processing – and this means that cell culture media need to be specifically evaluated and optimized for perfusion processes. This is a great example of why it is good to have a breadth of experience; it's not just about understanding media, but understanding the whole process and how the medium fits into it.

Does this mean that culture media should not be seen as a stand-alone product?

Right – cell culture media should be considered in the context of the whole process. For example, some cells are more shear-sensitive than others, so you may need to increase the amount of shear-protectant in the medium if you are operating under high-shear conditions. However this may have implications downstream so a change in the medium formulation might warrant additional changes elsewhere. Another example is when you have a cell line that is prone to clumping; we can often fix clumping by modulating the concentration of specific components in the medium. But again, this change needs to be evaluated from a holistic process perspective so that you don't surprise your downstream colleagues at a later stage. Therefore, you should never consider cell culture media in isolation.

What issues do your clients often ask you to solve?

A common issue is the trade-off between product yield and product quality. There is definitely a balance that needs to be struck, but addressing product quality comes first, followed by finding ways to improve titer without sacrificing your quality requirements. It isn't always an easy process to address product quality, but we have found that if post-translational processing isn't right, there are things we can tweak to get you the desired variants and the glycoprofiles. And it's easier to adjust processes and media upfront than to remove unwanted protein variants at a later stage! We recommend tweaking your parameters and media at the very beginning, when you are selecting cell clones that will move into process development for biomanufacturing.

Another time when clients may encounter problems is at scale-up – after a final cell clone has been selected. During clone selection and at the beginning of process development, you use ready-made, liquid media in small volumes. But when you scale-up, it is often easier to utilize powder media for a variety of reasons; longer expiry period, lower shipping costs and less demand on warehousing, to name a few. So as you scale-up, you use powder, it's shipped as a powder, and reconstituted at the site of use. But then the question becomes, is the liquid I used in the lab the same as the liquid being used at the site where my biotherapeutic is manufactured? The quality of the water used to rehydrate the medium may be different from site to site. Similarly, mixing with water at the liter scale on the lab bench is not the same as rehydration at large-scale. There can be issues of time, pH, sterile transfer methods, storage conditions, and stability. Reconstitution at manufacturing-scale is not straightforward; even such an apparently simple step can change significantly with scale-up.

How do companies choose the right cell culture media?

We advise customers to consider the cell culture medium as early as possible – right when they start thinking about cell line development. This is especially important given the tight time constraints associated with biotherapeutic development. So when you are choosing your clone, you should also be thinking about the cell culture medium and its impact on your complete process. Critical media attributes need to be thought through very early on to ensure that you find the right solution, or provide the right guidance to your supplier to create a custom solution. Do you want the medium to be chemically-defined and animal origin free? Do you want an off-the-shelf product, your own formulation, or one customized to your specific cell line and process? An off-the-shelf product will be more readily available, and there are multiple high-performing media out there, but a customized medium will be optimized for your own cell line, so you should expect better results.

Do you think that the next-generation processes will trend towards using ready-made media or customized formulations?

I believe that if you work closely with a quality, experienced media supplier then you can probably get similar results with off-the-shelf media as you would with customized media, in a much shorter time. Although granted, there are times when customization is required to achieve performance, process or efficiency goals. It's all about understanding your needs and how the cell culture medium fits into them. And that in turn suggests the ideal supplier profile; customers should choose a company which is flexible, accessible and communicative, and that has relevant expertise. This expertise should enable you to have a choice of off-the-shelf media developed with the latest insights, as well as the know-how to quickly customize a solution if the situation requires it. The supplier should also resemble the client in terms of exposure to the whole bioprocess. Cell culture media is not a stand-alone product, and customers need a supplier that understands both the media and the process as a whole, and how the chosen medium fits into the bigger picture. In my opinion, many suppliers are similar when it comes to their access to manufacturing facilities and the quality of raw materials they use. The big difference is in their understanding of the entire process, which affects the services and products they can offer – and ultimately this will have an impact on the final quality of the cell culture medium that is delivered.

The Rise of Asia's Biotech Tigers

The western world could be considered king of the biotech jungle, but eager biopharma tigers from the east are hungry for a piece of the action – and they are gaining ground. Can single-use technologies help them to catch up even faster? Jinghui Xu believes so.

The potential for biopharmaceutical growth in Asia is no secret – and it is estimated that around 50 percent of the world's new bioprocessing facilities are being built by companies in Asia, including both local companies and international giants. Jinghui Xu's goal as GE Healthcare's product leader for single-use in Asia is to use his background in polymer science, plastics and bioprocessing to help companies truly understand the best single-use components for their products and processes.

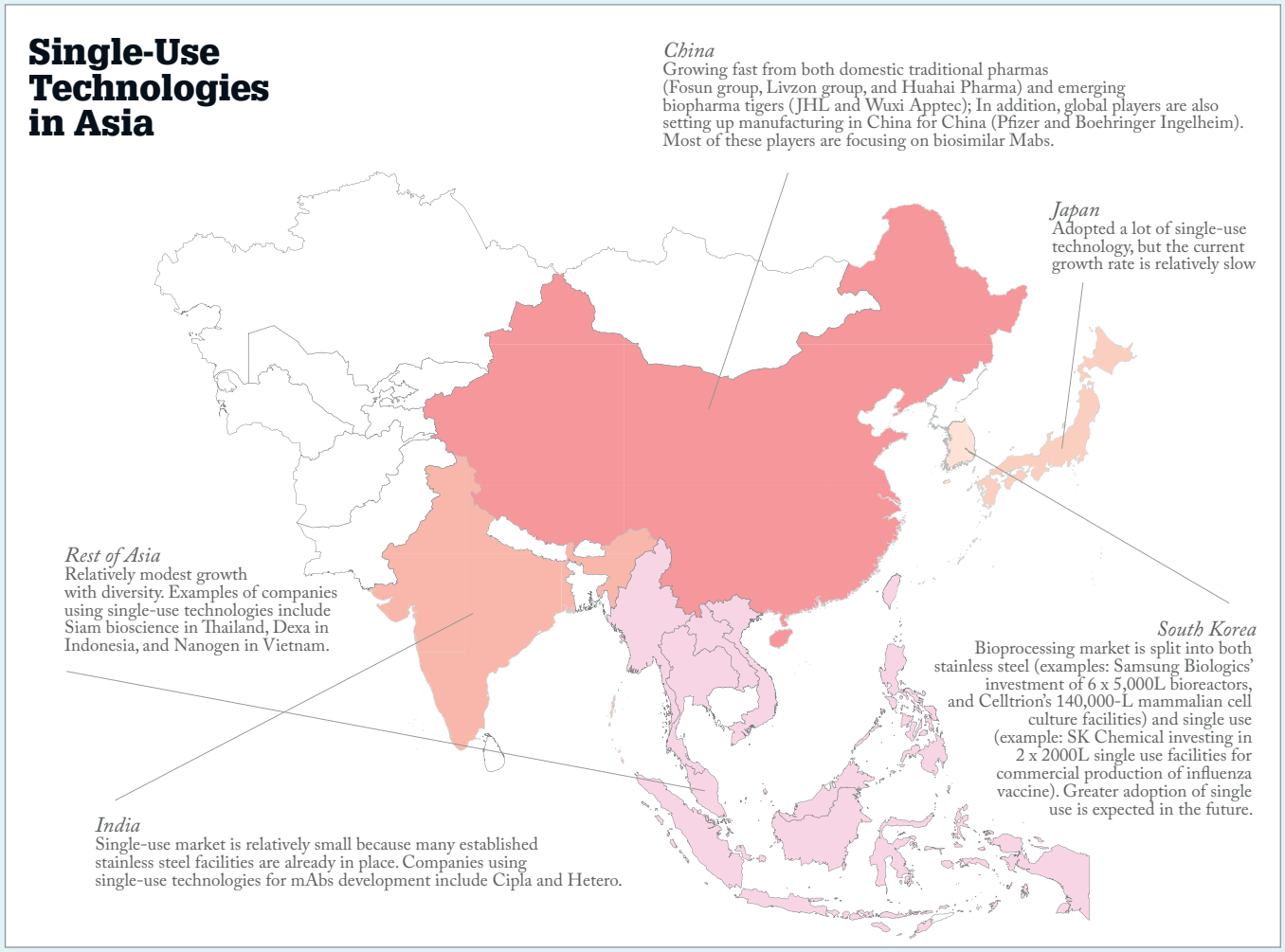
What are the latest trends in bioprocessing in Asia?

The biopharma industry in Asia started much later than in the West, but it's catching up rapidly. A number of Asian 'biotech tigers' are emerging and growing rapidly; to name just a few, Shanghai CP Guojian and Wuxi Apptec in China, Dr. Reddy's and Cipla in India, Chugai and Takeda in Japan, and Samsung Biologics, and Celltrion in South Korea. And there are many more that are also growing rapidly. That said, western biopharma companies are not sitting by idly; 60 percent of the world's population live in Asia, representing an enormous market opportunity, and many global companies are establishing a manufacturing footprint in Asia to supply the local markets.

The main focus in Asia at the moment is on biosimilars – particularly biosimilar monoclonal antibodies (mAbs). China is a big force in this area, with over 100 mAbs being developed by various Chinese companies. Vaccines are another large area for Asia, as governments develop initiatives to immunize their populations. Not surprisingly, these companies are keen to use single-use technologies as their benefits enable them to bring biotherapeutics and vaccines to patients more efficiently. Right now, the main focus is on upstream operations, such as suspension and adherent cell culture processes, aseptic connections, and mixings, as well as in later process steps including single-use chromatography, final formulation and storage.

And what differences are you seeing between individual countries?

Although there are common trends, each country in Asia has its own specific dynamics. I tend to divide Asia into five main geographies: China, India, Japan, South Korea, and then the rest of Asia. Currently, China is probably growing the fastest thanks to a combination of governmental support and an outpouring of private investments. It is also leading the way in terms of the implementation of single-use technologies. Chinese companies seem to be well aware of the advantages of these technologies; I mentioned before that biosimilar mAbs are a focus in the country, but one problem is that many companies are focusing on the same molecules, which creates competition. This competition drives urgency in getting their products



to market quickly and single-use technologies are a good way to achieve this since they are easy to deploy, flexible and eliminate the need for cleaning and cleaning validation, among other advantages.

India is currently recognized as the world's largest biosimilar producer and it also has a very well-established vaccine manufacturing industry. It has been building its biopharma industry for quite some time now and, as with the West, there are a lot of fixed stainless steel facilities. The focus now is further growth and industry upgrade. The appetite for single-use is perhaps not as strong in India as in certain other areas of Asia, but some companies are still seeking a competitive edge by choosing to upgrade aspects of their processing operations with single-use systems.

Japan is a developed country with a well-established and highly respected healthcare industry – and biotechnology is one area that the government is actively promoting. One of the drivers is that the country is considered to have the world's oldest population, with 33 percent of citizens being older than 60 years, according to data from 2014. This is a demographic challenge for the country and a catalyst for continued investments to ensure good medical supply in the future. Japan has adopted a lot of single-use technology – and is the second largest single-use market in Asia. However, the current growth rate is relatively slow compared with the country's overall biopharma market.

South Korea is reacting to biopharma the same way it reacted to the rise of the electronics industry – by making enormous investments in infrastructure and providing incentives to business willing to grow locally. I would say that the bioprocessing market is split between both stainless steel and single-use in South Korea, with investments being made in both areas. However, the emerging companies seem to prefer single-use – and a growing number

of established companies are looking to implement single-use in certain operations to improve efficiencies.

As for other markets throughout the rest of Asia, there are vast differences between the developed and developing countries. In Singapore, Amgen announced a $200-million biomanufacturing facility, which uses single-use in 90 percent of the plant's operations. Indonesia, Vietnam, Malaysia and many other countries throughout Asia are also investing in local biotechnology development programs that bring biotherapeutics and vaccines closer to their populations.

It seems single-use technologies are particularly enticing for Asian manufacturers...

Yes, Asian customers are very positive about single-use. A representative comment came from Scott Liu, CEO of Henlius Biotech, part of the Fosun Group in China, who told me, "Single-use is really changing the world of bioprocessing, and it is one great technology capable of delivering quality, speed, flexibility, and economy for us and the industry."

In Asia, a huge number of bioprocessing facilities are being built up; many of which are intending to use single-use technologies. I think this appetite for single-use is one important enabler in Asia's rapid biopharma growth. Many Asian biopharma companies are relatively new and are building their first bioprocessing plant, which means that they can select the most advanced bioprocessing technologies from the start when planning and building their facilities.

Some of the hottest discussions around single-use in Asia focus on economic comparisons between stainless steel and single-use. Cost is something that drugmakers must take into account, both in terms of establishing the facility and coping with the running costs throughout the projected life of a facility. Many studies cover this topic from various angles, looking at everything from different types of molecules to manufacturing processes, throughput, and scale – and in general they have shown that single-use has cost advantages over stainless steel. I believe that single-use is a great enabling tool to help the Asian biotech industry catch up with the developed bioprocessing plants in the western world.

What are the common demands of Asian companies?

There are three generalizations. Firstly, the supply chain in Asia wants both improved supply of single-use consumables and lower costs. Currently, most single-use consumables are made in the west. Manufacturing single-use consumables more locally for the Asian market would help resolve some of the problems – which will become more pressing as the region's demand for single-use consumables rises as commercial production increases.

Secondly, given that many Asian biopharmas are relatively new, they need more intimate support (technical, application, training, and so on) from suppliers. For example, they may need more advice than a western company in selecting the right single-use systems for their processes. Close collaboration is also important in terms of having a secure supply of consumables. For example, single-use becomes an indispensable component in continuous manufacturing processes, so both the manufacturer and the supplier need to set out a consumables forecast and mechanism to support constant manufacture.

The third point is the need for the evolution of single-use from a local regulatory perspective. The good news is that Asian regulators have started to place more emphasis on single-use and are developing regulations and guidelines. I'm seeing Asian regulators, end users and suppliers working closely together to understand single-use, in terms of how the components are designed and manufactured, and how they are used and applied in order to deliver appropriate guidelines. Currently, I am representing GE in working with the Chinese FDA on an 'International Single-Use Application Technology and Regulation Codification,' which will be published in early 2016.

Given the rapid pace of growth, do you foresee Asian biotechs potentially overtaking those in the west?

If we look at other industries, such as the automotive and electronics industries, you'll note that a lot of the big industrial leaders are now based in Asian countries (in particular, Japan and South Korea). Could the same thing happen with the biopharma industry? I think that Asia's biotech tigers have the ambition and capability to reach the same scale as western companies. But if we just look at the market in terms of single-use technology adoption, the Asian market is growing much faster than that of the western world. Western companies have existing stainless steel facilities that need to be used, and although there are opportunities for process improvements by introducing single-use in various parts of those facilities, it's much easier if you are building a new site from scratch – which is what many Asian companies are doing. They are also in the fortunate position where they can learn from the history and experience of bioprocessing in the west, selecting the most advanced bioprocessing technologies to form a really modern, cutting-edge facility. The very fast biotech growth that is currently being seen in many regions in Asia will probably slow as the markets mature, but I believe that the rapid adoption of technologies like single-use systems will allow Asian companies to reach a more level global playing field far more quickly than we as an industry have witnessed previously.