Strengthening Supply Chains

Supply chains are increasing in complexity, but collaboration can give you the confidence you need for supply robustness and control.

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INFOGRAPHICS

STAY AHEAD. SMART RISK MANAGEMENT

SINGLE-USE THAT'S READY WHEN YOU ARE

CHROMATOGRAPHY: FOR CONTINUOUS SUPPLY, BE TRANSPARENT

ALL EYES ON E&LS

KNOW THE RAW MATERIALS

WHITE PAPER: QUALITY RAW MATERIAL

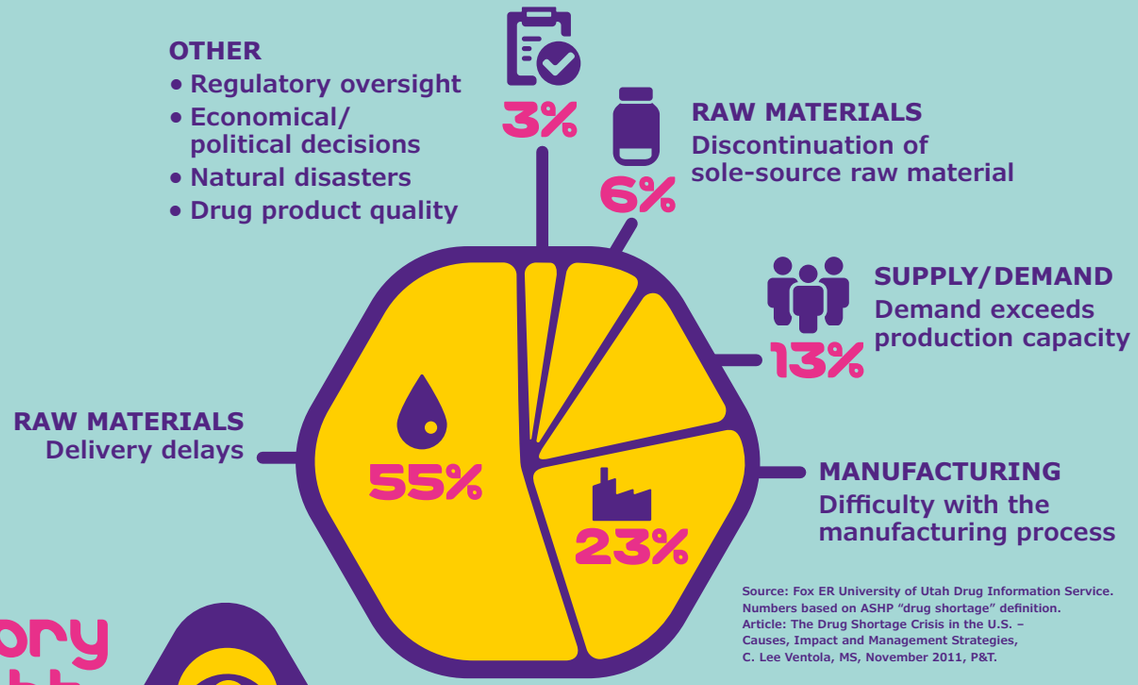
supply robustness and control.

Stay Ahead.

In the growing biopharmaceutical market, diversity and demand of biologics has increased the complexity and vulnerability of global supply chains to disruptions. As a leading partner and supplier to the industry, we continue to strengthen our supply chain to help you stay ahead.

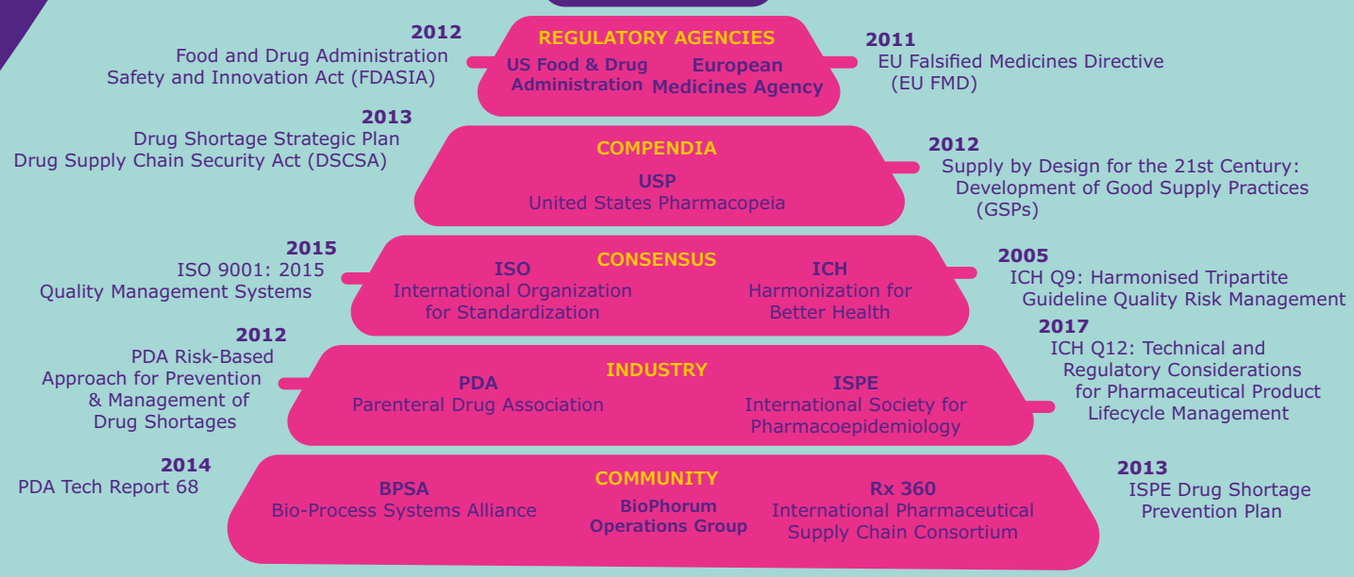
Drug shortage causes

In the USA 2011



Source: Fox ER University of Utah Drug Information Service. Numbers based on ASHP "drug shortage" definition. Article: The Drug Shortage Crisis in the U.S. – Causes, Impact and Management Strategies, C. Lee Ventola, MS, November 2011, P&T.

Regulatory oversight



our global footprint

Collaboration between biopharmaceutical manufacturers and suppliers is crucial for supply robustness and control. An accurate forecast will drive supply chain investments and capacity expansions at the right times in the right places to meet future customer demand.

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OUR FACILITIES

Cell culture media & raw materials

Lenexa, KS, USA: Cell culture media, dry powder, cell culture media - small scale development services

Cleveland, OH, USA: Buffers and cell culture raw materials

Saint Louis, MO, USA: Cell culture media and raw materials, liquid, process solutions, cell culture media - small scale development services

Irvine, UK: Cell culture media, liquid and dry powder, process solutions, cell culture media -small scale development services

Arklow, Ireland: Cell culture media raw materials

Berlin, Germany: Cell culture liquid media, process solutions

Darmstadt, HQ, Germany: Cell culture media, dry powder and raw materials

Buchs, Switzerland: Cell culture media raw materials

Nantong, China: Cell culture media, liquid and down-filling of dry powder, cell culture media - small scale development services

Songdo, Incheon, South Korea: Cell culture media - Small scale development services

Singapore, SA: Cell culture media - Small scale development services

Chromatography

Gernsheim, Germany: Chromatography resins

Altdorf, Switzerland: Chromatography resins

Buchs, Switzerland: Chromatography resins

Cork, Ireland: Chromatography resins

Burlington, Ontario, Canada: Single-use chromatography membranes

Filters

Jaffrey, NH, USA: Aseptic, TFF & virus membranes and filters

Cork, Ireland: Membranes

USA: Clarification filters

Single-use & stainless steel systems

Danvers, MA, USA: Bags and single-use assemblies

Beijing, China: Bioreactors

Wuxi, China: Single-use assemblies

Bangalore, India: Equipment & systems

Molsheim, France: Equipment & single-use sampling systems

Biodevelopment and contract manufacturing

Madison and Verona, WI, USA: HPAPIs

Saint Louis, MO, USA: ADC and Bioconjugation

Carlsbad, CA, USA: Viral and gene therapy

Shanghai, China: Biodevelopment and production

Boston, MA, USA: Biodevelopment and production

Martillac, France: Biodevelopment and production

Chemicals

Darmstadt, HQ, Germany: Chemicals and excipients

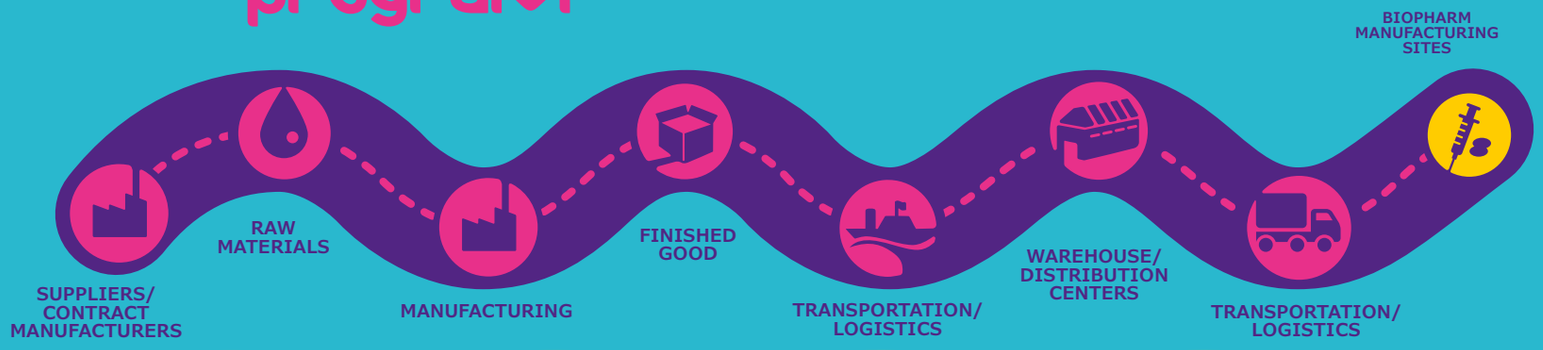
Buchs, Switzerland: Chemicals

Schaffhausen, Switzerland: Polymers and DDCs

Mollet del Vallès, Spain: Chemicals and excipients

Arklow, Ireland: Chemicals and excipients

our supply robustness & control program



- SUPPLY CHAIN RELIABILITY
- SUPPLY CHAIN RISK MANAGEMENT
- QUALITY CONTROL
- TRANSPARENCY OF INFORMATION

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Stay Ahead. Smart Risk Management

As supply chains become increasingly complex, collaboration between biopharmaceutical customers and suppliers is crucial for supply continuity and control.

By Dawn MacNeill

There is tremendous growth within the biopharmaceutical industry. Patient demand for life-saving and life-enhancing medicines is increasing; driving scientific and technological advances in drug discovery, development and manufacturing. As a result, biopharmaceutical manufacturers are intensifying their speed to market, increasing their capacity and optimizing their productivity. With rapid growth and geographic expansion comes an extended supply chain with more complexity and vulnerability to supply chain disruptions, such as natural disasters. At the same time, there is strengthened regulatory oversight of supply chains to assure patient access to quality drug products. To stay ahead, manufacturers and suppliers must collaborate to ensure continuity of supply.

Together, we must make "risk-smart" decisions to strategically balance the need to invest in capacity expansions and supply chain innovations to continuously supply customers with the right, high quality products in the right place at the right time with the need to continually mitigate risks and minimize supply disruptions. The routine, reliable supply of products depends upon a disciplined approach to supply chain management, from demand planning, materials/supplier management, production planning, and manufacturing to inventory management, warehousing, distribution, and logistics.

To maximize resiliency, we execute a multi-faceted, "risk-smart" approach to supply chain risk mitigation. Leveraging years of experience, market intelligence, product and process knowledge, we proactively identify and prevent potential risks through effective capacity planning, business continuity planning, supplier quality management, change control management, disaster recovery planning, supply chain mapping and continuous improvement.

Data transparency and real-time, shared information between biopharmaceutical manufacturers and their suppliers is critical to

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effective capacity planning. An extremely crucial element of "risk-smart" mitigation is the provision of up-to-date, accurate customer forecasts. Ideally, forecasts will evolve from those currently based on single raw materials to the sharing of molecule BOMs (bills-of-materials) and critical products.

Another important element of "risk-smart" mitigation is business continuity planning (BCP). BCP is the process for identifying, preventing, mitigating and responding to supply risks for specific products. Prioritization of BCP's is based on a business impact analysis. During the BCP process, a risk priority number (RPN) is assigned to a product or a process that quantifies the likelihood of occurrence, likelihood of detection, and severity of impact. Risks above a certain RPN must be mitigated. Business continuity many include Disaster Recovery Planning for the site in which the product is manufactured.

Yet another important element to "risk-smart" mitigation is supplier quality management, which is designed to manage the quality of all procured products and services that directly and indirectly support manufacturing of finished goods. We categorize suppliers as critical, essential and non-critical. Although every procured product and supplier could be categorized as critical (after all, we cannot make the finished good without all the required raw materials), our categorization process considers the complexity of technology, sites impacted, country of origin, compliance and corporate social responsibility (i.e., REACH, conflict minerals and animal welfare), sales and more. The categorization determines the assessment frequency and method, such as audits.

Agreements, in which we are given visibility into customers' biologics pipelines and critical product needs, enable us to prepare for capital investments, reduce concerns over capacity constraints, enhance relationships with our respective suppliers, improve inventory replenishment, prioritize business continuity and change control decisions, and more.

Ultimately, collaboration is key to being more predictable and reliable with improved delivery metrics. In turn, biopharmaceutical customers can better meet the demands of their growing patient populations and comply with regulations, such as FDASIA.

Dawn MacNeill is Marketing Operations Manager at MilliporeSigma.

Meet the Expert: Aida Tsouroukdissian

I am Head of Demand Planning, Integrated Supply Chain Operations, at MilliporeSigma. My team focuses on attaining an accurate demand and forecast to drive the right supply chain activities at the right times to meet customer requirements. We are responsible for securing and managing the global demand of our Process Solutions portfolio through a collaborative effort with our commercial, marketing and operations teams. The portfolio includes single-use systems, assemblies and components, aseptic, virus and TFF filters, chromatography, cell culture media, chemicals and more.

We use a Sales and Operations Planning (S&OP) decision making process to understand the market dynamics, drive production planning requirements, reconcile our demand-supply gaps, and inform our capacity plans and capital investments. The S&OP process is the basis of our monthly "consensus" demand plan for the next 18-24 months. On a quarterly and bi-annual basis, we review our portfolios with marketing to define a 5-year long range plan and a 10-year strategic plan, respectively.

This S&OP process has also been extended to some of our customers and critical suppliers directly, with whom we have partnered to increase transparency and reduce the risk of a supply disruption. These supplier-partner relationships are becoming more important to maintain service levels that keep pace with the anticipated ramp-up in the industry.

I find it very interesting and rewarding to collaborate with customers, suppliers and colleagues in this way. It's all about preparing for the future and mitigating risks!

Meet the Expert: Michael Donahue

I am Head of Production Planning, Integrated Supply Chain Operations, at MilliporeSigma. My team focuses on our upstream supply chain from materials management to finished goods manufacturing. We're responsible for buying raw materials, managing inbound material flow, warehousing raw materials, scheduling manufacturing on the production floor and subsequently managing outbound material flow. As a result, my team is responsible for developing and executing the materials management program at several of the manufacturing sites. Essentially, the program is about evaluating and mitigating risks related to raw materials, and therefore, our suppliers.

In production planning and materials/supplier management, predictability is very important. When we commit to having finished goods available on a certain date, we want to be reliable in meeting that commitment. We work closely with our suppliers to ensure we have robust supplier quality agreements in place that include quality controls. For our critical suppliers, we use specialized tools to perform risk assessments and more importantly, collaborate with them to develop risk mitigation plans – reducing risk upstream greatly improves the predictability of our finished goods output downstream!

To mitigate supply disruptions, supply chain mapping is essential. We use an effective tool from a leading supply chain mapping/resiliency company. Some customers and several suppliers use the same tool, which provides alerts on relevant world events. For example, if a man-made or a natural disaster strikes a manufacturing site location of a supplier, we will receive an early warning event alert that enables us to act, such as decide to re-route materials from a different warehouse.

Of course, we have several other risk mitigations in place. We may have dual sources and/or dual suppliers. However, this isn't practical for many single-sourced raw materials. We would hold safety stocks – often at separate locations in case of a disaster.

I am very passionate about our upstream supply chain and making sure that we have suppliers who understand our customers' requirements. I think of raw materials as an enabler (or disabler). If you do an excellent job, nobody notices. But, if you are not doing a decent job, then everybody notices!

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How to make your supply chain more robust with collaborative forecasting & transparency?

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Single-Use That's Ready When You Are

Biopharma has embraced the benefits of single-use, but with a growing number of available components and highly customized assemblies, the supply chain becomes quite complex. MilliporeSigma has designed a new program offering customized single-use assemblies with reduced lead times, and an enhanced level of supply security.

Sara Bell is fortunate to have been on both sides of the fence, spending 11 years in operations at Amgen before joining MilliporeSigma, where she is now Senior Marketing Manager of their single-use portfolio. Sara knows full well the challenges faced in biopharma manufacturing – and why single-use is seeing increased uptake. Here, we talk to Sara about trends in single-use systems and why supply security of these products is critical to drug manufacturers.

What are the pros of single-use?

I would highlight four key benefits. The first is flexibility, which is really beneficial to multi-product facilities and contract manufacturing organizations (CMOs) that need to produce a variety of different products at different scales. Demand for those products can change rapidly, so being able to adapt quickly – which single-use allows – is a huge advantage. Secondly, single-use helps lower costs by reducing plant footprints and upfront capital spend. For emerging markets looking to get into the biopharmaceutical market, single-use is a great option because it requires less investment than a traditional stainless steel plant. The third benefit is speed. It's often faster to get a product to market using single-use. There is no need for clean-in-place or steam-in-place, and no need for validation of these operations, which greatly reduces the time it takes to get a facility up and running. Finally, single-use reduces your risk profile in terms of contamination. As the name suggests, once you use the product you throw it away and install a brand new sterilized assembly, so the risk of product carry-over is completely eliminated. In addition, due to the closed nature of single-use, you have better biological and viral contamination control.

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And the cons?

There are risks and considerations to evaluate when implementing single-use, but I firmly believe that the benefits outweigh the risks. So, what is keeping drug manufacturers up at night when it comes to single-use? One of their biggest concerns is supply security. With traditional stainless steel manufacturing, the amount of consumables needed to run a process is limited to cell culture media, process chemicals, resins and filter elements. Additionally, production plans are primarily driven by turn-around time, or the time it takes to clean and sterilize vessels between batches. With single-use, the amount of consumables needed to run the process significantly increases, which makes the supply chain, especially procurement and inventory management, much more complex.

Many single-use suppliers use proprietary components, such as films, connectors and tubing – as well as their own technologies and assemblies for bioreactors, mixers and automated systems. Such non-uniformity means that it can be very challenging for end-users to dual source the consumables needed to run their processes. Therefore, they are forced to manage the risk by holding large quantities of safety stock, or performing tests to justify that two different products are "like for like". Varying supplier lead times and delivery delays can also impact production plans. These are challenges that we have sought to address through the Mobius® MyWay program.

What's the story behind the Mobius® MyWay Program?

The single-use market has seen significant growth over the past 10 years, and is predicted to continue to grow at a double-digit rate through 2025. Like many other single-use suppliers, we began to run into capacity challenges and it was important for us to define a scalable manufacturing model that met or exceeded end user expectations in terms of lead times, delivery, quality and supply security. The Mobius® MyWay program, which launched in January 2017, came into being to meet those end user expectations. Essentially, the program offers three options for customized single-use assemblies.

The first option is Mobius® Stock, which covers catalog items and high-volume repeat custom assemblies. With this option, we maintain stock of the assembly part number on our shelf and deliver when needed, which allows end users to maintain less inventory. Option two, Mobius® Select, allows end users to design configured assemblies from an optimized component library, and receive them within six weeks. We maintain safety stock of every component in this library, thus enabling fast and reliable delivery with an enhanced level of supply security.

The third option is Mobius® Choice, which allows end users to design customized single-use assemblies using our full Mobius® component library, and receive them with a traditional lead-time of 12–14 weeks.

Many single-use suppliers have chosen to address capacity challenges and custom business complexities using a different approach, by defining pre-configured standard assemblies. They offer solutions that they think end users will want. From our experience, no matter what you expect the end user to want, they will always want something slightly different! The Mobius® MyWay Program allows end users the flexibility to design a custom assembly and decide when they want to receive it.

Mobius® Select has been particularly popular...

Yes – and for good reason I think. If you look at the global market today, there are many dynamics impacting the biopharma industry. To remain competitive, drug manufacturers must examine how to cut costs, as well as how to increase flexibility and productivity. Biosimilars, emerging markets, novel therapies and next generation processing are just a few of the variables driving greater adoption of single-use. Many users are designing customized assemblies, using different components, from a variety of suppliers. It's gotten quite complex for end user networks to manage, so many are now looking to standardize and harmonize their single-use assemblies, by defining a set of preferred components – essentially a design space that they use to develop new assemblies. The Mobius® Select library provides them with just that; an optimized design space of pre-qualified components backed with supporting quality documentation and a growing dataset of extractables, tested per the BioPhorum Operations Group (BPOG) protocol. This significantly reduces the amount of testing required by the end user, and enables them to implement single-use faster. The six-week lead time allows end-users to hold less inventory and be more nimble with their production planning. And the biggest benefit with Mobius® Select is that it still gives end users the flexibility to customize their assembly, across a broad range of applications, to meet their specific processing needs and requirements.

How has the industry reacted to the new offering?

We saw adoption pick up significantly mid-2017. We find that once an end user experiences the entire process from the design of their assembly through to order receipt, they realize the value that Mobius® Select can provide – not only in terms of delivery time, but also in terms of quality assurance, reduced inventory costs, time savings, flexibility, and security of supply. These benefits drive the creation of new Mobius® Select assemblies and have also prompted end users to reach out to us with specific requests; for example, "I have X number of existing assemblies from MilliporeSigma or a competitor. Can you help me transition these to a Mobius® Select design? What components would I need to tweak to make this Mobius® Select compliant?" For common applications like mixing, storage, transfer and filtration, typically only minor component or tubing length changes are needed to make a design Mobius® Select compliant.

The program has proved to be very successful for both us and end users. The aim of the Mobius® MyWay Program was to meet drug manufacturers needs in terms of fast and reliable delivery, easing the implementation of single-use, and increasing the level of quality and documentation that they receive with the product. But the solution we came up with also enabled us to scale our manufacturing operations to ensure we can support the continuing growth of single-use through 2025 and beyond.

We are going to continue to enhance the program and evolve the library based on market needs. Towards the end of November, we are launching a web-based interactive tool that will allow end users to see which components are available in the Mobius® Select library. For more information on the program, or to request the help of a single-use specialist, I encourage readers to visit EMDMillipore.com/singleuse-myway. To directly link to the Mobius® Select tool, you may visit mobiustool.com

For Continuous Supply, Be Transparent

Single-source chromatography resin leads to requirements for supply security. MilliporeSigma explains views and solutions.

With Nina Weis and Matthäus Braun

MilliporeSigma's chromatography business has a long history – it was the first manufacturer of silica products for chromatography worldwide, starting one year after the discovery of the chromatography principle in 1903. Since then, the company has filed more than 50 patent families for process chromatography around the globe and offers a huge variety of chromatography products, including affinity chromatography resins, ion exchange resins, reversed phase media, membrane adsorbers and also pre-packed columns.

An important focus for MilliporeSigma is ensuring security of supply for customers. "Because of the unique product characteristics and performance, as well as the complexity and cost of qualifications, chromatography resins are often sourced from a single supplier. A chromatography resin can impact the drug product's quality, safety and efficacy – and the effect can vary when switching to a resin from a different supplier. It can take years to replace a chromatography resin in an existing biomanufacturing process. Because of this, supply and production shortages have a huge impact on biopharma customers, which is why supply security must be a priority," explains Nina Weis. Responsible for managing MilliporeSigma's near and long-term marketing strategy for ion exchange chromatography products, Weis has a strong focus on driving customer satisfaction.

According to Weis, supply disruption can easily equate to more than one million euros per day in lost revenue for blockbuster molecules, and it can potentially prevent patients from receiving essential medicines. "Chromatography supplies are essential for biopharma production. It is not sufficient for suppliers to focus only on delivering orders on time; it is also necessary to look to the future to better handle variations and minimize the impact of any unexpected events. In summary, long-term demand and capacity planning is crucial," says Weis.

Planning for all occasions

At MilliporeSigma, demand planning and forecasting is a collaborative process with commercial and strategic marketing. Demands can fluctuate; low demand could result in a facility being under-utilized; however, high demand can stretch a manufacturing plant, leading to bottlenecks and supply disruptions. Therefore, it's necessary for demand planning to partner with capacity planning to review and discuss potential high-growth scenarios.

"MilliporeSigma has a robust sales and operating planning (S&OP) process, which includes a monthly review of demand with commercial to understand our short and mid-term (0-18 months) customer requirements, and when orders will be placed," says Weis. "We also have a long-range plan for our business (3-5 years) in which we take into consideration market dynamics and product lifecycle. Twice per year, a plan is provided to supply chain operations for capacity planning, future investments, resources, supply planning and more."

Prepare for the black swan

Of course, no matter how intelligently you plan your demand and capacity, your information will never completely reflect future needs. Uncertainty must always be considered – for the short-, mid- and long-term. There can also be unexpected catastrophes, from natural disasters, to changes affecting raw materials, to breakdowns in equipment that affect capacity.

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Matthäus Braun is Site Director for MilliporeSigma's Altdorf, Switzerland site, which produces chromatography resins, among other products. He says that the importance of continued supply is something MilliporeSigma understands well since it is a biopharma manufacturer, as well as being a supplier business. "I like to say that it is in our DNA to look at supply risks and business continuity," says Braun. "We apply a holistic approach in the evaluation of any potential supply risks. For raw materials, for example, our business continuity plans involve supplier quality risk management, supply qualification, and established, long-term relationships with our key suppliers. Good relationships and trust are key for mitigating supply chain risk. We also have plans in place for other scenarios, such as breakdown of installations, or other unexpected events."

MilliporeSigma's processes for business continuity follow pre-defined, formally documented protocols that involve identifying a risk, determining and implementing an appropriate risk mitigation, which could be increasing safety stock of raw materials or qualifying a second source. Disaster recovery is also included in MilliporeSigma's business continuity plans. The Altdorf site is not located in an area prone to major natural disasters and the environment is quite stable, but Braun says that it is still important to demonstrate to customers that the company has assessed the risks and has structured plans in place to reduce any recovery timelines, should anything happen. Braun says, "Our integrated supply chain operations organization has other sites in which we manufacture chromatography products and have subject matter expertise."

"It's really important to stay ahead of customers and market demand," Weis says. "We watch industry trends very carefully and listen to what our customers are telling us; and we have invested steadily in our manufacturing capabilities to expand capacity and increase manufacturing standards according to the requirements of the biopharma industry. We have a large, state-of-the-art manufacturing network that produces our resins and membranes."

"Recently, we implemented a new production line in Altdorf to help us adjust to increased demand," adds Braun. "But we have the internal capacity to revert back to the previous production line if there is an issue with the new line. With everything we do, we also consider the 'black swan' situation and what might happen to production. It is important to have defined recovery plans and timelines."

Everybody wins

Whatever happens in the supply chain, both Weis and Braun agree that collaboration and communication with customers is crucial. "First of all, you can't just sell products without true knowledge about what they are used for," says Weis. "You also need to understand what clinical phase your customer is at – are they preparing to go into commercial manufacturing, for example? Are their demands suddenly going to increase? Transparency goes a long way to making sure we understand our customer's needs and can continue to supply our products at the right time, in the right quality. We also partner with our suppliers to ensure transparency and a true collaborative business approach – a win-win situation for both parties that can strengthen the supply chain."

Open, regular dialogue with customers also builds trust. Braun adds, "Customers need to be able to trust that their supplier has effective plans in place to make sure supply will not be interrupted. A good relationship is key. In Altdorf, customers really appreciated how we demonstrated product equivalence from the previous production line to the new line, and how we managed the change. We also have an excellent track record with audits – something that demonstrates how well we understand the needs of our customers."

Change Control: At the Heart of Business Continuity

By Katrin Jänicke, Marketing Operations Chromatography

Every change to our products creates risk for our customers: a change has the potential to affect drug product quality, safety or efficacy, as well as the process performance. If a change results in an update to a regulatory filing, this could have a negative impact on supply. At MilliporeSigma, we are highly focused on minimizing the risk that changes can bring. To address this, we have developed robust and comprehensive change control strategies that ensure changes are controlled, managed and communicated stringently to sustain security of supply.

There are two different scenarios why changes can occur; i) change is initiated by the manufacturer of the chromatography product resulting from continuous improvement efforts. ii) change is initiated by the manufacturer's supplier, such as a new supplier or a new raw material. One key element of our change control strategy is to communicate changes to our customers as early as possible to give sufficient time to prepare and assess the impact – we are targeting at least six months for change notifications prior to implementation of very complex changes. To ease our customer's risk assessment for those changes, we provide comprehensive comparability studies and the option to order samples from different lots in case a customer decides to perform additional testing. We understand that qualifying a change requires considerable effort; therefore we try to find a good balance between continuous improvement and minimizing the number of changes. In addition, we're actively seeking the exchange with the industry. One example for this is the one-on-one exchange with customers where we present a specific change, and give the opportunity to ask questions and to provide feedback on how we can further improve our change control strategy. Another example is our involvement in industry consortia, such as the BioPhorum Operations Group (BPOG), where representatives from our company meet with other representatives from the biopharmaceutical industry to discuss and align on change notification needs and best practices.

The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the US and Canada.

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All Eyes on E&Ls

Extractables and leachables require rigorous analysis to protect patient safety. Here, we speak with Saskia Haehn – an expert when it comes to diving deep into materials.

What is your role at MilliporeSigma?

I moved to MilliporeSigma around four years ago from a contract research organization, where I was working as a project manager in the field of extractables and leachables (E&L) studies. Today, as Manager, E&L and Packaging Materials at Site Management Analytics, I run a laboratory where, unsurprisingly, the primary focus is on E&L, coupled with some other packaging analysis work. Our services are available to all of MilliporeSigma's businesses, but much of our work is performing extractables studies for our life science business, which supplies single-use equipment and process materials. We also do quite a bit of work in the healthcare business.

Why is E&L so important for the industry and so fascinating for you?

E&L is a crucial topic for everyone in drug development because we all want to ensure that products and drugs are safe for patients. But from my perspective, it is also a very intellectually rewarding area to work in. Every material you examine is different, with different polymers, different uses, and the need for different extraction methods depending on the material. I am never bored! Once the first studies have been done and I've extracted the materials, the real puzzle begins. I rarely know what I am looking for, so I have to use a good number of orthogonal analytical techniques to cover everything that is in the extract.

Some confusion persists in the E&L space... Why?

Many people use the words "extractables" and "leachables" synonymously, but there's a big difference between the two. An extractable is a chemical entity, both organic and inorganic, that will extract from components of the packaging or process system into a solvent under controlled conditions (we usually experiment with harsher conditions than normal use) – we're talking about high temperatures, extended contact time, and the use of organic solvents or those with strong PH values. Extractables are important because they help us to identify the potential for leachables. Leachables are those chemical entities that migrate from components into the drug product over its lifetime, or during manufacturing.

E&Ls can theoretically come from any product contact material, such as primary packaging or process systems in contact with the drug product, but will vary depending on the activity of the material. A material like Teflon, for example, is very inert and we tend to only observe a few contaminant peaks (compounds) during our analytical tests. Natural rubber, on the other hand, can produce hundreds of peaks, all of which require thorough investigation.

Leachables can be a big risk to patient safety. In extreme cases, they can have a toxicological effect. They can also interact with the drug product, potentially reducing efficacy.

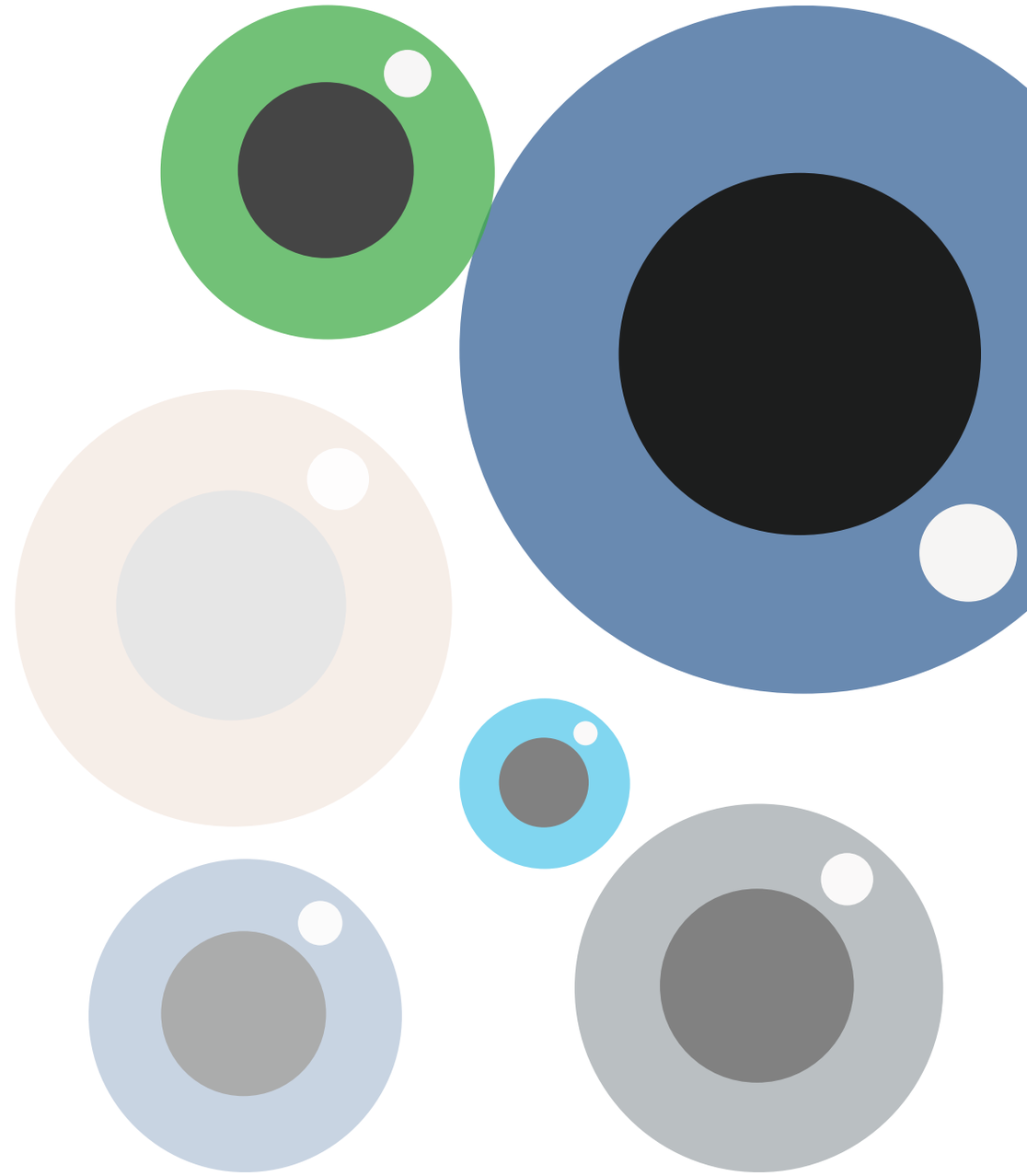
What do the regulators have to say about E&L?

E&Ls must be evaluated when determining the purity of the final product, but there are no clear regulatory guidelines on how to go about the analytical process. For primary packaging, there is USP <1663> and <1664>, but for process materials and single-use equipment, there is no real guidance – and that can be quite frustrating for the industry. Some industry working groups, such as the BioPhorum Operations Group have examined the issue and published a standardized protocol for performing E&L studies and defining thresholds for how deep your analysis has to go; however, not everybody uses this protocol, and so it can be difficult to compare results between two different vendors when trying to choose the right product.

What is MilliporeSigma's approach to E&L studies?

Actually, there is no one-size-fits-all approach for us either, because we have three business groups within MilliporeSigma that all need to deal with this topic. In the healthcare group, we must guarantee the safety of drug products and the E&L risk during production and packaging. In the life sciences group, we need to provide pharmaceutical customers with E&L information about MilliporeSigma's products, such as single-use systems. We conduct extractable studies according to standardized protocols, but if the information is insufficient then MilliporeSigma also offers BioReliance® Validation Services, which generate more E&L data in line with what the customer wants.

Generally, after performing our first extractables studies, we summarize the results, which includes the identification and quantification of extractables. Then we hand over the results to our tox department, which calculates a permitted daily exposure



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limit (PDE) and compares this with results from the extractable studies. If the amount of the extractables is below the PDE, then you're safe. If it's above, then you have to perform leachables studies and look directly into the product. Depending on the results of these studies, it may be necessary to change something in the packaging or the process.

For our performance materials group, where product performance is crucial and can be influenced by leachables, we need to be very specific in what we are looking for. Some leachables can have a negative effect on performance. And sometimes the limits for these substances are much lower than the toxicology limits for drug products.

What are the main techniques used in your lab?

We rely heavily on combinations of chromatography to separate substances and mass spectrometry MS to elucidate those substances. We use both normal and head space gas chromatography GC–MS, as well as liquid chromatography LC–MS, depending on the nature (molecular weight, for example) of the compounds, but we may also need to work with a number of other analytical techniques to cover all possible entities, such as inductively coupled plasma ICP-MS for elemental impurities or ion chromatography for ionic species.

We also perform some other a analytics, such as total organic carbon and non-volatile residues, to find the total amount of extractables present in the extract. In addition, there are some material specific analytical techniques, such as the determination of nitrosamines for rubber stoppers, for example. For nitrosamines, the limits are so low that conventional techniques don't capture them, so we have to use specialist analytical techniques, such as GC-TEA for nitrosamines or LC-MS/MS for perfluorinated compounds.

What is the biggest challenge you face in your role?

The biggest challenge is handling all of the requests I receive! Our laboratory is so important for MilliporeSigma's businesses – and the topic of E&L is only becoming more crucial as time goes on. We started in 2014 with just two people in the lab. There are now eight of us and there are also more people in the specialized labs that perform more detailed structure elucidation. We have worked hard to recruit people with the right skills. A good analytical background is key, of course, as is knowledge about the product and the materials that come into contact with drug products, including pre-treatment steps such as sterilization. You need to understand how substances

from the materials can be extracted and how they behave in the extract, and be able to set up a good study design. If the study set up is not adequate, then all the results you gain are useless.

Can E&Ls ever be completed eliminated?

I don't think so. I don't see E&Ls ever going away, despite the huge progress that has been made with companies really understanding their products, and developing specialized materials or coatings. Single-use products are becoming more popular in the pharma industry, but they are still relatively new and I don't think all suppliers out there at the moment can support their customers with good E&L data.

There will also always be changes in certain products. For example, if you look at resin manufacturers, they are often looking for new additives that can help them control costs. And when there is a change in the additives to the polymer, new compounds or substances will show up during extractables studies that we need to investigate.

However, I think the industry is constantly acquiring new knowledge around E&L, which can only be a good thing. In time, if we can move to more standardized approaches, then it will be a huge benefit to the industry, saving many companies a lot of time and money.

LINKS

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Extractable and leachables

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Know The Raw Materials

We asked customers what they wanted from their cell culture media suppliers and the reply was, "understand your raw materials". So nine years ago we set out to characterize and evaluate our raw materials – this is what we found...

By Chandana Sharma, PhD

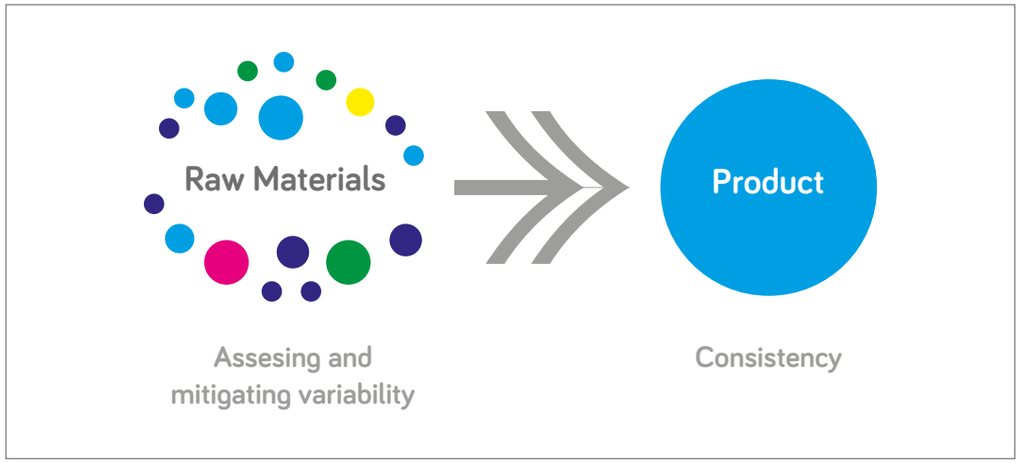
From our perspective as a cell culture media supplier, there are hundreds of possible raw materials which could be in a formula, including amino acids, vitamins, fatty acids, and salts, many with multiple functional groups. Raw materials can come from any number of possible sources, and even the same ingredient from multiple sources. Some raw materials are very well defined and others may lack a complete profile. Understanding raw material differences has become vitally more important to companies like ours. Our customers strive to understand variability and the impact on their biomanufacturing process, they look to improve their cost to manufacture and reduce risk to the patient. So they look to us to know more about our raw materials. This is exactly what our customers told us in late 2008 when we carried out a survey asking what they expected from cell culture media suppliers – the clear message was that a thorough understanding of raw materials and potential variability was crucial. And so MilliporeSigma set out on an ambitious program of raw material characterization and evaluation.

At the time, MilliporeSigma was focused heavily on developing cell culture medium rather than its building blocks, so we had to take a step back and decide on a strategy. Variability in cell culture raw material is, of course, inevitable, but too much variability can impact the overall performance of the culture medium, bioprocessing parameters and the process output. A cell culture media can consist of 70 to 100 different raw materials and the variability is cumulative, so it needs to be controlled within reason. A good understanding of the raw materials and variability builds a good picture of the medium as a whole and its performance.

A question of variability

The first question for our characterization program was, what should we study? With hundreds of raw materials in our inventory, we had to pick and choose, so we performed a risk assessment to identify "high risk raw materials." From this we created a prioritized list of raw materials. We then undertook an orthogonal approach to characterize those materials, which included chemical and biological assessment. Chemical assessment was focused on understanding the impurity profile, whereas biological characterization was focused on understanding the impact of impurities or variability on cell culture processes.

Using the right tools and techniques for the study was vital to get the best data, which meant investing time and resources into approaches such as mass spectrometry, liquid and gas chromatography, and multivariate data analysis tools. On the biological characterization side, we developed high-throughput biological assays and markers. We took a dose-response approach and studied raw materials in multiple cell lines. There have been some remarkable advances in the sensitivity of analytical instrumentation in recent years, which allowed us to carry out elemental analysis at the parts per billion scale. Overall, we produced a tremendous amount of data and learned what variability was normal and acceptable for our raw materials, and what was not.



Understanding your partners

One aspect of our raw material characterization program was to study and understand the inter- and intra-lot variability of a given supplier. We had in excess of one hundred different raw materials, but for each of those we also had two to three suppliers (it's always advisable to have some redundancy in the supply chain and not be dependent on one supplier). If, for example, we had L-Lysine coming from supplier A, we had to understand the variability within supplier

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Quality control programs

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A, as well as suppliers B and C. Overall, we had to understand how each supply of L-Lysine might differ, and then examine how the variability could be minimized.

We also realized the importance of integrating the characterization program with our quality systems to proactively prevent any variability in raw material from impacting the quality of the final product. Today, we have a two tiered approach of screening changes in the raw material supply. We also have very good relationships with our suppliers and discussed our findings with them. For example, if there was a problem with a certain raw material then we collaborated with the supplier on how we could overcome this.

Knowledge is power

The most important finding was that our raw materials were relatively pure, especially the defined small molecules, which was a relief! When we did see variability, it was coming from trace metal salts or undefined raw materials like hydrolysates. The trace metals finding was surprising because it was not an initial focus of our study. This changed with the results and we ended up diving deeper into the topic of elemental impurities, particularly because it was so important for certain inorganic salts like sodium chloride. In time, we expanded elemental impurity testing to all major raw material groups, including amino acids, vitamins and more.

There will always be some variability in raw materials – since some of our raw materials are byproducts of other processes, and we may not even be the primary industry for it. We have taken steps to ensure that our suppliers are safe, but we need to appreciate that we are one of many customers so we also need to have mitigation and quality control procedures at our end. For example, we learned less than a 1 percent impurity in poloxamer 188 had a huge impact on cell culture processes, and have such developed a quality control cell assay to detect and prevent entry into our supply chain. Thanks to our detailed study, we now have a great deal of information about our raw materials and the impact on cell culture. Information is never a bad thing – you may not choose to act on it, but it allows you to make informed decisions. Many of our customers have used the data we provide about our cell cultures to make changes to their formulations. For example, they may already know there will be a specific amount of manganese or copper as background impurity, so they can tweak their formulations or processes if necessary to account for the variability. Our data can also be used to advise on the most suitable cell culture medium for a given product. A biopharma company may require a cell culture medium with a certain amount of iron, but may have a product that is sensitive to zinc. Now that we have characterized the impurities contained within our raw materials, we can advise our customer that one of our raw materials, ferric citrate for instance, contains zinc. The customer might then ask what other sources of iron are available, to which ferric ammonium citrate might be the answer. We can then supply a cell culture medium that is tailored to the specific needs of the customer. I have seen many success stories where we have collaborated with our customers to overcome problems – all products are different and cell culture systems can be customized. Because of this, deep collaboration with suppliers is crucial. This is true for us with our suppliers, and also our customers.

Overall, the painstaking process of characterizing our raw materials and figuring out how they impact biological systems and our cell cultures has allowed us to be more transparent with our customers. It seemed like quite the task when we first embarked on the project almost a decade ago, but the hard work is now paying off in terms of deepening our relationships with customers and suppliers – securing the supply chain from top to bottom.

Chandana Sharma, PhD, is Head of Cell Culture Raw Materials, Upstream R&D, at MilliporeSigma.

LINKS

More information
Raw material quality program

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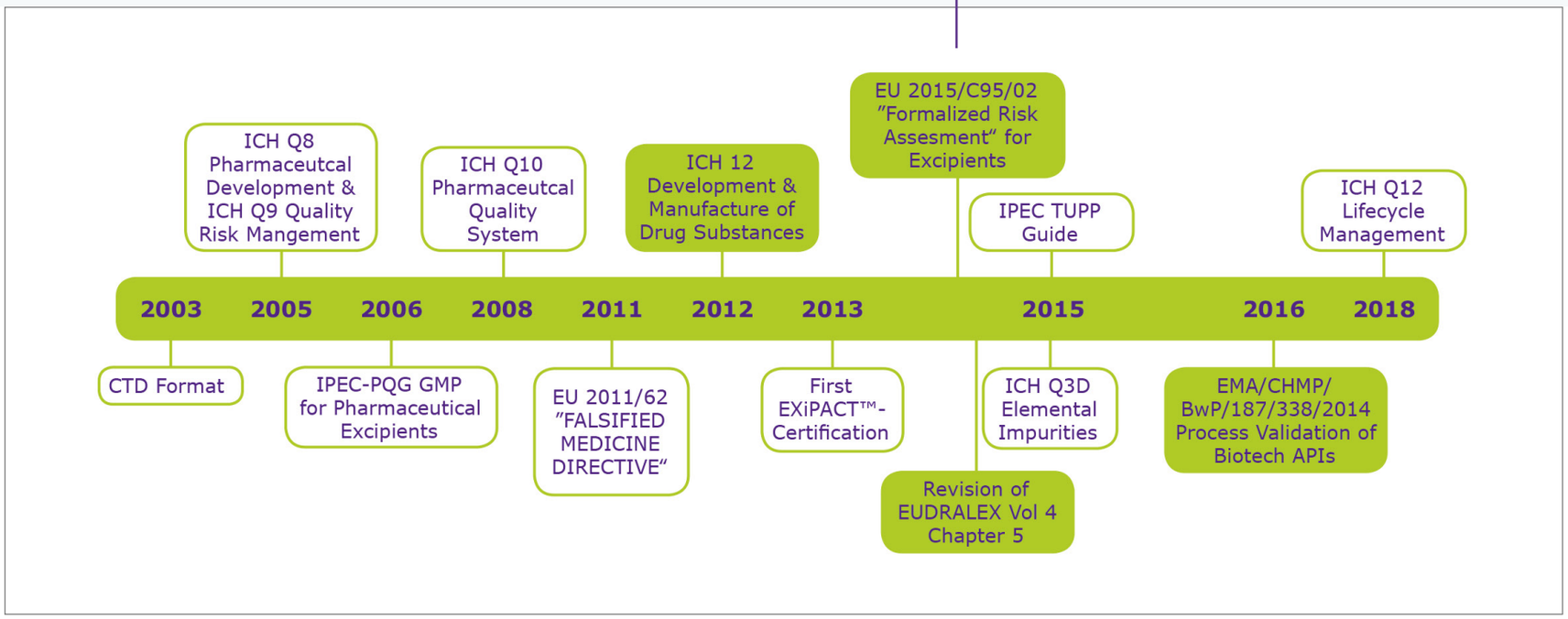
White Paper

Identifying Appropriate-Quality Raw Materials in an Evolving Regulatory Environment

In recent years, pharmaceuticals have become more complex, progressing from primarily small molecule drugs to an increasing array of recombinant proteins, monoclonal antibodies and cell and gene therapies. This has led to necessary changes in regulations to accommodate new, more complex manufacturing processes that have more steps and are more sensitive to variability and contamination.

By Douglas Bowman



Contamination, in particular, is a concern for the raw materials used in early steps of manufacturing and may impact drug safety and efficacy. However, while quality attributes for materials used in later manufacturing steps – those steps close to the final drug product – are well-defined, regulations for raw materials are still evolving.

At the same time, the supply chains for materials needed for manufacturing have also increased in complexity. The materials themselves are more difficult to characterize, distribution systems are changing and expanding, and new suppliers are emerging.

All these factors require manufacturers to ensure that the raw materials they use meet regulatory requirements and can be demonstrated to have appropriate, consistent and documented quality that mitigates risk and is traceable throughout the supply chain.

Regulatory environment for raw materials

Over the past several years, regulations for drug manufacturing have been updated to adapt to the emergence of new and more complex pharmaceuticals. Some of the recent regulations address aspects of raw material sourcing that are relevant to this discussion.

ICH Q11 Development and Manufacture of Drug Substances

ICH Q11 addresses risk assessment recommendations for raw materials used in drug manufacturing and has been adopted as a guideline by the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA) and Japan's Pharmaceuticals and Medical Devices Agency (MHLW/PMDA). It describes the need for manufacturers to do a thorough risk assessment of the entire drug product manufacturing process and applies concepts that are becoming ubiquitous – risk management, quality by design and critical control parameters.

The guidance states that drug manufacturers must have a deep understanding of their entire development and manufacturing process and the parameters that critically impact drug quality. It also makes it the drug manufacturers' responsibility to understand and define raw material attributes to control variability and risk of contamination by impurities. Although the ICH Q11 specifically states the need to include raw and starting materials in this assessment, highlighting biological processes, it does not set specific quality standards for them.

EudraLex vol 4, part 1, chapter 5

EudraLex vol 4, part 1, chapter 5 is a revision of the EU rules governing GMP for medicinal products, related to production. It adds strict guidance for steps that manufacturers should take to qualify suppliers of starting materials. For example, it states that "the selection, qualification, approval and maintenance of suppliers of starting materials … should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use.

Quality requirements should be discussed and agreed upon with the suppliers, and appropriate quality aspects documented in a quality agreement or specification. Supporting documentation for each supplier and approved material should be maintained.

EMA/CHMP/BWP/187338/2014

EMA/CHMP/BWP/187338/2014 is an EMA guideline on process validation for the manufacture of biotechnology-derived active substances and the data to be provided in the regulatory submission. With regard to raw materials, it provides guidance on risk assessment, supported by documentation, to control the impact of raw materials on the quality of the final drug substance. The guidance recommends that "in the light of the variability (e.g., intrinsic to the material, related to change in supplier) of certain raw materials and based on their potential influence on the quality of the product, the impact of these materials should be addressed as early as possible in the development process.

EU 2015/C95/02

EU 2015/C95/02 is a European guideline that addresses the quality attributes of excipients, and was recently adopted by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as a guidance document for the PIC/S Participating Authorities.3 It provides guidance on the formalized risk assessment for appropriate good manufacturing practice for excipients of medicinal products for human use. Manufacturers must define the appropriate GMP for their process and then ensure that the excipient meets those standards.

This guideline is also relevant to the discussion of raw materials because manufacturers may want to apply some of these principles to how they manage the quality of all raw materials. For example, required characteristics of excipients vary due to many factors including dosage form, route of administration, dosage quantity and frequency, possible interactions with the API and formulation technology – but only the drug manufacturer knows all these details. Therefore, only the drug manufacturer is in the position to determine the correct quality for each excipient used.

Excipient suppliers cannot warrant their products as "suitable for "a particular application but they do have the responsibility to follow established guidelines (e.g., IPEC-PQG GMP, EXCiPACT™) and to provide data and documentation to support the drug manufacturers' risk assessments. The risk assessment should be performed and documented in a formal way and the documentation prepared and available for review during regulatory authority inspections.

It is recommended that the drug manufacturer engage with the excipient supplier to work together to support continuous improvement and process optimization. Similarly, this model of formalized risk assessment for excipients can also be applied to the selection of other critical raw materials as many of the same risks apply.

European Biopharmaceutical Enterprises (EBE) Concept Paper: Management and Control of Raw

Materials Used in the Manufacture of Biological Medicinal Products, 29 November 2017, Version 1

This concept paper, developed by a biopharmaceutical industry consortium, "discusses background information related to raw materials regulatory requirements and industry challenges, and then

highlights key principles to consider in setting up a risk-based raw material management approach and control strategy ... then provides an example of how to translate those key principles into a detailed RM risk assessment methodology, and how to apply this methodology to specific raw materials. This document is effectively the first industry "how-to translation of the various regulations relevant to qualification of raw materials.

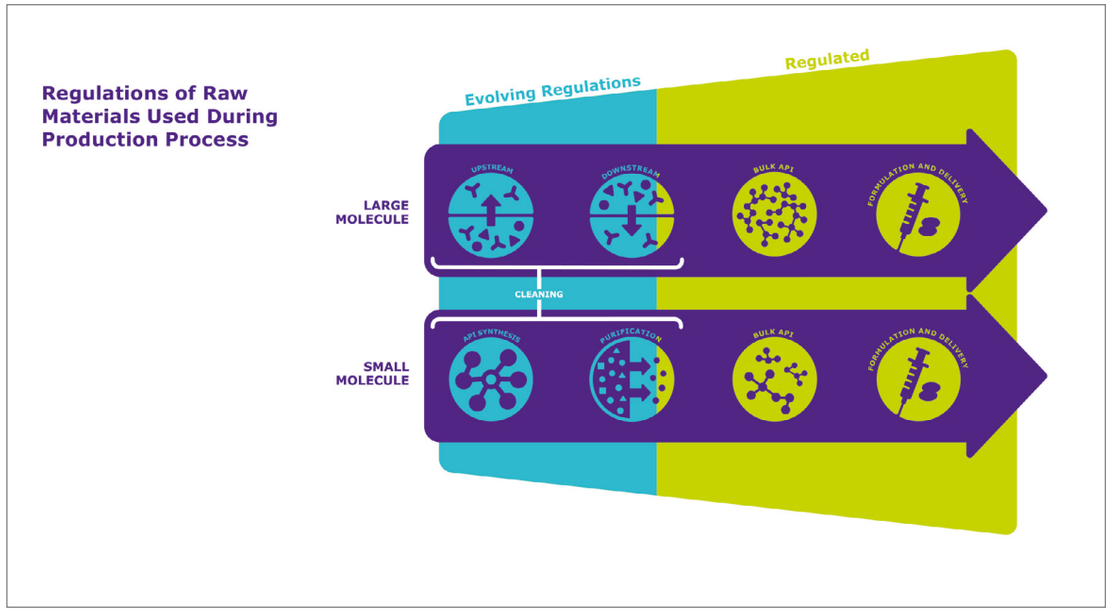
Ensuring Sufficient Quality for Raw Materials

- Raw materials' attributes: Understand & define raw materials' attributes to control variability & Contamination
- Supplier information: Appropriately document qualification & maintenance of suppliers
- Impact on quality of final drug: Address risk assessments to control raw materials' impact on final drug's quality
- Excipient model: Use regulatory approach for excipient quality as a model

Raw material and supplier selection, qualification and approval roadmap

- Drug manufacturers have the responsibility to understand and define raw material attributes to control variability and risk of contamination by impurities. Specific quality standards are not defined.
- Selection, qualification, approval and maintenance of suppliers of starting materials should be documented as part of the pharmaceutical quality system with a level of supervision proportionate to the risk of the material.
- Risk assessments to control the impact of raw materials on the quality of the final drug substance should be addressed as early in the development process as possible.
- The regulatory approach to quality attributes of excipients may be a helpful model for establishing similar strategies for selection of raw materials.

Risk assessment and quality by design are important topics for regulatory agencies, and manufacturers must stay current on recommendations for appropriate selection of raw materials and selection of suppliers. Control of manufacturing process parameters and raw material quality is necessary to mitigate risks. This risk assessment process demands a deep understanding by the drug manufacturer of raw material attributes and supply chains. However, although general regulatory guidance is given for "non-regulated or "evolving regulation raw materials, no detailed quality attributes are currently described, and manufacturers must develop their own strategies for risk management when it comes to establishing quality attributes for their raw materials.



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Part II of this article covers important supply chain considerations. The manufacture of biopharmaceuticals includes more steps than that of small molecule drugs and can involve dozens of chemical raw materials, as well as filters, single-use processing equipment and chromatography materials, all of which must be part of the risk assessment and mitigation strategy. Each material that is used can pose a contamination risk in terms of metal or elemental impurities, residual solvents, extractables, leachables and insoluble matter that can be carried into downstream steps.
Read the full article at: http://www.emdmillipore.com/Web-US-Site/en_CA/-/USD/ShowDocument-Pronet?id=201812.026

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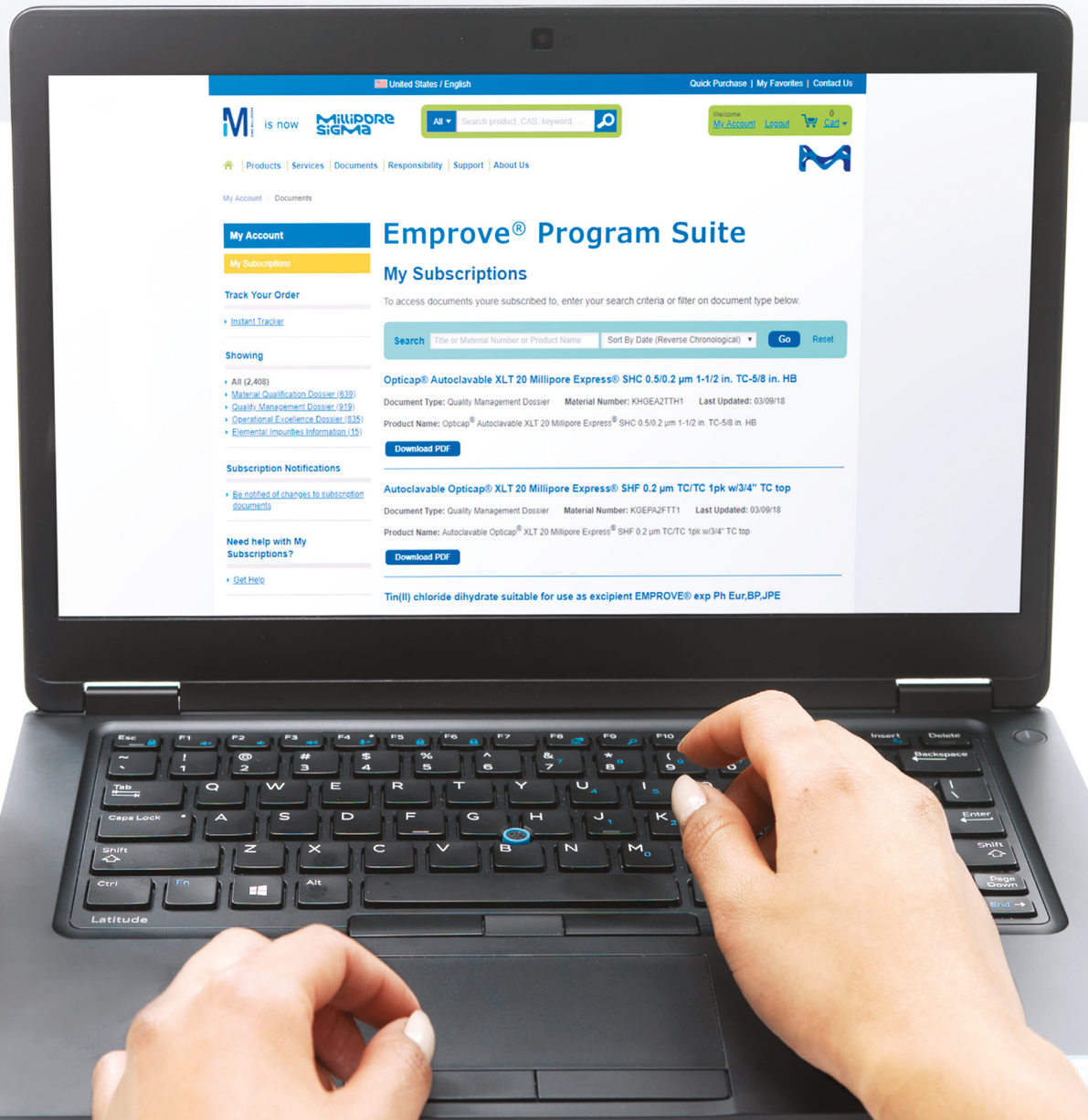

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