CELL & GENE THERAPY INSIGHTS

EXPERT ROUNDTABLE

CRITICAL NEEDS AND CHALLENGES FOR THE CELL AND GENE THERAPY RAW MATERIALS SUPPLY CHAIN

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Stefano Baila received his PhD in 2007 based upon translational research and development of gene therapies for hemophilia at the Children's Hospital of Philadelphia. Since that time he has been actively involved in the process development and manufacturing of advanced therapeutic medicinal products through business development and strategic marketing roles at Areta International, a CDMO, and by leading field implementation and commercialization activities for the cell processing unit of Terumo BCT. Stefano also worked as Industrialization Manager at Celyad where he led process development and automation efforts for CAR-T therapeutics. Now he serves as Director of Operations and Business Development for Anemocyte.

MARLIN FRECHETTE
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Marlin Frechette has over 25 years of experience in the Medical Device industry, servicing the Pharmaceutical and Biopharmaceutical customers. At Fujifilm Irvine Scientific she is currently the Sr. Director of Quality Systems/ Regulatory Affairs/Compliance Officer & ISO Management Representative. At Fujifilm Irvine Scientific she manages and performs review functions of the Quality Systems, Global Regulatory/ Product Compliance and Compliance/ EHS departments. She holds a Bachelor's of Science with a major in Business Administration & Personnel Management.

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Kristie Francis currently works at Regeneron Pharmaceuticals, managing the Material & Supplier Quality Team whose role consists of material qualifications, change notifications, alternative sourcing and SCARs. Graduating from Clarkson University with a degree in Biomolecular Sciences, she has experience in both raw material manufacturing and pharmaceuticals with 10 years of experience in quality. She is an active participant in the global, cross-functional Biophorum team (formally BPOG) for Raw Material Variability (RMV) and Risk and Business Continuity Management (RBCM) teams.

DIVYA GOEL
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As the VP of Business Development, Divya oversees platform development and technology licensing for Celltheon. As a bioprocess engineer by training, Divya is not only involved in external facing business opportunities, she also works with the technical staff to evaluate new bioprocessing technologies and develop efficient workflows that can be leveraged by the greater pharmaceutical industry. Divya regularly attends scientific conferences to present the Celltheon SMART TechnologyTM platform and discuss other advances that Celltheon has made in bioprocessing. Divya holds a BS in Biology from Drexel University and a Master's in Business and Science (MBS) from Keck Graduate Institute in Bioprocess Engineering and Business. Since joining Celltheon, many of the client molecules she has overseen have advanced into late stages of development. Divya is committed to overseeing the application of Celltheon's novel technologies to develop high titer, high quality products and ensuring seamless tech transfer.

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Q What are the keys to successfully implementing a risk-based approach to raw material selection and qualification?

SB: I think it's important to firstly clarify what we mean by 'raw materials' and the reason for this is that is there is a slight difference between Europe and the USA in this regard.

At the end of manufacture of a cell and gene therapy product, we have what can be termed as an 'active substance'. All the materials involved in generating that active substance, but that are not expecting to actually be in the final product, will be defined as 'raw materials'.

In Europe, everything that remains in the active substance is defined as a 'starting material'. However, the USA is slightly different in that raw materials implies everything that goes into creating the active substance. The US equivalent of what would be termed raw materials in Europe is actually 'ancillary materials'.

It is important to make this distinction at the start because there are many materials that enter into the picture but at the present time, in both Europe and the USA, there is limited availability of companion descriptions of these materials. It's very important to be able to qualify them. Usually, the best way to do so from a pharma mindset is to refer to either the USA or the European Pharmacopoeia. Unfortunately, in the case of raw materials for cell and gene therapy products, while there are guidelines and some good advice, they all go back to the risk-based approach.

Just for reference, the relevant European Directorate for the Quality of Medicines and Healthcare (EDQM) general chapter is at 5 2:12, while the corresponding US Pharmacopoeia chapter is at 10:43.

You need to do two things when looking at the risk-based approach: firstly, you need to look at the raw material to ensure it is suitable for the specific use to which you want to put it, meaning you must look at the identity, purity and the biological activity of the material. However, that on its own is insufficient – it is also necessary to look at the product that will ultimately come out of the process the material is to undergo. So we have to look at the impact of that process, too, meaning quality, safety and efficacy have to remain within the expected parameters that we have established at the beginning.

Risk-based assessment therefore forms the guidelines here: going back to the original question, the primary keys to success are to make sure the raw material is suitable for its given purpose, and that it doesn't impact in a negative way on the quality parameters of the final product.

Internally, we have decided to use a risk-based approach based on ICH guideline Q9 on quality risk management and especially, to employ the Failure Mode Effects Analysis (FMEA) strategy. Without going into too much detail, it allows us to prioritize risks and to try to tackle them from the highest to the lowest.

Finally, it is worth noting that in the US Pharmacopeia, they actually add an element of risk-based classification that can be very useful to give a numerical value to the risk associated with a material. It covers the spectrum from a raw material that is a licensed, approved drug down to something that is not produced with the proper standards and is not expected to be used for GMP cell and gene therapy production. Everything in-between is given its own risk value.

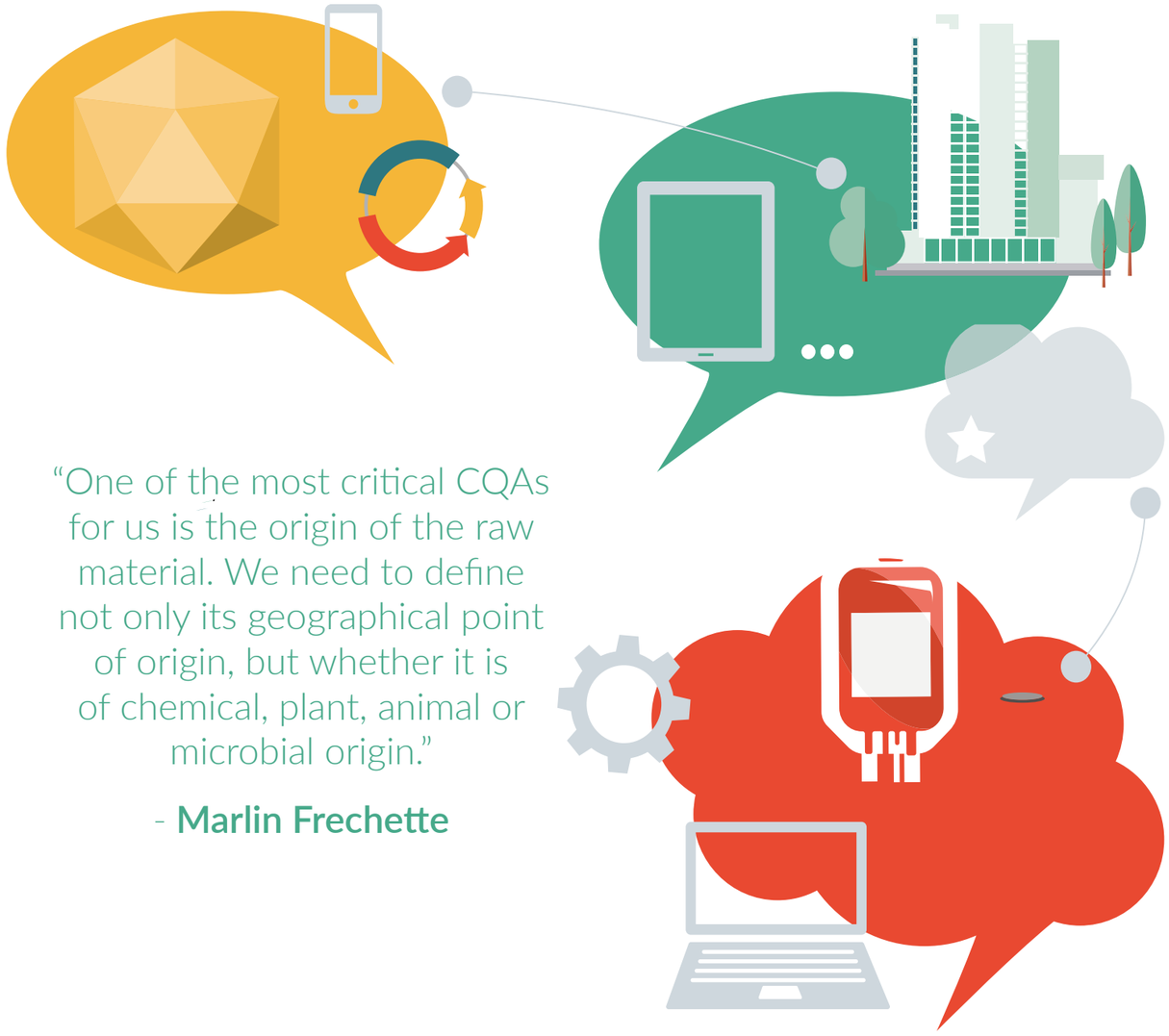
MF: Understanding the raw material function – for example, of the final cell culture medium we are developing - is of paramount importance to us. Once we understand this, then we can define the critical quality attributes (CQAs) for that raw material.

One of the most critical CQAs for us is the origin of the raw material. We need to define not only its geographical point of origin, but whether it is of chemical, plant, animal or microbial origin. If it is of animal origin, then we need to know what type of animal, and we need to understand what specific kinds of testing need to be done depending on that given species.

The method of manufacturing is also very important for us – whether it's a fermentation or an extraction method, for example. Again, specific testing depends on the manufacturing method used.

Another key CQA is the grade – whether it is USP, BP, JP, EP or multi-compendial, it is important for us to know what testing has been performed on that raw material.

DG: I come at this more from an early R&D perspective where we are still determining which kinds of supplements and raw materials we'd like to incorporate into our cell culture processes.



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– Marlin Frechette

Often in R&D, one of our scientists will choose certain raw materials for the purpose of understanding what the effect is on certain CQAs of our molecules. And it is a challenge to then translate that particular raw material, which may be of research grade, into something that can be used for GMP manufacturing.

It is therefore important for us to make sure we're well aligned at a very early stage in our R&D. We need to understand if there are multiple suppliers of a given raw material, if each supplier has a suitable alternative product available that can be used moving forward into GMP manufacturing, if the material meets USP testing standards, and so on and so forth.

Additionally, when transitioning from the research phase into a more stringent GMP manufacturing phase, we need to identify and analyze the changes we observe in the product profile of the raw material itself – for example, what are the impurity profiles and how are they changing? We need to establish a robust qualification procedure internally for testing the materials and the effects any changes to them have on the cell culture process, and on the quality of the molecule that's being expressed. We also need to ascertain if those effects change over time as we're passaging results for additional generations – in other words, how long it takes for the cells to become adapted to certain changes in raw materials.

Those are the kinds of things we want to think about internally when transitioning from early phase research into actual GMP production.

Q What are your chief needs and considerations for the raw materials supply chain during upstream process development?

KF: The first key thing for us when we look at new raw material selection and qualification is identifying what the key quality requirements are – whether it's a compendial grade material and whether it contains certain assays that we require for our process. On top of that, we need to understand the exact purpose of a raw material in our process.

> "[in early-stage R&D] you are looking for quick results, to obtain data as soon as possible, but it is critical to take the time to really demonstrate repeatability during upstream process development in particular."
>
> - Divya Goel

Taking a risk-based approach is a key part of our due diligence. We like to improve our understanding of the manufacturing process, the controls and supply chain. And we also place importance on the overall feeling that we have with a given supplier – whether they are focused on improving, whether they are a new supplier we've never utilized before – it's very important to audit our suppliers and gain experience of them.

For us, it's really a mixture of all these items. We can then rank the material from high to low, determine what kind of in process controls are needed as a result, and adjust accordingly.

DG: In early phase R&D, keeping future tech transfer in mind, we ideally want to make sure the materials we're utilizing have a suitable alternative we can use for later manufacturing in a GMP facility.

We've definitely run into some issues where we've used unique supplements and reagents in our cell culture processes that were only available from a single supplier, and that supplier has not been able to provide a suitable alternative for GMP manufacturing. That is why clear communication with our suppliers is of extreme importance – they have to work with us to prepare for when we need to start using that component in GMP manufacture, with the proper testing and analysis all in place.

In addition, we want to make sure that we characterize lot-to-lot variability in a particular reagent or supplement that we're using in our cell culture. It is often the case in early-stage R&D that you are looking for quick results, to obtain data as soon as possible, but it is critical to take the time to really demonstrate repeatability during upstream process development in particular. We need to make sure that the material we intend to use will give us the essential product quality we're looking for at manufacturing scale as well.

We also want to understand the manufacturing processes for the raw materials themselves, especially those materials we would ultimately like to use in a GMP setting and for tech transfer. We've had situations where the material itself has been qualified, it's been tested, but it may be manufactured in a facility where it is in close proximity to another reagent that is of animal origin, for example. Can the supplier provide us with a BSE/TSE certificate in that instance so we can claim that the material is BSE/TSE-free? This is essential so that we understand what kind of traceability there is for the material. That can also be a challenge and it brings me back to the importance in early development of establishing good lines of communication with suppliers.

SB: This is quite a challenging question in the sense that when you're in discovery mode or process development, you are supposed to be as free as possible to try anything in order to obtain the best out of your process. In reality, though, it is strongly recommended to have some idea of the end goal in mind, and perhaps to be a little bit educated in terms of the impact of the choices you will make: it's true tha t there are generally several options available in the marketplace for R&D-grade materials, but they will not necessarily translate into GMP grade.

In terms of key considerations, first of all, you need to keep in mind the origin of the product, as Marlin has already mentioned, because that has a critical impact.

The second thing is the reliability of the supplier and their ability to supply clinical-grade product at a later stage. The sustainability and the manufacturability of the materials that will go into your process really are key aspects that need to be kept in mind right from the beginning. I would also add to previous comments on the importance of a close collaboration with suppliers involving both the development team and where applicable, the industrialization team.

KF: One of the biggest things we have to take into account is raw material variability. It's something that, from an industry standpoint, we need to try to understand from both supplier and manufacturer standpoints. Open discussions are key to this. When it comes to managing lot-to-lot variability, having quality agreements in place between supplier and manufacturer is crucial, so that if anything changes, we will be made aware of it immediately and be able to quickly work with the supplier to make an assessment. Auditing, supply chains, and understanding complex supply chains are also key components that we really need to take into consideration when we're dealing with these experiences.

MF: By considering the supply chain issues up front or upstream, or during discovery even, you can avoid a lot of issues with lot to lot variability, toxicity, safety. So it's very important, even through its discovery stage, that you really include these factors about the raw materials. The raw material supply chain and the raw material quality, to ensure availability of that raw material prior to scale up production.

Q We've already touched on the major challenges that changes in raw materials can present – can you go deeper on this issue?

KF: As we've touched on previously, one of the big challenges we face as an industry is an inability to sufficiently characterize products. Raw material variability is a key aspect of this, and the situation is exacerbated by the fact we're in a very heavily scrutinized industry, but it's one where everything is very proprietary and well-guarded. The ability to share the relevant information can be very limited. I think the industry is working towards overcoming this with collaborative approaches, but it has been a huge challenge.

One of the key challenges in this industry is the regulatory requirements – ensuring you are compliant with those and abiding by them. Ultimately because patient safety is our first and foremost concern.

DG: I believe that for us, at an earlier stage of R&D, it probably doesn't have quite as big an impact – for instance, if you're already manufacturing a product either clinically or commercially and then your supply chain changes, a raw material substitution can have a much greater impact. You have to jump through so many hoops for the regulatory agencies to make sure that it is a safe addition or substitution. There are of course still time and risk components to raw material changes, in the event that they do not translate to the same level of product quality or performance that we achieved initially. We have experienced this in some cases. But I think that it is something we can overcome more easily than a company in the later stages of development or commercialization.

MF: Once you have a raw material already qualified and linked to a product, then certainly a change is very impactful.

You have to requalify the raw material as if it were brand new, which is not only very time consuming but very costly. This can have a major impact on final product specification and application. Changing a material can also lead to differences in the variability of that particular component, which of course further impacts the bioprocess and final product. Finally, there might be potential disruption and delay in the overall supply chain if the change is not handled properly.

SB: By definition, any change implies some consequence so it's very important to verify that any changes that are required or foreseeable do not impact the CQAs of the medicinal product in development.

If you look at the guidelines provided by the authorities, it's actually kind of implied that in a young industry like ours, there could be some evolution in the raw material that are available, and that it is incumbent on developers to always try to use the highest quality standard available. That means sometimes we start with something that is not ideal from a quality perspective, but then perhaps years later in the development phases, we are able to get closer to a GMP grade product.

Of course, all materials changes need to be properly evaluated. Comparability studies will of course be required more and more, and will be increasingly intense, up to and including potentially repeating some *in vivo* data. We mentioned previously that critical analysis as a way to identify what are the most crucial elements of the raw materials in place in a manufacturing step. If you change the most critical materials, you will probably have a higher comparability requirement at the end of the study.

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> - **Stefano Baila**

Q On a related topic, how does the 'domino effect' manifest in your own specific cases, and what are your approaches to reducing this impact?

MF: The 'domino effect' relates to raw material changes affecting everyone in the wider supply chain.

Everyone so impacted must perform a due diligence to properly evaluate the impact the raw material change has on them, and to seek to avoid any associated risk.

Most importantly, I think everyone in the supply chain is primarily trying to avoid disruption to product availability. The way to reduce this impact is by communicating the changes immediately and as thoroughly as possible. We require that our own suppliers communicate any changes to us as early as possible in order to give us time to do our own due diligence and assessment, and to prepare all the necessary information so we can provide it to our own customers in turn so they can do their own due diligence. And it's not only our customers – at times, we must also inform the regulatory authorities that hold the registration files.

So assessing any changes and addressing any risk up front is critical. Anticipating our customers' requirements in this regard and providing all the support they need for their own change due diligence and risk management is very important. We try to minimize the risk to our business and we try to minimize the risk to our customers' businesses. And again, above all, the most important thing is to maintain the continuity of supply.

KF: I completely agree. One of the key things we have learned about the domino effect is that the raw materials supply chain is very long and convoluted – it starts off with a raw material manufacturer and ends up in the patient.

There are many places in between where supply chain issues can occur caused by the domino effect. If you think about the initial raw material and how it gets to us in the biopharma industry, something happening upstream that is seemingly very simple – a particular silicone being discontinued, for example – can filter down and have a tremendous impact, and we work in an industry where supply chain issues carry a high risk of impacting patients. Fostering a really deep understanding of the supply chain is one of the key steps we employ to try to minimize and control the domino effect.

I know that a lot of biopharma companies and the suppliers that we utilize have different business continuity plans and alternative sourcing strategies to mitigate any such supply chain issues that we might experience. On top of that it's a lot of collaboration, safety stock, doing the supplier corrective action, to mitigate any of these risks that would potentially impact patients.

SB: The first things that come to mind in terms of our own experience is actually a sort of 'double domino'.

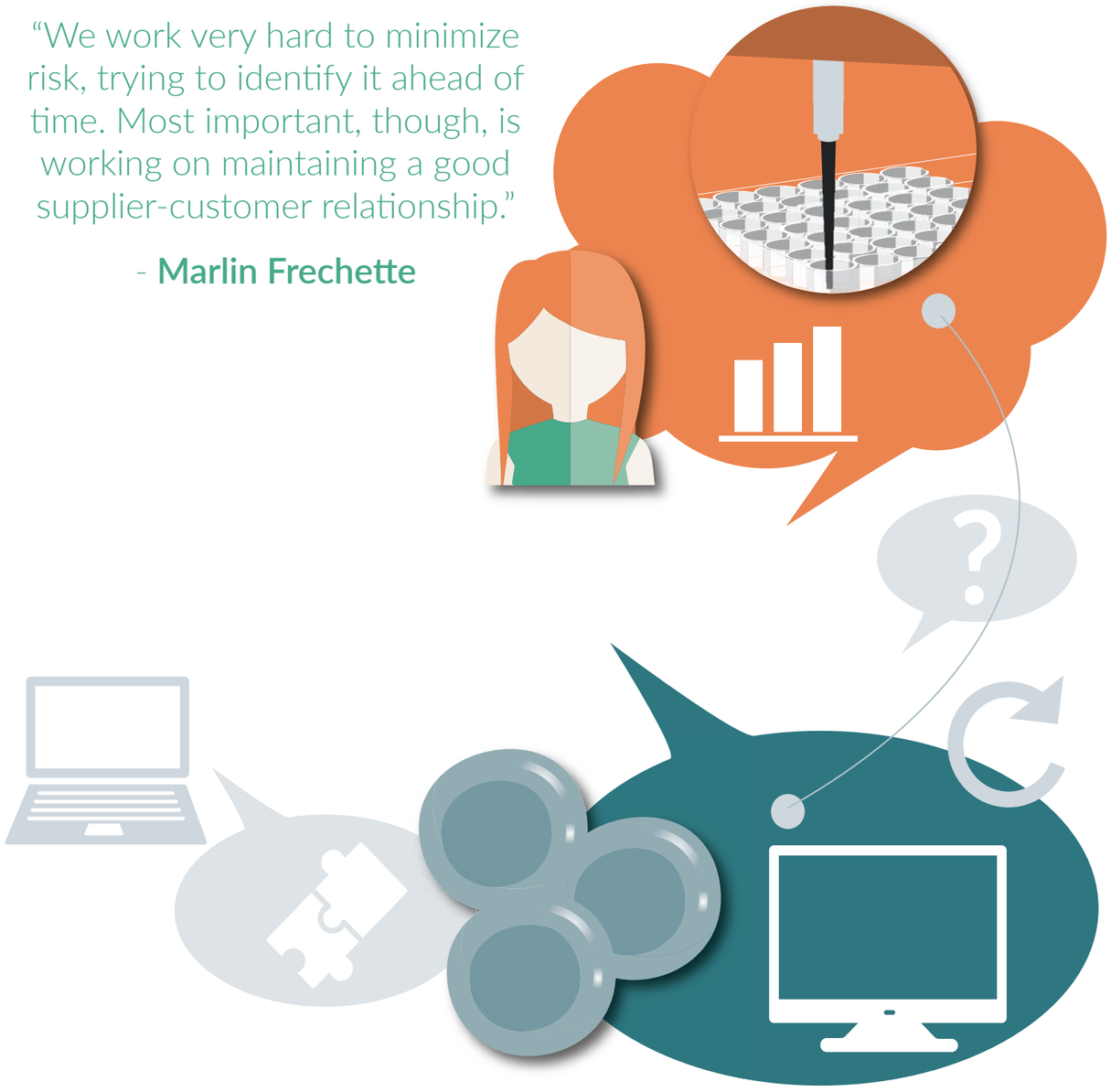
We once used an enzyme that could detach cells extremely effectively. However, it was from a porcine source, so it was necessary to keep track of all the risks relating to the origin of the product. A few years later, it became possible to source a corn-based enzyme from a different supplier, which obviously removed many of the risks and challenges related to the porcine product (even if we now needed to check for a specific adventitious agent typical in corn). However, just a few years further on, and we were able to access the complete, recombinant version of this enzyme, meaning a further change was required.

It is very important to be able to identify the safest possible material that can be used – product safety and the impact of the raw material on the patient who receives the final product

should always be at the forefront of our minds. That said, it's also very important to try to identify where the challenges are or will be in the future, and to try as far as possible to address them prior to starting down a particular avenue through risk assessment. Of course, that's simply not always possible, as in the example I just shared – those were changes we were obliged to make. And needless to say, it was very important on each occasion to retest not only the new material to make sure it was suitable for use, but also that it would not impact the quality, safety and efficacy of the final drug.

"We work very hard to minimize risk, trying to identify it ahead of time. Most important, though, is working on maintaining a good supplier-customer relationship."

- **Marlin Frechette**



Q How do you each cope with issues that can have wide-ranging effects on the global raw materials supply chain - for example, shortages of key raw materials?

DG: We've had a number of specific examples I could cite where we've faced shortage challenges head on. It is probably one of the most common issues in raw material sourcing and supply chain. Our risk mitigation has been to always keep secondary suppliers on hand that we can refer to in the case of a shortage or a backlog – that's in addition to keeping the primary raw material in stock to make sure we have reserve supplies, as far as is possible with expiration dates in mind.

On occasions where there is an important manufacturing campaign or milestone coming up, we've advised our suppliers to put down a master cell bank, for example, so that we not only ensure we have secondary suppliers we can go to if needed, but that we also have a reserve stock of the primary source of material.

SB: We've all shared our thoughts already on how important the quality of raw materials is. But quality is not enough: what's also important is to look at the supplier, the cost, the scalability of the material supply, and how easy or difficult it is to use it in your process.

With all of these elements in mind, when you look to go global through either a pivotal trial or launch of a commercial product, it's very important to make sure you have very strong, legally binding agreements in place with your suppliers in place to ensure you receive the necessary support.

It's not all about the amount of material, either. One additional issue we've faced recently relates to making sure you have the proper licensing elements in place. You also need to ensure your partner can support you with advice and expertise on country-by-country differences in requirements – that is especially the case in Europe, but also if you are looking further East to the Asia Pacific region, for instance. The supply chain on a global scale requires strong collaboration with the supplier. Making sure they understand our needs will ultimately help ensure we best serve the patient.

MF: Even the most robust raw material program can be challenging, especially when it's on the global scale. We have defined many components to help minimize that risk.

One is certainly ensuring that, where possible, you have a secondary supplier, preferably from a different country. Pay close to attention to safety of stock. Implement a supplier and quality agreement, change notifications, etc. – have all the documentation in place. And ensure your supplier understands they signed up to provide you information on any changes to raw materials as early as possible.

We qualify all of our raw materials and our suppliers using a risk-based approach. We also require that we do on-site audits with our suppliers, which are based on the risk and the challenges we could encounter with a given raw material: some suppliers are audited once a year, some every 2 years, and so on. We do supplier requalification on a routine basis as well as supplier performance evaluation, and we provide the results of their evaluations to those suppliers. We provide a score and a supplier corrective action report any time we encounter an issue – we find this encourages our suppliers to be very responsive whenever supply changes occur, for example.

We work very hard to minimize risk, trying to identify it ahead of time. Most important, though, is working on maintaining a good supplier-customer relationship. In fact, we no longer treat our suppliers as such – they are our partners. We are in this together and we try to establish a good and robust relationship, founded on strong communication and transparency while dealing with partners across the supply chain.

KF: One interesting recent trend is the growing number of business continuity programs involving biopharmas and their suppliers. These provide a platform to share information and ultimately, to work together to create alternative sources and risk mitigation strategies to really make sure that neither businesses nor patient safety are impacted by materials supply issues.

Q What are some of the unique raw material related challenges for CMOs, and what can their biotech partners do to alleviate them?

MF: As a supplier of cell culture media, it is very important that we are transparent with the CMOs we work with. We understand that one of the challenges in the supply chain is a lack of communication at times, or a lack of proper documentation – traceability of changes, traceability of raw material production or flow.

We are committed to help our CMO partners by implementing and managing a robust supply and raw material control program, by using industry standards and adhering to regulatory requirements.

We work very hard to earn our partners' trust with a core focus on protecting our customers' sustainability of supply, and providing our CMOs with the support that they need.

We know they have challenges, and we try to minimize them by first understanding them, and then providing with what they need ahead of time.

By having a commitment to providing a robust supply chain and raw material control program, we are ensuring that we are providing our CMOs and customers with the support they need.

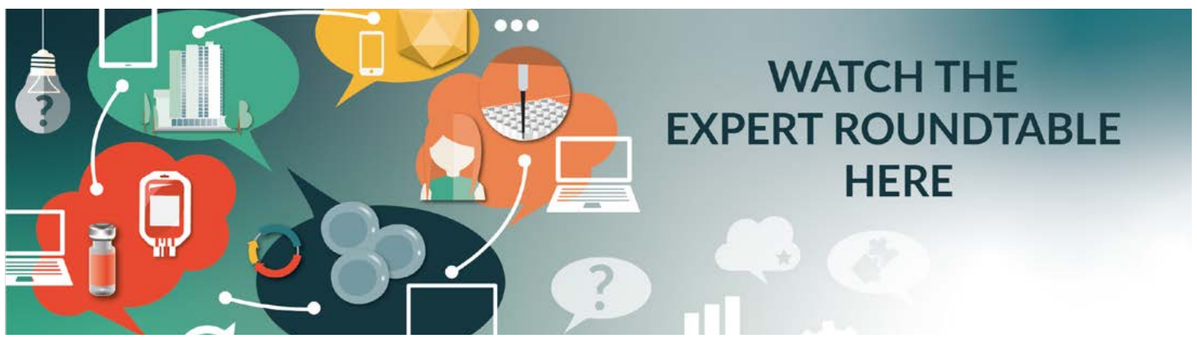
SB: I want to start with something that might sound like a joke but it is a reality! In a sense, one of the biggest challenges for a CMO like us in this regard is actually the clients themselves.

Sometimes you have clients – very well-established biotech or pharma entities – that are very clear on the importance of raw materials. They can very often be the first to proactively identify a particular supplier and research and understand the unique challenges around a specific raw material. At other times, though, you have to deal with start-ups that are maybe new to the industrial setting and while they are very strong in the science, they are not necessarily so strong when it comes to the big picture of GMP requirements.

It can be very hard to explain to those companies why certain reagents cannot be used, or why they are obliged to change their supplier of certain materials (perhaps at extra cost) just because it's necessary to work with a higher grade material.

A second challenge relates to the suppliers themselves – sometimes we have to ask a supplier to make and innovate, unique product just for us, because a certain tool or specific material is not manufactured already for use with cell and gene therapy products. We may have to ask them to adapt their whole manufacturing strategy just for us. So it's very important to get their support, but it's also very important for them to help us out by educating us on how we can and should utilize their products.

An additional challenge we face, especially here in Europe, is the fact there is no Drug Master File (DMF). In the USA, it's very easy to cross-reference a specific raw material with the DMF, especially when a material supplier is not happy to share their secret recipe. A DMF is a good way to overcome this challenge but in Europe, it's not possible – as a result, we sometimes have to find a way of digging into the secrets of the supplier. European suppliers are quite used to that – US suppliers, a little less so…



Q Finally, any wrap-up comments from the panel?

KF: One of the key raw material challenges we have relating to CMOs and biotech partners also relates to highly proprietary information. I do think that as an industry, we're really growing and becoming more collaborative, though. This increased transparency, and communication platforms like this forum really have been helpful, because we've been able to tackle a lot of serious global supply chain issues that have occurred not just to Regeneron, but to many biopharma and raw material companies.

"One of the key raw material challenges we have relating to CMOs and biotech partners also relates to highly proprietary information. I do think that as an industry, we're really growing and becoming more collaborative, though."

- Kristie Francis

DG: I'll conclude with a more general comment and issue from my experience with an early-stage R&D organization.

As you transition through bioprocess R&D and towards full manufacture, you really want to have an understanding of the definitions that are used for certain compendial statuses between different raw material providers – unfortunately, they can be very different from one provider to another.

Having a clear, streamlined understanding of what the definition is, what analytical testing is being done, whether it's to certain regulatory standards if you're using regulatory nomenclature – all of that's helpful. But if you are also using internal nomenclature, how do you then translate that to specific regulatory standards? Some standardization in this regard would really help us in transitioning from research-grade to GMP-grade materials.

And again, I think it really comes down to clear communication – understanding what the needs of the customer are, but also how the supplier intends to communicate with us through things like change notifications and supply throughout the year.

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