INTERVIEW with Kasey Kime, Senior Manager of Regulatory Affairs Clinical and Compliance, and **Michael Brewer**, Director and Global Principal Consultant, Regulatory at Thermo Fisher.

"The quality of raw materials needs to be considered according to the stage of development of the cell or gene therapy..."

Enabling cell & gene therapy raw materials standardisation and regulatory compliance

Kasey Kime, has 15 years of global quality and regulatory affairs experience in Life Sciences. She is part of Thermo Fisher Scientific's regulatory affairs division and is overseeing regulatory compliance of technologies developed for cell and gene therapy applications. Her areas of expertise include raw material risk assessment for biopharmaceutical development and regulatory compliance of instruments and consumables developed for automating cell and gene therapy manufacturing. Kasey holds a Bachelor's degree in Medical Laboratory Science and postgraduate degrees in both Microbiology and Quality Systems Management.

Michael Brewer is the Director, Global Principal Consultant, Regulatory for the BioProduction Division (BPD) at Thermo Fisher Scientific. In this role, Michael is responsible for providing global support to BioProduction customers and serving as the regulatory thought leader and expert across all technology areas within BPD. Prior to moving to this role, he led the team responsible for product applications including Microbiology, Analytical Sciences and Quality control. The products are fully integrated, solutions for

Glycan profiling, Bacterial and Fungal identification, Mycoplasma and Viral detection and host cell DNA and protein quantitation. Michael has over 30 years experience in the Biopharma industry, including, Scios, Synergen and Amgen in a variety of roles including Discovery Research, Analytical Sciences and Quality Control. Prior to joining Thermo Fisher Scientific, he led a group at Amgen that developed qualified, validated and implemented molecular methods for host cell DNA quantitation, contaminant (Mycoplasma, Virus and Bacteria) detection, contaminant identification, strain typing and genotypic verification of production cell lines.

Cell & Gene Therapy Insights 2019; 5(11), 1457–1460

DOI: 10.18609/cgti.2019.153

Q What are the key elements to consider when selecting reagents and media at an early stage of R&D?

KK: Performance is always going to be very important in early R&D although quality and safety should also be considered. The quality of raw materials needs to be considered according to the stage of development of the cell or gene therapy, acknowledging the quality profile does evolve during clinical development. However, it is still important to assure patient safety even in early clinical development.

MB: In addition, it's important to choose reagents, components of your process, media, etc. early on that will meet the most rigorous regulatory expectations that will come later in development. This avoids the need to make changes, justify those changes and go through the change control process as you get closer to the clinical and commercial stages.

Q Delving deeper on the topic of supporting documentation and certification, can you explain the specific utility and benefits of the various options in this regard? (RSFs, DMFs, COAs, COOs)

KK: It is important for cell and gene therapy developers to be aware of any safety risks within media or reagent products especially, if they contain biological-derived components within their formulation and/or manufacturing process. CGT developers should begin assessing raw materials for suitability in manufacturing by reviewing the supplier's COA and COO. Both of these documents will provide the end user with the data to begin further risk assessments.

Master Files can be useful in regions that support master file processes for raw materials such as USA, Canada and Japan. Master Files are popular for suppliers as they limit the amount of confidential information disclosed to the end users. However, many regions do not support master file processes for raw materials and often the information within the master file is also desired to be disclosed to the end user. In these situations, suppliers may provide Regulatory Support Files (RSFs) under CDA to clinical customers. The RSF is likely to contain a CMC-style summary of the same data that is within the Master File. Often it will provide qualitative levels of components rather than quantitative levels to protect confidentiality concerns on media/reagent formulations.

Japan has a very unique raw material certification process that enables media and reagent suppliers to submit evidence to the PMDA that their raw materials comply with Japanese Standard for Biological Ingredients (SBI). If the PMDA approves the raw materials meet the requirements as per the SBI, a certificate is issued to the supplier. The supplier can share the certificate of SBI compliance with developers in preclinical phases so they can make informed raw material choices thereby helping to assure correct raw material choices early in the process. This process reduces the burden for raw material risk assessment on the developer, the supplier and the regulatory agency.

Q What degree of importance do you place on AOF certification and why?

KK: Animal origin free is definitely the goal. It is desirable because it helps to reduce adventitious agent risk concerns which are still one of the main regulatory filing deficiencies for CGT customers using biological-derived reagents. By having a certified animal origin free product you remove the need to prove viral safety of biologically-derived components. However, we still need regulatory agencies to agree on the definition of AOF and the levels of AOF such as primary level or secondary level or beyond. Suppliers and CGT manufacturers

> "By having a certified animal origin free product you remove the need to prove viral safety of biologically-derived components." -KK

> "...choose solutions that have been successfully validated and implemented into a manufacturing process similar to yours." -MB

need to ensure the supply chain involved in the manufacturing of media and reagents destined for use in CGT, are educated and understand the need for accurate AOF statements for their components.

Q What differences do you see between the USA and Europe in terms of the degree of importance developers and manufacturers place on key certifications and compliance with various standards/guidelines?

KK: I notice that both the USA and EU expect raw and ancillary materials to comply with the associated pharmacopeia chapters as applicable. In the USA this is general chapter USP <1043> while in the EU this is Ph Eur 5.2.12. Both regions want well characterized, high quality/GMP products intended to be used as raw/ancillary materials in CGT manufacturing processes. Supplier relationships are very important. Developers want to ensure a good relationship with their suppliers of critical raw materials to enable timely answers to questions posed to them by regulatory agencies. They want to ensure their supplier will work with them to obtain answers to unusual requests or modify products/testing as and when required.

Q Why do these variations exist, and how do you go about identifying an optimal approach in each region and overall?

KK: At Thermo Fisher we have a global regulatory affairs team that continuously monitor the regulatory landscape for new and emerging regulations and assess the impact of these on our products and services. Our general approach is to incorporate both customer and global regulatory agency expectations into our product requirements. We are frequently audited by customers and have direct dealings with agencies on raw/ancillary material CMC matters so we do get a lot of useful feedback to ensure we have global acceptance of our products. This global approach is important for developers using Thermo Fisher products in clinical trials in multiple countries.

For some regions, such as Japan, our products are already designed to meet the SBI requirements so in this case we apply for the SBI certificate because this is a regional expectation but it is also of global value to customers looking to perform clinical trials in Japan.

Q Standardization of raw material quality testing is a major priority for the sector – how is Thermo Fisher Scientific helping to drive this?

KK: Our global Regulatory Affairs team help support customer and regulatory inquires on Thermo Fisher reagents and media in CGT manufacturing and actively contribute to standards development and regulatory initiatives for raw/ancillary materials. Our R&D and Product Management teams also actively contribute to industry working groups addressing topics such as the importance of standardization of raw materials.

One of the things we do at Thermo Fisher is to ensure we factor in global regulatory requirements for raw and ancillary materials into our product design process. New and emerging requirements are also considered in our product design because we know the most suitable raw and ancillary materials are those that are designed for this purpose.

Publication of the new ISO working draft for Ancillary Materials present during the production of cells and cellular therapeutic products is also highly anticipated. Once finalized, this will represent globalized guidance to suppliers and developers on best practices to ensure consistent, high quality and safe raw/ancillary materials.

Q Addressing the issue of regional differences between regulatory requirements relating to changing raw materials, what for you is the best strategic approach to this challenge?

> "One of the things we do at Thermo Fisher is to ensure we factor in global regulatory requirements for raw and ancillary materials into our product design process." -KK

KK: One of the questions developers need to ask themselves is whether they need to consider a global raw material approach early on. It is true there are regional differences and some regions may have more detailed requirements

DOI: 10.18609/cgti.2019.153
Cell & Gene Therapy Insights - ISSN: 2059-7800

"Partnering with a vendor that has experience in guiding qualification, validation and regulatory filings that have been accepted can streamline the implementation process and reduce the risk of extended regulatory review."-MB

on particular characterization or viral safety expectations than others. In some regions, detailed raw material requirements may not yet be published or there may be multiple interpretations leading to confusion around the regulatory requirements. For these reasons developers should aim to choose well characterized, high quality raw materials intended for use in cell and gene therapy manufacturing processes that meet the current regulatory guidance's in the major markets (such as USA, Europe and Japan). The use of such materials should ensure regulatory acceptance and avoid the need to make changes to materials due quality or regulatory deficiencies.

Q What is your advice to cell therapy developers in terms of selecting and optimizing their contaminant and impurity testing regimes with current regulatory requirements in mind?

MB: Although there are many potential options available, my advice is to choose solutions that that have been successfully validated and implemented into a manufacturing process similar to yours. Partnering with a vendor that has experience in guiding qualification, validation and regulatory filings that have been accepted can streamline the implementation process and reduce the risk of extended regulatory review.

Q Can you go deeper on the benefits rapid mycoplasma testing in particular can bring to cell therapy manufacture?

MB: As many cell-based therapies have limited shelf life, a rapid result from the required Mycoplasma test is needed to ensure the product is free of Mycoplasma prior to patient treatment. In particular, some qPCR-based Mycoplasma tests have been shown in validation to be sensitive, specific and reliable enough to meet regulatory expectations for Mycoplasma testing. Ask for examples of successful validations and regulatory acceptances as part of your due diligence in selecting a solution for your testing needs. I recommend selecting a vendor partner that has the support team and experience in place to support your implementation process.

Q Can you pick out some key considerations and specific issues when designing environmental testing programs across different regulatory jurisdictions?

MB: My advice would be to start by reviewing USP <1116> Microbiological Control and Monitoring of Aseptic Processing Environments. This chapter is quite comprehensive and provides a great foundation for sponsors to understand the process and how it could be applied in their manufacturing environment. Engaging an experienced consultant can also be an advantage when implementation needs to be accelerated.

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The authors received no financial support for the research, authorship and/or publication of this article.*

Article source: Invited.

Publication date: Nov 15 2019.