JULY 2022 Volume 8, Issue 6

CELL & GENE THERAPY INSIGHTS

SPOTLIGHT ON: Global regulatory update

Guest Editor:
Alexis Cockroft,
Regulatory Consultant,
Lex Regulatory Ltd

CELL & GENE THERAPY INSIGHTS

Volume 8, Issue 6

CONTENTS

Spotlight

Global regulatory update

Latest articles

Volume 8, Issue 6

Supply Chain Channel

Driving the digitization of cell & gene therapy supply chains

COMMENTARY: Critical success factors to consider before digitizing a cell & gene therapy supply chain

August Zepka & Charles Wilfong

CELL & GENE THERAPY INSIGHTS

GLOBAL REGULATORY UPDATE

SPOTLIGHT

REGULATORY PERSPECTIVE

A need for a novel regulatory framework for individualized neoantigen-specific therapies

Amy Hardwick & Kathleen Francissen

Manufacturing of individualized neoantigen-specific therapies for patients takes place one batch at a time. The existing regulatory mechanisms for post-approval changes for traditional products can be applied for limited types of changes to either controls or manufacturing processes for some individualized Advanced Therapy Medicinal Products. However, these existing mechanisms become untenable given the rapid pace of evolution among these therapies and constant innovations in manufacturing technologies (such as next-generation sequencing and bioinformatics workflows). There is a need for a novel regulatory framework for these therapies and mechanisms of pre- and post-approval lifecycle management (such as a predetermined change control plan) that allow for streamlined process updates, to ensure that patients receive products manufactured using the best technologies and most accurate data based on a continuous improvement mindset. The application of relevant medical device regulatory mechanisms to individualized neoantigen-specific therapies is proposed here, as devices have mechanisms for iterative improvements managed in a risk-based approach. While there are ongoing attempts at harmonization of regulatory expectations for lifecycle management, new regulatory mechanisms (and leveraging existing frameworks where available) are needed to avoid some existing pitfalls. A novel regulatory framework is proposed to consider the genomics and bioinformatics workflows as integral parts of the design and end-to-end manufacture of individualized neoantigen-specific immunotherapies.

Cell & Gene Therapy Insights 2022; 8(6), 671–680

DOI: 10.18609/cgti.2022.101

Advanced Therapy Medicinal Products (ATMPs) (which include cell and gene therapy (CGT) products) pose many new challenges, and also bring new concepts and opportunities that are not necessarily applicable to conventional biologicals. The ATMP field is highly dynamic with numerous rapidly evolving technologies in the manufacturing processes and the products themselves. As a result, traditional regulatory frameworks and lifecycle management mechanisms may not be well suited to these innovative medicines and thus call for fit-for-purpose approaches.

As the regulatory frameworks for ATMPs are being established globally, they need to be better aligned across countries and regions as highlighted by the WHO white paper on Considerations on Regulatory Convergence of Cell and Gene Therapy Products [1]. The regulations for ATMPs also need to enable the interface with regulations for devices and diagnostics, and other requirements (such as those for genetically modified organisms).

With the advent of ATMPs came fully individualized or 'make-to-order' medicinal products that are custom made for each patient; they include well-known modalities like autologous CAR-T cell products, and newer modalities like individualized neoantigen-specific therapies (iNeST). These iNeST products are sometimes referred to as 'cancer vaccines', being recognized as therapeutic vaccines (rather than preventative), but are more appropriately recognized as cancer immunotherapies. The iNeST class of products seek to mount a natural immune response to the patient's tumor-specific (neo)antigens, and can be messenger RNA (mRNA)- or DNA- or cell-based in their final form, but all begin with the identification of tumor-specific mutations called neoantigens which are only expressed in each patient's solid tumors [2–4]. The manufacturing processes for iNeST products require next-generation sequencing (NGS) and bioinformatics workflows as an integral part of their neoepitope identification processes. NGS and bioinformatics technologies are rapidly evolving, with continual improvements in instrumentation and methods being implemented on short timelines.

Indeed, the development of iNeST products has been enabled by the rapid and profound evolution of genome sequencing, which continues today. The dramatic reduction in the time and cost of sequencing [5] has allowed identification of each patient's neoepitopes by applying NGS technology for the production of each patient's batch of iNeST product. The nucleic acid extraction, library preparation, library sequencing, and mutation calling must be done in a matter of days to minimize the turnaround time for manufacturing the product while the patient waits for iNeST treatment.

While iNeST manufacturing processes begin with the acquisition of patient tumor and blood samples, these tissues are used for analysis (i.e., genome sequencing and bioinformatics) with the resulting data and information being used for production of each batch of product. It is recognized that the patient-derived tissues/cells are critical for the production of the batch and are thus considered 'critical materials' for manufacturing for this specific process but are not considered raw materials, nor are they considered starting materials since they do not form an integral part or significant structural fragment of the final product [6]. Indeed, the quality and reliability of genomic data is critically dependent upon maintaining sample integrity as it affects the DNA and RNA integrity and, in turn, the downstream performance of the NGS steps [7]. These critical materials are analyzed using NGS followed by bioinformatics analysis to identify and prioritize the candidate neoantigens for each batch of the product.

In order to keep pace with ongoing improvements in NGS technologies, it is important to establish appropriate change management practices for the genomics process steps, particularly when iNeST products are approved globally and different review timelines per region apply. For example, a new sequencing instrument and associated software and reagents are launched every 2–3 years by

DOI: 10.18609/cgti.2022.101

Illumina, a well-known instrument manufacturer, followed by phased discontinuation of older instruments in a relatively short time [8–11]. In the absence of a streamlined approach to implementing NGS process changes, the manufacturer would eventually have to use obsolete instruments that are no longer supported by the vendor. Therefore, regulatory mechanisms must keep pace with these technological advancements to ensure that the most current and complete information is used for the design and production of iNeST products, and to avoid manufacturing based on out-of-date technologies.

CHANGE MANAGEMENT CONSIDERATIONS

To date, much work has been done to enable mechanisms to streamline and reduce the regulatory burden of change management throughout the life cycle of biopharmaceutical products. Though progress varies by region, traditional examples of available mechanisms include but are not limited to Post-Approval Change Management Protocols (PACMP – EU), Comparability Protocols (CP submitted as Prior Approval Supplement (PAS) – US), and potential opportunities outlined in ICH Q10 Annex 1 [13]. More recently, ICH Q12 has sought to complement these regulatory approaches in the post-approval setting through the introduction of established conditions (ECs) and recognition of changes that can be implemented with supportive information but do not require reporting [14]. Throughout these approaches, a risk-based assessment is warranted to accompany the change evaluation process.

Manufacturing process changes are normally implemented for biological products by conducting a comparability exercise to ensure there has been no adverse impact on the product quality, safety, or efficacy. Indeed, the comparability principles described in ICH Q5E should be applied to ATMPs using a risk-based approach, while recognizing that the typical data packages and practices for demonstrating comparability may not be suitable for certain innovative modalities [12]. The design of comparability exercises (e.g., tests to be performed; acceptance criteria to be applied) are typically described in comparability protocols prior to initiating the exercise for post-approval changes.

While the approach described in ICH Q5E for demonstrating comparability can be applied to changes in the downstream manufacturing steps for iNeST drug substance or drug product, changes in the upstream neoepitope selection process require new concepts to maintain product quality since head-to-head comparisons are not meaningful. Indeed, the genomics and bioinformatics workflows are analogous to analytical processes, and each and every product batch contains unique patient-specific sequences; therefore, it is not necessarily meaningful to try to assess comparability at the product level. Certain changes in the neoantigen selection process are intended to improve accuracy. For example, bioinformatic algorithms and databases (such as the publicly available Immune Epitope Database (IEDB)) [15] used during the neoepitope selection process should be updated to leverage growing amounts of relevant data. Updates in the algorithms and NGS steps should be evaluated for their performance using appropriate metrics rather than an assessment at the product level. For example, a change in the NGS sequencing kit chemistry version on the same sequencer platform (e.g., kit v1.0 to v1.5) would need to meet or exceed the vendor-specified performance criteria and the pre-specified NGS QC criteria for the specific instrument and read length set by the developer/manufacturer (one example criterion being average base call quality Q30 ≥ 85%). The developer/manufacturer maintains control of the sequencing workflows to ensure quality of the resulting data.

While updates in manufacturing processes and controls are tracked in the pharmaceutical quality system/quality management system (PQS/QMS) using change control processes, the more substantial changes should be made transparent to regulators while balancing the

need to make iterative improvements to keep up with NGS technology and bioinformatics updates. This balance is better for the accuracy of neoepitope selection processes and ensures that the quality of the data generated during the manufacturing process keeps pace with the state-of-the-art process technologies.

In support of the lifecycle of iNeST products, a novel change management mechanism is being devised to ensure the appropriate product quality while maintaining state-of-the-art neoantigen selection. To enable robust development and iterative improvements in the genomics and bioinformatics steps, which are considered by health authorities in major regions to be an integral part of the end-to-end manufacturing process, a medical device regulatory mechanism is being adapted. Since software is being used directly in the manufacturing process, rather than indirectly by controlling equipment, software as a medical device (SaMD) regulatory mechanisms can be leveraged. This entails the use of a pre-specification plan (PSP) or predetermined change control plan (PCCP) as a mechanism which defines a 'region of potential changes' to provide an appropriate level of control over the unit operations of the workflow while allowing the flexibility to incorporate technology improvements as they become available in a 'do-and tell' approach. This approach allows pre-defined changes and performance metrics to be implemented in the manufacturing process as available and ensures transparency to regulators at regular time intervals (e.g., annually or at the next submitted amendment). A PCCP strategy incorporates elements similar to those described in several recent publications [16–19]. Further, this approach is aligned to the 'least burdensome' concept outlined for medical devices by US FDA CDRH/CBER [20].

Specific unit operations are clearly defined within the NGS and bioinformatics workflows. By defining the unit operations and pre-specified acceptance criteria for their performance, the goal is to demonstrate and document incremental improvements to the process. When using the PCCP, improvements are introduced into the workflows when better techniques and knowledge become available and can be incorporated into production to ensure the process is not becoming obsolete or using outdated technologies. The planned changes under the PCCP undergo a full assessment by the developer/manufacturer, and data are collected during this assessment to ensure the proper performance characteristics of the unit operations are met. When substantial changes outside of the PCCP are proposed, the developer/manufacturer should take a risk-based approach to assessing the change, and seek prior approval from health authorities in order to implement the change.

It should be noted that the PCCP approach was proposed by US FDA CDRH for use with Artificial Intelligence/Machine Learning (AI/ML) in Software as a Medical Device [19]; as such, an accepted device regulatory mechanism is being leveraged and applied to the software used during iNeST manufacturing. The PCCP approach is novel and regulators in major markets have only theoretically agreed to this approach at this time. Proposal of a PCCP to regulators as part of the clinical development process begins the conversation around the pre-specified changes and performance metrics against which those changes will be evaluated. The intent of the PCCP is to ensure the same or better quality of process performance, or non-inferiority of process performance, as was previously defined. Regulator acceptance of changes within scope of the approved PCCP will enable the neoepitope selection process to evolve quickly along with the rapidly evolving underlying technologies.

Developers/manufacturers and regulators should understand that the PCCP will continue to evolve during clinical development as more technologies, information and data emerge. The final PCCP for post-approval modifications with pre-defined acceptance criteria should be proposed and included in the Initial Marketing Application. Changes within the scope of the PCCP would be implemented, documented within the quality management system (QMS), and reported at

DOI: 10.18609/cgti.2022.101

regular intervals to regulators via an annual report or at the next available opportunity. Changes that fall outside of the pre-specified criteria, and changes to the PCCP itself, should be submitted to regulators for prior review and approval per local regulations.

A PCCP should include the:

- Category (type) of pre-specified changes for a specific unit operation in the workflow
- Scope of assessments/studies to demonstrate performance for each unit operation
- Pre-defined acceptance criteria for each unit operation – one or more performance metrics along with the acceptable cutoff or range for that metric, and
- Specific examples of changes planned

For example, a portion of a PCCP for genomics could include:

- Category: Sequencing instrument change (from same vendor)
- Scope of Assessments/Studies: Instrument I/O/PQ; Comparative sequencing study with post-capture libraries sequenced on both current and new sequencing instruments
- Pre-defined Acceptance Criteria: NGS data must meet or exceed vendor requirements and/or developer/manufacturer pre-specified performance criteria
- Specific Examples of Changes: Change from the Illumina HiSeq 4000 instrument to NovaSeq 6000 instrument

NEOEPITOPE SELECTION WITHIN THE MANUFACTURING PROCESS

A novel regulatory framework is proposed here and includes the neoepitope selection process as an integral part of manufacturing of iNeST products, rather than as a device or diagnostic. The rationale for defining the genomics and bioinformatics as manufacturing steps lies within the definitions of 'intended use' and 'medical device.. From a practical standpoint, this integrated regulatory strategy acknowledges the inter-dependency of the neoepitope selection process and the final product, and ultimately patient outcomes.

FDA's labeling regulations define 'intended use' as the objective intent of the persons legally responsible for the labeling of the drug or device [21]. Per Section 201(h) of the Food, Drug, and Cosmetic Act, a device must have an intended use 'in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals...' [22]. The objective intent of the neoepitope selection process is to support the *design* of the individualized medicinal product, and does not itself have a medical purpose; therefore, it does not constitute a medical device (or IVD). Instead, these genomics and bioinformatics workflows are part of the end-to-end process for manufacturing the iNeST product and fulfill their intended purpose, which is a individualized medicine designed to the particular tumor-specific mutations of each patient. Defining the workflows as part of the manufacturing process provides a critically important line of sight to the full manufacturing process and product batch design for both Chemistry, Manufacturing, and Control (CMC) and Clinical regulatory reviewers.

It should be noted that genome analysis can generate a broad array of data types; the neoantigen selection process aims to identify neoantigens specific to the tumor only, rather than self antigens. Additionally, the US FDA CDRH Guidance, *Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) – Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases (April 2018)*, explicitly states that it is *not* applicable to RNA sequencing or tumor genome sequencing [23]. Further, the neoantigen selection process is not used to identify patients where the benefits outweigh the

potential risks of treatment nor to monitor response to treatment, and is initiated only *after* a treatment decision has been made, thus its objective intent is the design of the product for each patient.

Along these lines, there are broad, complicating implications of whether the NGS and bioinformatics procedure were designated as part of the manufacturing process or as a diagnostic (CDx). As described above, we have taken the position that the neoepitope selection process for iNeST manufacturing is an integral part of the production process, and is not designated as a diagnostic. If the neoepitope selection process were considered an IVD, it would create a disconnect since it would be regulated under medical device regulations in the United States (CDRH) and Europe (Notified Bodies and IVDR), while the downstream drug substance/drug product manufacturing process would be regulated under biologics regulations (CBER and EMA, respectively). Additionally, classifying the process as a diagnostic/CDx would require the workflow to be conducted under the requirements described in 21 CFR 820 and ISO 13485 [24,25]. Similarly, in order to be a stand-alone manufacturer of a device, a company is required to establish a quality system aligned with and in fulfillment of device regulatory requirements.

DEFINING FIT-FOR-PURPOSE QUALITY MANAGEMENT SYSTEM

The neoantigen selection process for production of iNeST therapeutics is novel and does not fit readily into existing regulatory and quality frameworks. Currently, there are few guidelines and standards to follow for the use of NGS and bioinformatics as part of a manufacturing process, thus there is a lack of clarity regarding regulatory requirements that should be incorporated into a QMS. The upside is that there is recognition that a flexible framework on what guidelines, standards, and regulations may be applicable to define 'good practices' is required. However, the challenge remains to determine what is appropriate and exactly what should be incorporated into this flexible framework for genomics and bioinformatics workflows used in manufacturing of the iNeST product.

In order to aid in this determination, the following points should be considered:

- The neoantigen selection process and the downstream manufacturing process (drug substance/drug product) should be considered as an integrated end-to-end process given that they are inherently interdependent, and together they result in a clinically evaluated product
- The current GMP expectations for ATMPs have been described in guidelines issued by EMA and PIC/S Annex 2A [26,27]
- The production of individualized (i.e. make-to-order) ATMPs involves interfaces with new types of compliant environments, such as good clinical practice (GCP) or good clinical laboratory practice (GCLP) during clinical development [28], and CAP/CLIA, JACIE/FACT accredited facilities and/or ISO 15189 certified environments during commercial production [29–31]
- Controls need to be appropriate for the particular steps in the manufacturing process, and certain steps may be carried out under device requirements
- Elements of existing quality compliance requirements should be leveraged. For example, NGS steps carried out as part of a diagnostic test already have defined validation requirements as described by CAP; these existing requirements should be reviewed to determine their sufficiency for a commercial product requiring NGS process steps
- Consensus of which items apply to the QMS may be achieved through technical cross-functional vetting and gap assessment

Developers/manufacturers should review and consider pertinent guidelines, regulations (where they exist), and industry standards to define a quality management system that is

DOI: 10.18609/cgti.2022.101

appropriate for NGS and bioinformatics processes. A fit-for-purpose QMS for iNeST may include an amalgam of pharmaceutical and medical device standards and practices, and leverage existing GxP frameworks, where deemed appropriate. Once the QMS requirements are defined, the authoring, training and implementation of revised and/or new internal policies and standard operating procedures (SOP) would naturally follow. Further, the developer/manufacturer should incorporate into the QMS how to assess the acceptability of a contract manufacturing organization's (CMO) QMS. The developer/manufacturer should consider what expectations should be codified in new or existing quality agreements (QAG).

CONCLUSION

The rapid pace of technological advances in the cell and gene therapy field requires correspondingly rapid adaptation of solutions, including regulations, to progress beyond established systems in order to ensure that the appropriate patients can benefit from these innovative medicines. Regulations for ATMPs must enable the interface with regulations for devices and diagnostics, and other requirements (such as those for genetically modified organisms). The regulatory strategy described herein for this innovative new class of iNeST products is an example of a fit-for-purpose approach that is being established to maintain the appropriate quality of the product, particularly through the generation and use of genomic sequencing data for designing each batch. When developers/manufacturers call for flexibility in regulatory requirements, this flexibility should uphold high standards, and do so in pragmatic ways that properly leverage existing regulatory mechanisms whenever appropriate. This being said, when highly innovative products, such as iNeSTs, truly challenge the status quo and require new concepts, this should be thoughtfully approached and enabled so that such promising products can be delivered to patients.

We ask the reader to consider lifecycle management mechanisms that tend towards iterative improvements over time, consistent with ICH Q12 and those used with next-generation sequencing and AI/ML for Software as a Medical Device, to provide the best possible product to patients. Predetermined Change Control Plans (PCCP) may be used to streamline updates by establishing a 'do-and-tell' approach with regulators to support innovation in production processes that use rapidly evolving technologies. Process performance metrics, rather than product comparability, are appropriate to ensure consistency in the manufacture of this class of make-to-order ATMPs. A comprehensive risk assessment and appropriate discussion with global regulators will enable developers/manufacturers to evaluate and document pre-specified changes within their Quality System, and report these pre-specified changes as part of an annual report or at the next available opportunity.

In summary, a novel regulatory framework is proposed to consider the genomics and bioinformatics workflows as integral parts of the design and end-to-end manufacture of individualized neoantigen-specific immunotherapies. Considering the NGS and bioinformatics workflows as part of the overall end-to-end manufacturing process (rather than as a diagnostic) provides regulators with much-needed transparency of the entire manufacturing process while enabling the manufacturer to update the genomics and bioinformatics neoantigen selection processes in a timely manner. Thus, developers/manufacturers and regulators ensure that the best product is made available to patients. Leveraging elements of NGS IVD guidance, where applicable and appropriate, provides some structure for the regulatory framework in aspects of design, development, and analytical validation. However, it should be noted that this guidance is not wholly applicable to the current scenario. Flexibility, not leniency, should be the goal when establishing internal quality frameworks; developing a fit-for-purpose QMS entails picking the appropriate elements and applying where reasonable or possible. Finally, developers/

manufacturers of individualized neoantigen-specific immunotherapies should review and consider pertinent existing guidelines, regulations, and industry standards, and consult with regulators, to define the requirements for NGS and bioinformatics workflows that should be incorporated into the quality management system.

REFERENCES

1. *World Health Organization.* WHO considerations on Regulatory Convergence of Cell and Gene Therapy Products. https://cdn.who.int/media/docs/default-source/biologicals/ecbs/who-public-consultation_cgtp-white-paper_16_dec_2021.pdf. 16 December 2021. (Accessed Jun 2022).
2. Delamarre L, Mellman I, Yadav M. Cancer immunotherapy. Neo approaches to cancer vaccines. *Science.* 2015; 15;348(6236):760-1. doi: 10.1126/science.aab3465.
3. Capietto AH, Jhunjhunwala S, Delamarre L. Characterizing neoantigens for personalized cancer immunotherapy. *Curr. Opin. Immunol.* 2017;46:58–65. doi: 10.1016/j.coi.2017.04.007.
4. Capietto AH, Jhunjhunwala S, Pollock SB *et al.* Mutation position is an important determinant for predicting cancer neoantigens. *J. Exp. Med.* 2020;217(4):e20190179. doi: 10.1084/jem.20190179.
5. *National Institutes of Health*. National Human Genome Research Institute. The Human Genome Project. https://www.genome.gov/human-genome-project. (Accessed 28 April 2022).
6. *International Conference on Harmonization (ICH).* ICH Q7 Harmonized Tripartite Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. https://database.ich.org/sites/default/files/Q7%20Guideline.pdf. November 2000. (Accessed Jun 2022).
7. International Conference on Harmonization (ICH). ICH E18 Harmonized Guideline: Guideline on Genomic Sampling and Management of Genomic Data. https://database.ich.org/sites/default/files/E18_Guideline.pdf. August 2017. (Accessed Jun 2022).
8. Illumina. Illumina Expands World's Most Comprehensive Next-Generation Sequencing Portfolio. https://sapac.illumina.com/company/news-center/press-releases/press-release-details.html?newsid=bfe93522-f1a9-4d1e-b048-e3070373d3ec. December 1, 2015. (Accessed April 2022).
9. *Illumina.* Illumina Introduces the NovaSeq Series—a New Architecture Designed to Usher in the $100 Genome. https://sapac.illumina.com/company/news-center/press-releases/2017/2236383.html. January 9, 2017. (Accessed April 2022).
10. *Illumina*. Illumina Announces New Sequencing System, Partnership with Roche and Software Suite to Accelerate Adoption of Genomics. https://sapac.illumina.com/company/news-center/press-releases/2020/e50aaf5d-31d4-4a16-920b-4b65dc479d3f.html. January 13, 2020. (Accessed April 2022).
11. *Illumina.* The HiSeq 3000/HiSeq 4000 Systems have been discontinued. HiSeq 3000/HiSeq 4000 Overview. https://www.illumina.com/systems/sequencing-platforms/hiseq-3000-4000.html. (Accessed April 2022.
12. *International Conference on Harmonization (ICH).* ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. https://database.ich.org/sites/default/files/Q5E%20Guideline.pdf. June 2005. (Accessed Jun 2022).
13. *International Conference on Harmonization (ICH).* ICH Q10 Harmonized Guideline: Pharmaceutical Quality System. https://database.ich.org/sites/default/files/Q10%20Guideline.pdf . June 2008. (Accessed Jun 2022).
14. International Conference on Harmonization (ICH). ICH Q12 Harmonized Guideline: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf . November 2019.
15. Immune Epitope Database (IEDB). https://www.iedb.org/. (Accessed April 2022).
16. Friends of Cancer Research (FoCR). White Paper: Charting the Course for Precision Medicine. https://www.focr.org/sites/default/files/Friends%20Alexandria%20White%20Paper.pdf . 2018. (Accessed Jun 2022).
17. EBE-EFPIA. Position Paper on Next Generation Sequencing. https://www.efpia.eu/media/412288/ebe-efpia-position-paper-ngs_final_09102018.pdf . 09 October 2018. (Accessed Jun 2022).
18. *US Food and Drug Administration (FDA).* Discussion Paper and Request for Feedback: Proposed Regulatory Framework for Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical

DOI: 10.18609/cgti.2022.101

Device (SaMD). https://www.fda.gov/media/122535/download . April 2018.

19. *US Food and Drug Administration (FDA).* FDA Action Plan: Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD). https://www.fda.gov/media/145022/download. January 2021. (Accessed Jun 2022).

20. *US Food and Drug Administration (FDA).* The Least Burdensome Provisions: Concept and Principles – Guidance for Industry and FDA Staff. https://www.fda.gov/media/73188/download. February 2019. (Accessed Jun 2022).

21. 21 CFR 801.4, Meaning of Intended Uses. *US Code of Federal Regulations.* https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=801.4 .

22. 21 USC 321(h), Definition of "device". US Code. https://codes.findlaw.com/us/title-21-food-and-drugs/21-usc-sect-321.html . (Accessed Jun 2022).

23. *US Food and Drug Administration (FDA).* Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) – Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases – Guidance for Stakeholders and FDA Staff. https://www.fda.gov/media/99208/download . April 2018.

24. *US Food and Drug Administration (FDA).* 21 CFR 820. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820 .

25. *International Organization for Standardization (ISO).* ISO 13485:2016, Medical devices — Quality management systems — Requirements for regulatory purposes.

26. *European Medicines Agency (EMA).* Guidelines relevant for advanced therapy medicinal products. https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products .

27. *Pharmaceutical Inspection Co-operation Scheme (PIC/S).* Annex 2A: Manufacture of Advanced Therapy Medicinal Products for Human Use. https://gxp-academy.org/upload/iblock/89f/89f7a80f0effc218f88e350b0c6f6cfa.pdf . (Accessed Jun 2022).

28. *World Health Organization (WHO).* Good Clinical Laboratory Practice (GCLP). https://www.who.int/tdr/publications/documents/gclp-web.pdf . 2009. (Accessed Jun 2022).

29. *International Organization for Standardization (ISO).* ISO 15189:2012, Medical laboratories — Requirements for quality and competence.

30. *Clinical Laboratory Improvement Amendments (CLIA).* 42 USC 263a. https://www.law.cornell.edu/uscode/text/42/263a . 1988. (Accessed Jun 2022).

31. *The Foundation for the Accreditation of Cellular Therapy (FACT) and the Joint Accreditation Committee of ISCT-EBMT (JACIE).* Seventh Edition FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing and Administration. http://www.factwebsite.org/ctstandards/ . March 2018. (Accessed Jun 2022).

AFFILIATIONS

Amy Hardwick
Program Director, PT Cell & Gene Therapeutics Regulatory
Genentech, A Member of the Roche Group

Kathleen Francissen
Global Head PT Cell & Gene Therapeutics Regulatory,
Genentech, A Member of the Roche Group

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 recieved support from Genentech, A Member of the Roche Group for this manuscript. Francissen K owns stock or stock options in Roche. Francissen K recieved Support for attending meetings and/or travel from Genentech, A Member of the Roche Group. The authors have no other conflicts of interest.*

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

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited; externally peer reviewed.*

Submitted for peer review: *May 17 2022;* ***Revised manuscript received:*** *Jun 20 2022;* ***Publication date:*** *Jun 30 2022.*

DOI: 10.18609/cgti.2022.101

CELL & GENE THERAPY INSIGHTS

GLOBAL REGULATORY UPDATE

SPOTLIGHT

INTERVIEW

Regulatory learnings for the next wave of cellular immuno-oncology agents

David McCall, Editor, *Cell & Gene Therapy Insights*, talks to **Robert Pietrusko**, Chief Regulatory and Quality Officer at Vor Biopharma

DR PIETRUSKO currently serves as Chief Regulatory and Quality Officer at Vor Biopharma in Cambridge, MA and leads the Regulatory strategy for engineered hematopoietic stem cell therapy for hematologic malignancies including AML. He has directed the worldwide approval of more than 30 new products in multiple therapeutic areas. As an early team member at Voyager Therapeutics, Dr Pietrusko pioneered regulatory strategies to translate gene therapies from research into the clinic. Prior to Voyager, he was Vice President of Global Regulatory Affairs & Quality and Executive Officer at ViroPharma, Inc. He also served as Senior Vice President of Regulatory Affairs at Millennium Pharmaceuticals, spearheading the accelerated approval of Velcade® in the US and in more than 90 countries worldwide. Earlier in his career, he was Vice President of Regulatory Affairs at SmithKline Beecham (now GSK). He has played a key role in shaping US regulatory policy for cutting edge medicines, such as recently pioneering the concept of an expedited pathway to approval for cell and gene therapies that led to the Regenerative Medicine Advanced Therapy (RMAT) designation process that was included in the United States 21st Century Cures Act. He currently serves as Chair of the Regulatory Affairs Committee of the Alliance for Regenerative Medicine (ARM) and is an appointed member of the Regulatory Affairs Committee of the American Society of Gene and Cell Therapies (ASGCT). Dr Pietrusko holds a Bachelor of Science degree in biology, a Bachelor of Pharmacy degree from Rutgers University, and a Doctor of Pharmacy degree from the Philadelphia College of Pharmacy and Science. He completed his residency training in hospital pharmacy at Thomas Jefferson University Hospital and is the author or co-author of over 50 scientific publications.

Cell & Gene Therapy Insights 2022; 8(6), 663–670

DOI: 10.18609/cgti.2022.100

Q What are you working on right now?

RP: I work at Vor Bio, a biotechnology company located in Cambridge, Massachusetts developing treatment-resistant Hematopoietic Stem Cell (HSC) transplants that allow new, potentially curative targeted therapy opportunities for blood cancers. The company was founded on the premise that targeted therapies, such as chimeric antigen receptor T cell products (CAR Ts), are specific for certain protein markers on tumor cells but are not truly 'targeted' to tumor cells alone. It is known that because healthy human cells, from which the cancer cells are derived, also have these targets, toxicity can occur as a direct targeted effect on the patient's normal blood cells. The first successful CD19-CAR Ts target B-cells, which fortunately, we can live without for a time before they regenerate – hence the fact those CD19 CAR Ts can be tolerated by the patient apart from the serious risks of cytokine release syndrome (CRS) and neuropsychiatric toxicity. However, in trying to expand beyond B-cell malignancies, the field has encountered significant on-target, off-tumor toxicity barriers. Vor Bio's approach is to remove these targets from the patient's normal blood cells in order to protect them from the targeted therapy. In a condition like acute myeloid leukemia (AML), a human leukocyte antigen (HLA)-matched volunteer's donor blood cells are collected and then those targets (in this case, CD33) are edited out from these normal HSCs. When the cells are administered to a patient undergoing a stem cell transplant and engrafted, they will not have that marker. When the targeted therapies then are administered, they should kill the tumor cells, but not the patient's normal blood cells. In vitro and in vivo animal data support this hypothesis.

Data from preclinical studies in multiple independent laboratories show that CD33 can be removed from HSCs without any deleterious impact on cell biology. However, we believe the strongest support for our approach comes from existing human genetics data suggesting the non-essential nature of CD33 function in humans. In studying the Genome Aggregation Database (gnomAD), we found there are at least 75 healthy individuals in the world who do not have CD33 and are otherwise normal.

Currently, around 40% of patients with AML who receive a Hematopoietic Stem Cell Transplant suffer a relapse of their cancer, with two-year survival rates of less than 20%. Thus, there is a high unmet medical need, and a new treatment approach is necessary.

We are now working to bring this therapy and the possibility of a cure to patients with high-risk AML, a disease that carries a poor prognosis despite aggressive therapies including traditional HSC transplantation, the standard of care for decades. In partnership with leading transplant centers across North America, we are actively enrolling patients with high-risk AML who are first-time HSC transplant candidates to participate in our first in-human Phase 1/2 proof of concept clinical trial (VBP101). The treatment is called VOR33, which is administered during the transplantation process. It is composed of modified or engineered hematopoietic stem cells lacking the CD33 protein marker. VOR33 is utilized in conjunction with Mylotarg™ (gemtuzumab ozogamicin) which is administered post-transplant. Mylotarg is an anti-CD33 product currently on the market. It is an antibody drug conjugate that releases the toxin when it interacts with the CD33 marker.

DOI: 10.18609/cgti.2022.100

Q As one of the initial drivers behind the introduction of cell and gene therapy (CGT)-specific expedited regulatory pathways - an effort which culminated in the regenerative medicine advanced therapy (RMAT) designation - what are your views on that pathway today, and its adoption and implementation so far?

RP: Data from the FDA indicate that the RMAT designation is frequently being utilized in the CGT arena and is now the more common approach taken by companies, versus the breakthrough therapy designation.

There are several key features of the RMAT designation that are different from breakthrough designation or other expedited pathways. The RMAT criteria to fulfil are somewhat like breakthrough therapy in that you do need to provide supportive clinical data; however, for the breakthrough designation, the therapeutic candidate must be for an unmet medical need for which there are no other available therapies. Therefore, the hurdle might be considered slightly less for RMAT in that the product must address an unmet medical need, regardless of whether there are other available therapies.

Once RMAT designation is awarded, it is noted that the FDA needs to consider the feasibility of an accelerated approval based upon a biomarker or an intermediate clinical endpoint. Companies are looking at ways to bring these products to a greater patient population including many rare genetic diseases. For cell and gene therapies, specifically, there is an opportunity to enhance or modify a specific gene or marker which is reasonably likely to predict clinical benefit. There is also the possibility for accelerated approval in rare orphan diseases based on an intermediate clinical endpoint. Full approval could then be based upon either survival or another agreed upon measurable clinical benefit.

An additional feature of RMAT is that for accelerated approval, the requirements for a confirmatory study are different. One could either use an expansion of the initial patient cohort to replicate the results seen in the initial trial or provide confirmatory evidence based upon real-world data.

Q What could be the next targets for further regulatory guidance evolution in the space?

RP: The industry had been requesting two critical guidance documents, one for genome editing and one for the development of CAR Ts. There are modifications and iterations for the next generation of CAR Ts that are being developed and this latter guidance will be useful in addressing

"Data from the FDA indicate that the RMAT designation is frequently being utilized in the CGT arena and is now the more common approach taken by companies, versus the breakthrough therapy designation."

the FDA's expectations of what should be included in IND submissions. Both draft guidance documents were issued recently.

There is a third guidance document that is not out yet, which covers expectations around potency assays. This is a timely but difficult topic because how do you make uniform cells on a consistent basis and how can you determine this? How do you test their potency? The ultimate goal is to have a rapid *in vitro* test for lot release. Previously, people had relied on *in vivo* animal testing. For Zolgensma® (onasemnogene abeparvovec), the initial potency test was a one-year animal study, which was not practical. How can you release a product, which is manufactured as a single lot per patient, that must wait a year for a potency test result in animals?

Figuring out validated potency tests of new CAR Ts and expectations for these newer products is a difficult assignment. With some of the cellular products, the mechanism is unknown, so coming up with a potency test requires a sound scientific approach and much planning. Work needs to be performed alongside input and feedback from the Agency because it is critical to have agreement on a potency test to ensure the product will work consistently and reliably in patients based on product quality characteristics.

Another area for guidance to be considered is how the agency can quickly communicate toxicities that are occurring in clinical trials. For example, we have been aware of initial toxicities with adeno-associated viral (AAV) vectors; however, new toxicities associated with these products were occurring in the clinical trials. In response, the Agency called in an advisory committee in 2021 to discuss concerns regarding AAV vector toxicities beyond those that had been seen previously. As we move forward with CAR Ts and other newer CGT products, we must find a way for the Agency to convey these concerns early, without breaching confidentiality, so that other companies designing their preclinical studies and clinical protocols can monitor for these toxicities. It will benefit companies and patients in the long run to provide that type of information and to implement an early warning/notification system during clinical development of these novel therapies.

Q 20 years ago, you were involved in the successful accelerated approval program for Velcade® (bortezomib). What learnings from that experience are relevant to today's advanced therapies space, where accelerated clinical developments are almost the norm?

RP: Velcade is a product that would have been considered a breakthrough therapy by today's standard as the initial clinical results looked very promising. At that time, it was approximately 50 years since the last product was approved in the multiple myeloma space. We talked to our investigators and looked at the history. They said if we could get a 'molecular' cure with complete remission - it would be a miracle. We set a criterion of a 10% molecular cure rate in patients. Despite some doubts that it would be possible, we hit this target.

It was very important to meet with the FDA and have the Agency agree with this endpoint. We had experts in the field attest to the relevance and significance of this endpoint. In addition, we submitted the protocol for special protocol assessment (SPA). That SPA process proved arduous and time-consuming, but in the end, the result was a buy-in from the FDA. Upon

DOI: 10.18609/cgti.2022.100

submission of the NDA, the Agency found the data convincing and approved the product well before six months, the targeted priority review date under the Prescription Drug User Fee Act (PDUFA). If the product you are working on has dramatic results, you need to find a way to show that this is truly remarkable and convince the Agency of those meaningful endpoints prior to filing the BLA or NDA. That was a key learning point for me. In addition, we submitted a confirmatory study protocol in an earlier stage of multiple myeloma and then were able to demonstrate an overall survival benefit.

Q What are the specific regulatory considerations for Vor's engineered hematopoietic stem cell (eHSC) therapeutics, from the translational and clinical R&D standpoints as well as manufacturing?

RP: This approach had never been done before. Volunteer HLA-matched donors underwent a process called dual mobilization. This was necessary because we needed at least triple the amount of eHSCs, to manufacture the product, do the analytical testing, and retain a rescue dose (non-engineered cells), should the engineered cells not engraft. Patients would enroll, and clinicians would put patients into the trial, only if there were a backup amount of non-engineered transplantable stem cells available.

We also had to work with the transplant centers to find suitable patients and to find donor collection sites for the apheresis so the apheresis would be done in a consistent manner. We performed research to document donor-to-donor variability, and we had to balance that variability from the donors with the product we were manufacturing based upon analytical testing and the manufacturing process.

We also had to determine the appropriate degree of editing of these cells using CRISPR/Cas9 and a guide RNA. We tested this in various animal models to ensure that the engraftment and cells would be protected, and that the stem cells would reproduce continually.

This degree of CRISPR/Cas9 editing, both on-target but also off-target for next-generation sequencing, had never been done before. Today, we have the IND in place, and we are actively enrolling patients. We are looking forward to seeing clinical results in the second half of 2022.

Q What is your take on how the CGT industry has responded so far to heightened regulatory stringency around CMC, and do you have any specific points of focus or related words of advice for the future?

RP: Despite dramatic life-altering successes in patients with serious conditions such as Spinal Muscle Atrophy (SMA), there are no shortcuts or areas of flexibility in the manufacturing standards and requirements for approval of a CGT product. There is no compromise in the quality of the product, no matter what condition or how small the population may be – that is a key learning point.

We do have some regulatory flexibility in the requirements for GMP for initiating clinical trials, which is sometimes known as fit-for-purpose or phase-appropriate GMP. Typically,

the hurdle is relatively low compared to what would be necessary in the final GMP scenario required for product approval.

The real problem is rapidly moving towards a pivotal trial, which requires qualified analytical tests and a higher degree of quality control. Then in registration, the hurdle is even higher, which many companies don't fully anticipate. There is a large amount of testing and input necessary to bring the product to the finish line. Expedited clinical development can leap ahead of the manufacturing controls and validation required for the product. GMP requirements for a Phase 1/2 study are not the same as GMP required for a pivotal trial and certainly not for commercialization.

In small companies with limited resources, it can be a push to get into the clinic quickly, which needs to be balanced against investing for the long-term by trying to get a product that is almost final before bringing it forward into the clinic. Agencies prefer the latter approach. However, due to lack of an abundant amount of investment, getting there before you have proof of concept in the clinic can be difficult to achieve. Showing that a product works in the clinic is ideal for generating additional investment, rather than attempting to take a further developed product into the clinic with millions of dollars already invested and then having it fail. Before companies are going to take that big risk, there needs to be proof of concept showing that the product works.

We may be getting there with CAR-Ts because we already have approved products on the market. In the wider cell therapy area or for other rare diseases, we do not know enough yet. With AAV vectors, for example, there are so many variables that could influence efficacy, including the required degree of exposure and penetration into individual cells. We are still on the learning curve in this field, and there are going to be failures. Another thing to consider is that therapies, such as AAV- based products, have the problem of pre-existing immunity to overcome. Questions being raised include if patient response wanes over time, how can another dose be given? Is it ethical, and what can be done to minimize any problems of immunogenicity with a second dose? Should corticosteroids be administered to all patients before administration of an AAV based therapy?

Other issues include viral vector availability and cost. The waiting time for lentiviral vectors is out to two or three years now. The cost of goods for a particular product or therapy is going to be expensive, even for just one patient. Reimbursement is another major issue for many of these 'one-and done' therapies.

Q How is the CGT field doing in coming to terms with post-marketing requirements?

RP: The current requirement is a 15-year follow-up of patients from the clinical trials for any gene editing or vector-integrating program. If you are optimistic and you do everything right, you will have some additional time to look at long-term data for those treated patients. It will also be important to look at registries. It is too early to know what those post-approval requirements will be. In the future, there will be more questions about how to follow individuals long-term, whether it remains at 15 years or becomes longer still. A current issue is how much persistence data are required for approval. There is a high degree of uncertainty about how much longer-term data are required for approval vs. what may be

DOI: 10.18609/cgti.2022.100

acceptable as a post-approval requirement or commitment.

Q Finally, what will be some key goals and priorities, both for yourself in your own work and for Vor Bio as a whole, over the coming 12–24 months?

RP: The next step we are taking is working on an anti-CD33 CAR T (VCAR-33), which eventually can be used in combination with our VOR33 product. We plan to file an IND next year for VCAR33. After assessing that product in the clinic, we plan to combine it with VOR33 so we can directly measure the benefit of the combination.

> "Regarding the future, we are looking at multiplexing, i.e., editing out two or more proteins. If you alter two targets or markers as you are killing tumor cells, the tumor cells should be less likely to develop resistance than with a single marker change."

Regarding the future, we are looking at multiplexing, i.e., editing out two or more proteins. If you alter two targets or markers as you are killing tumor cells, the tumor cells should be less likely to develop resistance than with a single marker change. The next step is testing if our platform can knock out three or more proteins. We are looking at how to do that with various approaches to gene editing. In our next program, the dual multiplex markers to be removed are CD33 and CLL1, both of which are produced by AML tumors and are on the patient's normal cells.

Our overall goal is to provide safe and effective therapies for these cancer patients who do not have other alternatives with the potential to provide cures.

AFFILIATION

Robert Pietrusko
Chief Regulatory and Quality Officer
Vor Biopharma

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 author has no conflicts of interest.*

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

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited.*

Submitted: *March 15 2022;* ***Revised manuscript received:*** *Jun 16 2022;* ***Publication date:*** *Jun 27 2022.*

DOI: 10.18609/cgti.2022.100

CELL & GENE THERAPY INSIGHTS

GLOBAL REGULATORY UPDATE

SPOTLIGHT

Recent gene-editing guidance from FDA – clarifies some gene-editing development questions with room for additional recommendations

Kathleen Candando & Karl Whitney
Precision BioSciences, Inc.

VIEWPOINT

"...this newly released guidance document [Human Gene Therapy Products Incorporating Human Genome Editing] from the FDA is very helpful in delineating some expectations for sponsors."

Cell & Gene Therapy Insights 2022; 8(6), 721–724

DOI: 10.18609/cgti.2022.107

In March 2022, the US Food and Drug Administration (FDA) released a draft guidance for gene editing products (Human Gene Therapy Products Incorporating Human Genome Editing). Gene editing products in this context include those that add, delete, alter, or replace DNA sequences at specified locations in the genome of human somatic cells, in vivo or ex vivo. This guidance is a timely addition to the body of FDA recommendations given the ever-increasing number of in vivo and ex vivo gene editing products in development. In addition to many useful points relevant specifically about gene editing products, the guidance reiterates best-practice recommendations similar to those that might apply to any development program. Particularly informative in this new guidance is some understanding of how the FDA will view the risk/benefit profile of gene editing products, including a reference to the 'significant risk and an uncertain potential for benefit' in gene editing clinical studies. It is also worth noting that although this guidance addresses topics across the Chemistry, Manufacturing, and Controls (CMC), nonclinical, clinical, and general regulatory disciplines, its breadth is complemented by more focused deeper-dive guidances previously developed by the FDA including a detailed CMC-specific guidance released in early 2020 (Chemistry, Manufacturing, and Control [CMC] Information for Human Gene Therapy Investigational New Drug Applications [INDs]) and a similarly in-depth nonclinical-focused guidance released in late 2013 (Preclinical Assessment of Investigational Cellular and Gene Therapy Products).

A major theme running through the document is the need to extensively characterize and minimize off-target editing in gene editing products through thoughtful product design and robust and reliable safety evaluations. In manufacturing and design considerations, FDA notes that limiting the in vivo persistence of the direct gene editing components can curtail off-target edits, as can restricting distribution of gene editing components to specific anatomical sites using elements like tissue-specific promoters. Thoroughly evaluating the effects of off-target activity is also important, and the Agency provides specific and clear instruction—demonstrate comprehensive evaluation of the type (presumably insertion/deletion or conversions), frequency, location, and biologic consequence (when available) of all off-target events in the genome. FDA appreciates that this will likely need to be accomplished using more than one method and indicates that multiple orthogonal approaches should be considered. Furthermore, these genome-wide investigations should be conducted using target cells from multiple human donors.

Similar to the recommendations regarding off-target editing, this latest guidance also contains instructions for assessing genomic integrity, another key safety evaluation for gene editing products. Specifically, FDA recommends looking for chromosomal rearrangements, large insertions or deletions, integrations of exogenous DNA, and potential oncogenicity of insertional mutagenesis. Taken together, FDA's advice on both off-target editing and genomic integrity assessments comprises a useful list of assessments that sponsors of gene editing products will be expected to conduct. Indeed, this feedback is very similar to product-specific advice we have received for multiple products. Specific details related to target cell types for these assays as well as 'cut-off' criteria for off-target editing events will be decided on a by-product basis and could be useful topics for discussion in a meeting with the FDA. Such early-stage discussions could take place in the context of either INTERACT or pre-IND meetings, although the former have been difficult to obtain and, indeed, this guidance provides sufficient details to resolve some questions such that an INTERACT meeting may not be needed or granted.

As indicated above, substantial attention in this guidance is given to the gene editing components themselves. By contrast, relatively few points of guidance are provided regarding the different delivery mechanisms that have been employed in the field. FDA notes that gene editing components can be delivered via viral vectors or nanoparticles. Interestingly,

DOI: 10.18609/cgti.2022.107

the Agency indicates that certain nanoparticles used for in vivo delivery of gene editing components may be regulated as devices. No further criteria for which nanoparticles might qualify as devices are provided, and additional clarification from the Agency would be helpful when this guidance is finalized, given that developing a biologic-device combination product requires significantly more investment and resources than that of a biologic alone (other FDA guidance documents including Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology are similarly vague on this point and indicate that nanoparticles are designated as devices or non-devices on a case-by-case basis). Again, sponsors may need to address this issue in focused consultations with the Agency or by way of a Request for Determination.

Finally, in addition to the separate manufacturing and nonclinical assessment guidance documents mentioned above, the genome editing guidance also offers preliminary information on considerations for clinical studies of gene editing products. As mentioned above, the potential risks of gene editing products are reinforced here by the FDA. In that context, the Agency's advice is that first-in-human studies should at least initially enroll only subjects with no other treatment options. An interesting point within FDA's recommendations for selecting a trial population is that subjects with more advanced disease, although potentially more likely to accept the risks of a gene editing product, may also be more likely than subjects with less advanced disease to experience adverse events (AEs). Given this consideration, sponsors may choose to enroll subjects with early-stage or moderate disease. Further, as with other high-risk products with no precedents, the Agency recommends staggered enrollment with waiting periods based on the product's expected in vivo duration of action and which are also sufficiently long to monitor for acute and sub-acute AEs. Special safety monitoring recommendations include observing for events related to off-target editing, aberrant cell proliferation, tumorigenicity, and immunogenicity. The Agency also reinforces the existing recommendation for a 15-year long-term follow-up period for subjects exposed to in vivo or ex vivo gene editing products.

Overall, this newly released guidance document from the FDA is very helpful in delineating some expectations for sponsors. Given that no in vivo gene editing products have yet to be approved by the FDA, these recommendations are likely to become more numerous and specific as the field of gene editing products evolves and marketed products set regulatory precedents. It will be very interesting to see how this document changes as it is finalized by the Agency and potentially augmented by additional related guidance documents.

BIOGRAPHIES

KATHLEEN CANDANDO, PhD, RAC, is a Manager of Regulatory Affairs at Precision Biosciences (Precision), a gene-editing biotechnology company located in Durham, NC. At Precision, Dr Candando focuses on regulatory content generation and strategy for allogeneic chimeric antigen receptor (CAR) T cells for hematologic malignancies and in vivo gene-editing products for diseases with unmet medical need. Prior to working at Precision, Dr Candando led the authoring of regulatory submissions and contributed to product development strategy for a wide range of pharmaceutical clients across multiple therapeutic areas, including allergy and immunology, infectious diseases, oncology, and neurology. Dr Candando received a PhD in Immunology from Duke University in 2016.

DR WHITNEY has over 20 years' experience in the pharmaceutical industry. He is a regulatory affairs generalist with a focus on regulatory strategy, clinical regulatory, and integrated product development. Dr Whitney is the Vice President and Head of Regulatory Affairs at Precision BioSciences, a gene-editing biotechnology company located in Durham, NC. Precision's programs focus on developing allogeneic CAR T cells for oncology indications and in vivo gene-editing approaches to address a variety of rare and significant genetic diseases with unmet medical needs. Prior to working at Precision, Dr Whitney's product development work focused on a wide variety

of cell, gene, and small-molecule therapeutics. His therapeutic area experience ranges widely: oncology, infectious disease, metabolic disease, dermatology, hemophilia, ADHD, pain, schizophrenia, and other CNS indications, for products spanning the development lifecycle from early preclinical to marketing application preparation and submission. Dr Whitney received a PhD in pharmacology from Duke in 1999. He has lived in Durham since 1994 but no longer lives and dies by the Blue Devils' success/failure. His hobbies include woodworking, cooking, website coding, photography, anything outdoors.

AFFILIATIONS

Kathleen Candando, PhD
Regulatory Affairs Manager
Precision BioSciences, Inc.

Karl Whitney
Vice President,
Regulatory Affairs
Precision BioSciences, Inc.
Co-Founder,Co-President, Board Member
International FOXP1 Foundation

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 have no conflicts of interest.*

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

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited.*

Submitted: *Jul 4 2022*; ***Revised manuscript received:*** *Jul 12 2022*; ***Publication date:*** *Jul 13 2022.*

DOI: 10.18609/cgti.2022.107

CELL & GENE THERAPY INSIGHTS

GLOBAL REGULATORY UPDATE

SPOTLIGHT

INTERVIEW

Inside the UK's brave new world of ATMP regulatory innovation

David McCall, Editor, *Cell & Gene Therapy Insights*, talks to **Dr Jacqueline Barry,** Chief Clinical Officer at the UK's Cell and Gene Therapy Catapult

JACQUELINE BARRY is the Chief Clinical Officer, responsible for Clinical Translation and Delivery activities and an Executive Director of the Cell and Gene Therapy Catapult. She has extensive experience in the development of advanced therapy medicinal products and leads a multi-disciplinary team of Nonclinical, Regulatory, Clinical Operations and Programme Management specialists. She also leads the coordination of the UK Advanced Therapy Treatment Centre Network and is a Director of the Global Alliance for iPSC Therapies. She feels passionately about making advanced therapies available for patients and works closely with the MHRA and the NHS on the development of the ecosystems to support the adoption of these therapies. Prior her time at Cell and Gene Therapy Catapult, Jacqueline worked at the Scottish National Blood Transfusion Service where amongst other activities she designed the regulatory strategy for the Cellular Therapies for the Blood Transfusion Service and acted as Qualified Person for their release. She has a PhD from the University of Aberdeen and did post-doctoral research in neurophysiology at the University of Edinburgh.

Cell & Gene Therapy Insights 2022; 8(7), 775–780

DOI: 10.18609/cgti.2022.117

Q What are you working on right now?

JB: At Catapult, I am working on several things. We are establishing our new site in Edinburgh, which will be in the University of Edinburgh Institute for Regeneration and Repair. We are building this manufacturing development capability to bridge the gap between the R&D process development activities carried out at our London site, and what is required to move these processes to scale and to GMP, then technology transfer to say, either a CDMO or to a developer's own facility. Our primary focus will be on pluripotent stem cell work, as this is an area that is really starting to take off now. We will also have translational regulatory support capability.

My team are working on supporting the collaborators we have from academia and industry, both within and outside of the UK, to help them design their regulatory strategy, regulatory submissions, and market access strategy.

I am spending time securing further funding for the Advanced Therapy Treatment Center (ATTC) network, which we have been coordinating for the past 4 years. This is a network of centers spanning the whole of the UK, a true collaboration with both the NHS and industry. We have been helping with education, institutional readiness, development of technological solutions, and with clinical trials. This was all funded through the Industrial Strategy Challenge Fund (ISCF), which has provided £47 million over the last four years. The ISCF no longer exists. We have funding internally to continue wither the Network activities until March of next year and are in discussions about potential further funding.

Q It's obviously been a particularly tumultuous period in the UK. As the nation emerges from both Brexit and COVID-19 and moves forward, what do you see as some of the key directions/priorities – and also challenges – firstly in terms of ATMP regulatory evolution?

JB: Following Brexit, we are no longer part of the European Medicines Agency (EMA), the centralized submission pathway and the new clinical trial regulation being implemented in Europe. That means we are not part of the market of Europe.

The flipside of that is we have a standalone regulator that is really embracing innovation. The UK Medicines and Healthcare products Regulatory Agency (MHRA) have redesigned their operations, and they have introduced an innovation accelerator. They are focusing on the systems to assist innovation and are looking at streamlining of approvals and systems. For example, advanced therapies that use human tissues and cells are covered by tissues and cells legislation and overseen in the UK by the Human Tissue Authority. However, the medicines are covered by the MHRA. The hand-off between those two directives has always been clunky, but they are now looking at how that can be streamlined, which is a real positive.

MHRA are also looking at clinical trial regulation for the UK. They released a public consultation, and I was happy to see how bold they were being. They are looking in-depth at what can be done to accelerate approval and conduct of trials and reduce the administrative burden

DOI: 10.18609/cgti.2022.117

whilst ensuring safety, which is paramount in clinical trials. They are reassessing the requirements for adverse event reporting and have already introduced a streamlined submission portal for both ethics and regulatory approval.

> "COVID-19 has allowed people to act quicker, and many people in the NHS do not want those lessons and that boldness to be lost."

Hopefully, they will be able to also introduce things like bringing local R&D approval and GMO legislation and approval into a single submission, in order to provide a one-stop-shop for approval. And in what I believe is a world first, they have introduced the Innovative Licensing and Access Pathway (ILAP), which uniquely considers regulation, reimbursement, and commissioning for these innovative medicines. ILAP provides a platform where you can have the appropriate people in the room and have those discussions to help developers move along the pathway quickly. Unlike other international schemes, this allows provision of data early on, even before you have much, if any, preclinical data.

The benefits that the COVID-19 pandemic brought in terms of the real-time implementation of research into clinical practice can be demonstrated by the introduction of dexamethasone in the treatment of COVID-19. It was seen that dexamethasone had improved the outcome of patients with severe and critical COVID-19 disease. This was announced one morning and by that afternoon, it's prescribing was implemented in the NHS. That is astonishing. COVID-19 has brought a nimbleness to the regulators and the NHS. The NHS is the third-biggest employer globally and as someone who used to work there, it is very dear to my heart – but as with all huge organizations, it can sometimes be slow to act. COVID-19 has allowed people to act quicker, and many people in the NHS do not want those lessons and that boldness to be lost.

Q What are the main directions, priorities, and challenges relating to ATMP clinical development environment in the UK?

JB: Priorities lie in accelerating clinical trials through more permissive clinical trial guideline development. Support from regulators for clinical trial development through things like ILAP gives developers the means to speak to these people and have confidence in what they are doing.

The lessons learned from COVID-19 and the interactions it brought with people working together in a way that had not been done before are key. Collaboration is much stronger now, as is signposting for where you can go to get assistance. This will help accelerate clinical development.

For things like ATMPs, we are still gaining the knowledge of the mechanisms of action and the potential adverse events. Importantly, the regulators are also gaining that knowledge. In previous years, the dialogue has been scientifically driven, and it continues to be so, but today, with both parties learning fast, the regulators are being much firmer in their requirements.

If regulation is not appropriate it can slow development, but if it is helps aid knowledge of requirements, that can act to accelerate development. If it's proportionate, which I believe it continues to be, then for some innovative medicines, clearer regulatory requirements are a good thing.

Q And what is the future direction regarding increasing patient access to ATMPs in the UK?

JB: The ATTC network was a global first. It was farsighted of the UK government to understand that this was the last piece of the jigsaw in the supportive ecosystem for these innovative medicines. As the number of these therapies starts to increase, we must share the learnings from early adopters, say between the hematologists and the oncologists and the neurologists.

Regardless of indication there are common learnings, and ways that processes can be standardized, such as in training staff to handle living cell products, having a pharmacy with adequate liquid nitrogen, or the implementation of suitable governance structures. With the ATTC network, we have tried to produce frameworks that can be re-used throughout the NHS.

The Innovative Medicines is an important development step in increasing patient access to these innovative medicines. As was the revision of the National Institute for Health and Care Excellence (NICE) methodology.

Another thing that is important is the understanding that patients need to be involved with development and trial of products from the beginning. Sometimes clinicians and drug developers think are indicators of patient benefit do not necessarily align with patients' requirements. Patients know what is important to them and what will improve their quality of life the most and therefore improve patient access.

Q In what ways is Cell and Gene Therapy Catapult specifically going to help drive progress in the translation of ATMPs towards and onto the market?

JB: We continue to perform environmental shaping to understand what would accelerate innovation in the UK. We do that within the reimbursement, the regulatory, and the manufacturing spaces.

> "...patients need to be involved with development and trial of products from the beginning."

We continue to work closely with the UK MHRA to understand the perceived barriers for developers, and whether these are true barriers stemming from the regulatory authorities, or myths that need to be broken down.

We continue to spend a lot of energy on building skills, whether it be through apprenticeships or through the Advanced Therapies

DOI: 10.18609/cgti.2022.117

Skills Training Network. We aim to build skills at all levels, whether it be to operating in a cleanroom, understanding analytics, or working through regulatory challenges.

The third aspect is on-the-ground supply. This involves supply from a manufacturing point of view, accelerating cluster formations, supply chain formation and logistics, and ultimately NHS adoption. Looking at this in a holistic and connected way from process development through to adoption is important to drive progress. This encourages developers and academics to work with the end in mind form an early stage, thereby reducing unnecessary duplication or reworks. Having a translational pathway with the end in sight can be beneficial for marketing authorization.

Q Are there any specific developments relating to the MHRA and ATMP regulation in the UK that you expect to see in the foreseeable future, and why might they be important for the field?

JB: The MHRA are supportive of innovative trial design, which is needed for these types of products. It is key to have a regulator that understands and balances risks against benefits, and a clinical trial system that accelerates approval and cuts down on the administrative burden. Again, as we are no longer part of the European system, the revisions to clinical trial regulation needs to be clear and effectively communicated, especially if there are going to be radical changes made. If those changes are implemented in the way described in the consultation paper, they should accelerate clinical trials.

Another thing to look out for is the point of care manufacturing initiative from the MHRA. That is going to be exciting, not only for ATMPs, but also other innovative medicines such as the 3D printing of medicinal tablets. This could lead to localized at-the-bedside production of tablets for an individual patient.

We are also seeing collaborations and agreements with global regulators. When we are accepted into a mutual recognition scheme for the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), this will act to reduce the burden for developers of mainstream medicinal products. Then, if we could get mutual recognitions for ATMPs, that would be very beneficial for the entire field and, of course, for patients.

Q Finally, what are some key goals that you have for your work over the next couple of years?

JB: Our focus continues to be that the UK is attractive to developers and supports accelerated access for these life-changing and potentially life-saving medicines.

Panos Kefalas, the Director of Access Strategy at Cell and Gene Therapy Catapult, is looking after the regulatory team and the health economics and market access team. Between us, we will continue to work with MHRA, NICE and the NHS Accelerated Access Collaborative to ensure that the reimbursement and innovative payment models are functional for both the NHS and the developers.

Personally, my focus will be obtaining further funding for the ATTC network and the opening of the Cell and Gene Therapy Centre in Edinburgh to provide support to the north of the UK.

AFFILIATION

Jacqueline Barry
Chief Clinical Officer at the UK's Cell and Gene Therapy Catapult

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 author declares that they have no conflicts of interest.*

Funding declaration: *CGT Catapult and the ATTC receive support from IUK.*

Article source: *Invited.*

Interview conducted: *Jul 4 2022;* ***Publication date:*** *Aug 4 2022.*

DOI: 10.18609/cgti.2022.117

CELL & GENE THERAPY INSIGHTS

GLOBAL REGULATORY UPDATE

SPOTLIGHT

INTERVIEW

Evolving ATMP regulations in the EU & UK, & the role of the Qualified Person

David McCall, Editor, *Cell & Gene Therapy Insights*, talks to **David Caulfield**, Assistant Director of Pharmacy and Qualified Person at The Newcastle Upon Tyne Hospitals NHS Foundation Trust, and Director of Caulfield Pharma Consulting.

DAVID CAULFIELD is currently Assistant Director of Pharmacy – Quality Assurance at Newcastle upon Tyne Hospitals NHS Trust, he has spent his career working in the NHS, briefly in clinical pharmacy roles and latterly in production and quality assurance roles. David is passionate about delivering high quality care and with a love for science and innovation he was drawn to the field of advanced therapies. David passed his Qualified Person VIVA in 2016 and has been an operational Qualified Person across numerous dosage forms since then. He is now a Qualified Person Assessor on behalf of the Royal Pharmaceutical Society, and is passionate in supporting candidates within the NHS and industry in their own QP journeys, including lecturing at The University of Manchester where he did his original undergraduate degree. He has a unique perspective of the disruption that can face the NHS in adopting these exciting therapies, but also an understanding of the extremely complicated and highly regulated area of manufacture, David now assists industry in the shaping the design of the next generation of ATMPs to optimise adoption, maximising the incredible promise many of these therapies offer.

Cell & Gene Therapy Insights 2022; 8(6), 697–705

DOI: 10.18609/cgti.2022.106

Q What are you working on right now?

DC: I put my role into three distinct areas that have overlapping synergies. Firstly, there is my role as a Pharmacist in the UK NHS. There, I'm supporting the adoption of disruptive therapies, including the marketed advanced therapies. That includes providing initial advice to the companies commercializing the approved therapies around considerations to minimize disruption, thus helping to ensure the therapies get used in the way they are supposed to be used. It involves the IT infrastructure and how we are going to use cell tracking systems and the information governance (eg. how the patient information is going to be used). And this role also involves leading the contract discussions – sending the contract out to the NHS Foundation Trust lawyers and ensuring it complies with all the procurement laws, and that the contract presents in a balanced manner.

Secondly, we have five manufacturing sites within Newcastle Hospitals (two for nuclear medicine, a conventional pharmacy, and two for advanced therapies) and my remit is providing quality leadership for all of them. (We are currently building a sixth, which will be a PET tracer site. Hopefully there will be some overlap between the PET tracing and advanced therapies – for instance, in terms of the labeling and tracking of cells *in vivo*). I'm very well supported – there are Heads of Quality at each site. It is more of a strategic support role where I try to make sure we can provide for both the translation of the Newcastle Advanced Therapies-derived ideas, as well as contract manufacturing services. The number one priority is to ensure that Newcastle patients are first in line to be able to access innovative therapies.

Finally, I am a Director of a small company through which I offer consultancy services, including as a Qualified Person (QP) to ATMP manufacturers. I serve as a contract QP to both Autolus and TC BioPharm, and I am in the midst of developing new relationships with larger conventional biopharma companies that are just getting into the cell and gene therapy space, as well as some very small start-ups that are working in point-of-care manufacturing – something we will discuss more a little later on.

Q Newcastle Advanced Therapies has been a stalwart of the field in the UK for many years – what are your reflections today on how the organization and facility have advanced in step with the cell and gene therapy space?

DC: I would say that when Newcastle first invested in ATMPs, it was seen as a bit of a punt – a case of 'let's see what happens' – which really reflected the status of the nascent field in general. And as with all these things, it has evolved since. The focus of activity used to sit very much within stem cell research whereas today, after becoming Newcastle Advanced Therapies, the department has become an integral part of pharmacy. Basically, if we manufacture a product and it is administered into a patient, in a hospital it sits best as being part of pharmacy. Clearly, not all such products are medicines, per se – bone marrow transplants, for example – but the manufacture and preparation aspects sit within the governance structure of pharmacy nonetheless.

DOI: 10.18609/cgti.2022.106

I feel that by becoming a site that actually does ATMP manufacture for patient use, we became a lot more institutionally ready from a relatively early stage to deal with these disruptive technologies. The benefit to us as a hospital has primarily been that we've been able to say 'yes' to the huge majority of clinical trials and to all the commercial products, and we have also had the governance and regulatory infrastructure in place to allow us to offer these treatments in a controlled environment to our patients. Clearly, there's still work to do to ensure there continues to be enough of an internal academic R&D pipeline coming through, not least because the demand for contract manufacturing is growing rapidly.

"To me, the infrastructure is more than just the buildings. It's the people, the training, and the governance that has to follow that then unlocks the ability to do things in the hospital."

Related to Brexit, we are also seeing a lot of investment and opportunities coming from outside the UK now and interestingly, at a recent conference I learned from one UK ATMP contract manufacturer that about 90–95% of their business currently comes from outside the UK. That does make us ask the question of what's driving it – is it our capabilities? Is it that we are cheaper than elsewhere? Is it that we don't have enough funding in the UK at the moment to bring homegrown biotech companies through? (As I mentioned, I do work for two UK-based companies, but they are both now on the NASDAQ). I think it is an interesting question to consider.

To me, the infrastructure is more than just the buildings. It's the people, the training, and the governance that has to follow that then unlocks the ability to do things in the hospital.

Q What have been the key areas of regulatory guidance, legislation, and/or evolution relevant to advanced therapies that have impacted your role in recent times?

DC: The legislation is constantly evolving. Several years ago now, the GMP for ATMPs guidance came out from the EMA. I would say it met with a mixed reception, largely because of the fact that it was designed as a standalone piece of GMP guidance. However, things have moved on from there. Clearly, COVID has been horrendous, but I think one of the major silver linings from the pandemic was how the UK MHRA approached the regulation and licensing of the vaccines. They looked to fast-track, seeking efficiencies and asking whether processes be done in parallel rather than sequentially. Communication was also improved – for instance, if they found a problem during their initial review, they pushed that back to the vaccine developers and manufacturers and asked them to be looking at the issue while the regulator continued with the review. That sort of approach is potentially more labor intensive for the regulator, but for the companies working in that space, for patients wanting that intervention, I believe that change delivered real benefits.

The EMA's Clinical Trials Regulation has come in now into force, and the MHRA just recently closed the consultation on proposals for legislative changes for clinical trials. This consultation is asking stakeholders in a structure way what needs to happen in the clinical trial environment in order for the UK to remain competitive but also taking to opportunity to ask if they should retain the efficiencies realized during the vaccine approval processes. I welcomed the flavor of the clinical trial consultation but also the aspiration, in that the MHRA are really pushing the boundaries. They are going beyond a small evolution and trying to think about what needs to be legislation versus what could be guidance only, thereby providing more autonomy, which will help future-proof the regulatory environment. Clearly, the products, the facilities, and the controls are all changing. Therefore, you have to be careful when writing legislation to make sure you don't stifle innovation. Of course, the Clinical Trial Regulation was meant to help innovation, but I am not sure whether it is going to change enough in mainland Europe to allow that to happen. They have got the single submission process in place, which does make things more streamlined, but that has never really been a key barrier in my experience, at least not for industry. On our academic side, it will make a small difference.

But I think the most important thing the MHRA have done in the clinical trial consultation is to ensure that this is going to be a patient-centric process moving forward. The proposal asks how/if we are going to engage patients when we design trials, and the knowledge sharing in general with patients is going to improve considerably. That lived experience of the disease is very important for informing clinical trial designs. I heard an interesting talk from the Head of Cell and Gene Therapy at Pfizer recently. He said they went to the patients with their (Pfizer's) perception of what the patients wanted from a therapy for a particular rare disease, and they found that those assumptions were not accurate. It actually clarified what the secondary endpoints should be for the trial in question, as they started to realize they weren't measuring what was most important to the patients themselves. So I think that's a really exciting development that is ongoing.

Another consultation period that closed relatively recently relates to point of care manufacturing. When I first came into this space, we used various closed system automated manufacturing platforms for what was then termed as decentralized or distributed manufacturing models. I think the initial idea was that there would be a similar manufacturing platform in every hospital, and they would simply make their own products – CAR T cell therapies, etc. But then everyone seemed to realize that manufacturing is one thing, but the product characterization and QC testing is another thing entirely – let alone the regulatory requirements for quality systems, infrastructure, etc. that a hospital needs to be able to satisfy in order to become a registered ATMP manufacturer in the first place. Consequently, the distributed manufacturing piece doesn't seem to have gained much traction, certainly not in the engineered cell therapy space.

However, point of care manufacturing becomes a necessity in some instances where it is either not possible to have a manufacturing facility (eg. on a battlefield) or where the product simply doesn't have the shelf-life to allow it to go through 'conventional' ATMP manufacturing processes. I'm working with a company that's looking at chronic wound care with a blood-based intervention (not an ATMP, but somewhat related) and that product has

DOI: 10.18609/cgti.2022.106

an incredibly short shelf-life. The point of care consultation is starting to consider about the processes need to transition clinical trial processes through to marketing authorization. It is a response to the fact that there is now a lot of compelling clinical data for some of these products. (It's not just ATMPs: there are medical gases, as well as therapy for use after serious trauma on the battlefield).

The legislation is very clear when processes are classified as manufacture. When something becomes 'manufacturing' of a medicine, then it falls under the medicines legislation albeit there are several circumstances that can exempt the need for formal manufacturing authorizations. It's about applying controls in a commensurate nature, whilst not stopping the benefit to patients. I think it's a fascinating area – it will be very interesting to see exactly where the legislation eventually lands.

In the early clinical development phases for products manufactured at the point of care, it has been possible to have a QP and an MHRA inspector sat at the patient's bedside. But that is not a scalable model, so what is the answer? Pursuing a hub-and-spoke arrangement, where a QP sits in a centralized control site with a QP advocate – someone who can be the 'eyes and ears' of the QP – located at every clinical site may be the risk-appropriate solution. For these processes, it is critical that we redesign and ensure robust feedback loops and mechanisms for trending. We need to think about how scale-out works. The MHRA are clear that the core of medicines legislation will remain the same – the question will be, what additional piece of legislation do we need to allow regulatory compliance and ensure patient safety?

Elsewhere in the regulatory sphere, EU GMP Annex 1 looks very likely to come through this summer. While many aspects and principles have already been adopted, it will have a very significant impact on how we start shaping manufacturing process and designing the associated manufacturing facilities. The headline is utilizing a Quality Risk Management (QRM) principles in an overarching contamination control strategy, whereby one seeks to identify all the risk presented and apply mitigations holistically in a manner commensurate to those risks.

For example, when I first started manufacturing T cell products, we had open-fronted cabinets and open processes. Clearly, the technology readiness levels have improved significantly since then – now we are able to minimize (with an aim to eliminate) processing within the Grade A environment. The revised Annex 1 means that anything involving an open cabinet is going to become prohibitive to manufacture due to the controls that will be required. Automation is of course part of the answer, but the technologies while developed significantly are still in their infancy, relatively speaking – many of these companies are still transitioning to becoming compliant to a level where the technologies can be used in the manufacture of marketed medicines. While this presents a challenge,

"It's about applying controls in a commensurate nature, whilst not stopping the benefit to patients. I think it's a fascinating area – it will be very interesting to see exactly where the legislation eventually lands."

these companies work in a nimble manner, and ATMP manufacturer who engage early can help shape and evolve these technologies to make sure they are fit for purpose.

So Annex 1 is definitely going to have a huge impact. It is going to push us out of the Grade A cleanroom environment, and towards closed systems where everything has to link together. I think we are reaching a point where we need standardization in the components used i.e. plastic tubing materials and diameters. This will aid the ability to use manufacturing equipment in a modular format while allowing closed system transfer via sterile welding. I see the whole network and infrastructure of manufacturers, developers, analytical laboratories, and tool providers really starting to work together. It feels like nobody has all the answers, and so it's about trying to evolve something that doesn't just work for one manufacturer, but works for everybody. We have seen an excellent example of what can be achieved with this type of collaborative approach in the COVID vaccine response, and the cell and gene therapy space has the opportunity to follow suit. But I think the solution providers in particular need to collaborate in terms of standardizing, in contrast to perception that to not do so presents a commercial risk to the outliers.

Q As a QP, what have been the key changes you have seen in terms of the batch data presented to you and your role in reviewing it? What do you perceive to be the key areas of recent advancement or evolution in cell and gene therapy QC/release testing?

DC: When you are acting as a QP, one size doesn't fit all. Clearly, if you are a company making autologous ATMPs and doing so at scale, you are going to have a lot more infrastructure, automation, electronic batch records, hard barriers to stop people using out of calibration machinery, etc. A lot of the checks required are system-based, and that's absolutely the way controls have to develop. It's about creating systems with intrinsic controls to ensure that things are going to happen the way you want them to, but then also documenting and triaging in a contemporaneous nature whenever something unplanned does occur.

When considering whether a product is suitable to be QP-certified, in simple terms, I think of the black, the white and the grey – a kind of Venn diagram of QP certification. The white area is where everyone knows the product is fine. The black is a product clearly unsuitable for administration to patients. I think it is in the overlapping grey area where the QP really adds value to the certification process. This said, I actually think the QP currently adds the most value outside of the certification process itself – in product and system design. In sharing that knowledge and ensuring we learn and remain proactive, so that we can create a process that is robust, easily trainable, and that can be validated. Its import to recognize the variable nature of the patient-derived starting materials – as such, the concept of design space and process analytical technology are paramount to defining optimal manufacturing parameters on a batch-by-batch basis. With these strategies we increase the chance of meeting the product release specifications, defining our product not by a fixed manufacturing process, but instead by how we characterize the product.

DOI: 10.18609/cgti.2022.106

We also need to consider the sheer volume of paperwork that these complex manufacturing process create – files upon files of it for a single batch. On the flip side, though, it is noticeable how many more well-trained QA personnel are working in the cell and gene therapy space today, who are supporting the QP and instrumental in reviewing these documents. There is now a healthy mix of people who have both cell/gene therapy knowledge and QA knowledge. This results in the batch records and QC data being presented in a really good way, which allows the QP to very much focus on the exceptions. The QP can then concentrate on evaluating the impact of any deviations and what options exist to best serve the patients concerned. I often joke that the QP is the one who isn't ashamed to ask the stupid questions! We are not the scientists; our role is to lean on the expertise that surrounds us to ensure patients receive compliant and safe products.

As a QP, one of the hot topics in my world at the moment is potency tests. I've seen a lot of potency tests, and often as data is gathered there is limited correlation to clinical efficacy. But a representative potency test is instrumental in creating a design space and allowing continuous improvement to happen in the manufacturing processes.

Q You mentioned Brexit earlier – do you anticipate any further changes to, or repercussions for, the QP role stemming from it?

DC: We have always had really great collaboration and partnerships with our European colleagues and actually, that has continued. For example, we are involved currently with German-led grants, and one of our collaborators on our dendritic cell products is Dutch. We are treating patients in Spain, we are importing products from Switzerland, and we have a reciprocal agreement with a hospital in Germany where we bring their products into the UK and do the QP oversight piece, while they certify our products that go to the EU via Germany. The supply chains have clearly got more complicated as a result of Brexit – ATMPs going to Spain pay a visit to Germany first for QP certification, for instance. But I think these collaborations and partnerships are there because we are all united in putting the patient first.

Holoclar is a marketed Tissue Engineered Autologous ATMP that is manufactured in the EU, and therefore needs the oversight of a Responsible Person (import), or RPi, in order to be used within Great Britain. I'm the RPi for Newcastle, which is supplying all of the NHS with this product. We have found the UK MHRA to have been really pragmatic in allowing us to fulfil this duty on a virtual basis. Consequently, we are able to supply the treatment centers for this product in London, Liverpool, Nottingham,

"As a QP, one of the hot topics in my world at the moment is potency tests... a representative potency test is instrumental in creating a design space and allowing continuous improvement to happen in the manufacturing processes."

and Newcastle. And the product doesn't have to physically come via us in Newcastle – it is a robust paperwork review exercise. This echoes the risk proportionate approach that the MHRA advocates, is compliant with the legislation, and is most importantly a patient-centric approach.

I think what isn't likely to change is the UK MHRA's perspective. The EU has made its decision with categorizing the UK as a third country following EU Exit, and I think it's unlikely that decision is going to change. When one listens to June Raine from the MHRA talking in recent times, their viewpoint seems to have shifted away from Europe and more towards the US and Asia Pacific, very much thinking of a global marketplace. I do hope and believe there will always be very close relationships and a lot of cross pollination between the UK and EU, though. A large portion of the staff working in the UK ATMP manufacturing originate from mainland Europe, and I feel access to this wider workforce has been important in the early success of these companies.

Clearly, many ATMP companies are global these days. I suppose that does beg the question of whether we will see an increase or a decrease in the number of QPs needed in the UK, but at the moment, it certainly seems that the demand for QPs is as strong as it has ever been. (In fact, regarding the RPi role I mentioned earlier, the MHRA initially wanted that to be performed by a QP, but there simply weren't enough QPs available). Looking to the future, I see no reason for this situation to change, either. ATMP supply chains are complex. I believe that at one point, some global pharmaceutical companies thought they would lose their UK-based QPs, but what they have actually done is to recruit more. They realized it was cheaper to get UK QPs than to make the requisite change to the complex supply chains.

When I'm talking to relatively new companies in the space, they often ask whether they need a specific type of QP – an ATMP QP, if you will. My view on that is that breadth of knowledge, experience, and skill set is one of the most important things a QP can bring to discussions with these small companies. So personally, I think it's important that the QP study guide stays the same. Clearly, the study guide is evolving iteratively with Brexit, as new legislation comes in, but I don't think it should become compartmentalized by product type. And in fact, the assessment process is mindful that not everybody will be an expert in every type of product, which would simply not be possible. The core fundamentals of validation, quality systems, and taking proportionate actions whenever something untoward happens apply regardless of the product type being manufactured.

Q Finally, can you sum up some chief goals and priorities for your work over the coming 12–24 months?

DC: My chief reflection from COVID19 is that life is too short, so in the past six months I've gone part-time. I've decided I need more time with my young family.

I think finding that balance is my most important goal, but I'm also equally excited and feel privileged to be working in this field as we start to see increasing patient numbers and scaling up of the manufacturing. For one thing, I do think we're going to see some really promising allogeneic products coming to market in the really near future, and it will be

DOI: 10.18609/cgti.2022.106

interesting to see how we deal with those. We are seeing some of them in the UK, testing the water through the Specials market and there are others in later phases of clinical trials. It will be particularly interesting to see how adoption evolves and where in the treatment pathways these allogeneic products sit, as the cost of goods is clearly one massive aspect of the first part of my role: an NHS Pharmacist. I can see quite a few companies creating a strategy to bring down that cost of goods to make delivery at scale much more palatable and affordable to healthcare systems.

I think the outlook for these therapies and actually, the whole of life sciences and personalized medicine, is really exciting. There is a huge investment into genomic medicine at the moment in the UK – plans to review the approach to routine genetic sequencing as we increasingly understand the underlying aetiology of these diseases, through to working out who is going to benefit most from certain therapies. I think data management is probably one of the elements that I'm going to be watching most closely – I hope that the NHS really grasps and improves this aspect. There's a lot of good infrastructure already, but I think getting all the systems to talk together will really be the key to delivering these therapies to patients at scale.

AFFILIATION

David Caulfield
Assistant Director of Pharmacy and Qualified Person
Newcastle Upon Tyne Hospitals NHS Foundation Trust,
Director of Caulfield Pharma Consulting

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 author has recieved consulting fees from TCBiopharm, Autolus, Kings College London. The author has stock or stock options in Novartis AG and Autolus Therapeutics. The author has no other conflicts of interest.*

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

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited.*

Interview conducted: *Mar 29 2022*; ***Revised manuscript received:*** *Jun 28 2022*; ***Publication date:*** *Jun 7 2022.*

CELL & GENE THERAPY INSIGHTS

GLOBAL REGULATORY UPDATE

SPOTLIGHT

INTERVIEW

Cell & gene therapy R&D & regulatory evolution in the United Arab Emirates

David McCall, Editor, *Cell & Gene Therapy Insights*, talks to **Asawari Bapat**, Vice President Clinical and Regulatory Affairs at Questar Enterprises

ASAWARI (ASA) is a Medical Doctor (MBBS, Bachelor of Medicine and Bachelor of Surgery, MGIMS, Sevagram, India) with her specialization in Clinical Pathology,Transfusions, Transplants, Cellular therapies and Gene Therapies, Biotherapies, Lab Medicine and Immunology (DPB, Post Graduation in Pathology and Bacteriology from College of Physicians and Surgeons, India). She specialises in operating, and managing facilities, and projects globally (PGDHHM, Hospital and Healthcare Management). Asa has 20+ years of 'Leadership' experience, in executing projects and operating facilities such as, complex Diagnostic labs, hospitals, and facilities for Cord Blood Banks, Apheresis (Blood Products, Plasma Products), Transfusion medicine, Transplants, Biotherapies (Cellular, tissue and gene therapies) and Regenerative Medicine. She has been piloting and spearheading specialized Labs, Cord Blood Banks, Cell and Gene Therapy Facilities and Biotech Companies towards quality, compliance and financial success. nAsa is performing a critical part of creating, innovating, designing and establishing novel technologies in the field of regenerative medicine as a subject matter expert. Her expertise involves, encompassing new devices, validating new treatment protocols and new products through their life cycle of designing, complying to the regulatory requirements, creating prototypes, technology transfers, testing, verification, validation and scaling for bringing quality in therapeutic solutions to the patients. Asa has been instrumental in document submissions and in representing clients at CBER, CDER, FDA as a consultant and subject matter expert for TRIP submissions, INTERACT and Type A,B and C meetings for Expedited pathways such as Fast Track Approvals, RMAT's.

Cell & Gene Therapy Insights 2022; 8(6), 655–660

DOI: 10.18609/cgti.2022.098

Q What are you working on right now?

AS: My current focus is on educating and creating awareness around the field of Regenerative Medicine. I speak at events and conferences about cell and gene therapies, novel therapies, and regulations. I have been advocating for the need to update the existing regulations or adopting new regulations that can be brought in. Post-Covid, there are more patients who are now waiting in line for us to help them, so that has been my primary focus for the last six months.

On the professional side, I am working as a consultant for many cell and gene therapies globally. Several new facilities are being opened currently in the UAE, as COVID taught us that we need facilities closer to our homes and especially, outside of the US and Europe. Easily accessible facilities should be made available to the people who need them, as we require many on-site visits and off-site audits in order to provide the best possible healthcare solutions.

Q Can you give us a brief history of cell and gene therapy in terms of R&D activity in the UAE over the last two decades?

AS: The UAE has been a part of the field since the opening of the first cord blood bank in Dubai in 2006. There were fewer regulations around at that time, and they followed the accreditation standards of the Association of Advancement in Blood and Biotherapies (AABB), Therapeutics Good Administration (TGA), and the Foundation for the Accreditation of Cellular Therapy (FACT).

We have been studying the regulations and the regulatory frameworks from the US, Europe, and the UK, including China, Japan, and Korea. Despite the similarities with the regulatory framework of the USA FDA - in regard to the minimal manipulation of cells, for instance - the UAE has adopted its own evidence-based regulatory framework. For example, stromal vascular fraction (SVF), which is also known as a type of adipose stem cell therapy, is available in the UAE. Additionally, UAE was one of the first countries in the world to allow platelet-rich plasma (PRP) to be used in certain conditions.

Although at this point of time we are not developing gene therapy ourselves in the UAE, we are open to adapting to the developments in Europe or the US. For clinical trials in areas such as gene therapy, UAE has limited machinery, being a small country, but we do have a multiracial, diverse pool of around 200 different nationalities living here. This gives us a highly diverse gene pool in which to test investigative drug products through clinical trials, which can be attractive to certain companies and in certain indications such as rare diseases.

In the last two decades, I have seen much development in the region. There has been an increase in knowledge of regenerative medicine, cell and gene therapies, and stem cells, even within the general population. There are cord blood banks and adipose cell facilities where cells and tissues are collected, processed, and then returned to the patients (the majority of the cell therapy treatments available in the UAE are autologous). There are also small contract

DOI: 10.18609/cgti.2022.098

research organizations (CROs), and contract development, and manufacturing organizations (CDMOs) present here locally to help companies navigate through the local regulations.

Since 2018, we have seen many oncology treatments being made available in this region and this will remain a strong focus over the next two years, as the medical tourism market is of interest especially in the current geopolitical circumstances. The UAE provides high-standard healthcare to patients through their internationally accredited facilities.

Q You mentioned oncology is going to be a key focus, including CAR-T products. What are the other important areas for cell and gene therapy currently?

AS: In the UAE, there are many incidences of consanguineous marriages. Due to the marriages in close communities the populace is prone to rare diseases, sometimes consisting of metabolic disorders and inherited disorders. The Al Jalila Foundation, based in Dubai, is a great example of the UAE's commitment to healthcare, which focuses on children's healthcare, including rare diseases and metabolic disorders. Over the last two decades, we are witnessing a renewed focus on genetic testing. The UAE is amongst few countries who have introduced pre-marriage counselling, in order to prevent consanguineous marriages.

The UAE will enter into the foray with the advent of gene therapy, despite the limitations I mentioned earlier. We want to see this field develop and be proven safe and effective, so that in the future, we can all benefit from it here.

Primarily, UAE is promoting an open, progressive atmosphere where vital ideas can be strategically translated into clinical applications. For example, CAR-T is available for hematological malignancies, and is now being explored for solid tumors. In this region we have a high incidence of gastrointestinal (GI) cancers and breast cancers. For the right company in this niche, this can be a key application area moving forward.

In many countries the regulations have remained stagnant, but here, we have seen the regulatory framework being constantly updated and adapted to address the needs of patients. Every two or three years in the UAE, the regulations have been updated. We have seen hematopoietic stem cell (HSC) therapy guidance being revamped. We have also seen new regulations around the adipose stem cells. This frequency of change and improvement is not happening anywhere else in the world currently.

Coming back to gene therapy, we are in the process of investigating relevant guidelines from around the world. We utilize the framework of the US, but we are also looking at the Korean FDA, for instance. Overall, we are looking to take a cautious approach with gene therapy, in terms of not being too progressive, but at the same time allowing fast-track approvals and compassionate use

"... we have seen the regulatory framework being constantly updated and adapted to address the needs of patients."

of biotherapies for patients. We have ethics committees conducting timely reviews of biotherapies and their usage. The focus on the regulatory end is to provide a good, robust environment for people to come and set up cell and gene therapies in the region. The UAE has several incubators, and world class internationally accredited labs to provide diagnostic care, and to aid in processing and manufacturing of biotherapies.

During the COVID pandemic, the UAE approved a new advanced therapy after enrolling itself on clinicaltrials.gov, and was approved for a clinical trial. With the successful recruitment and completion of the patient arms, we are now in the process of building a new hospital in Abu Dhabi to provide fast-track patient access to regenerative medicine against long COVID, and other complications arising from similar diseases.

Q What does the regulatory organization and infrastructure look like in the UAE?

AS: From an outsider's perspective, there has been some hesitancy in this regard in the past because the UAE consists of seven separate emirates, with different agencies regulating each of these regions. In Abu Dhabi, there is the Department of Health (DOH) with its own policies, documentation, and regulatory framework, whereas the Dubai Health Authority (DHA) develops the guidelines for Dubai. The Ministry of Health and Prevention (MOHAP) provides policies and documentations for the rest of the emirates to follow. Today, though, many of the hospitals and facilities in Dubai and Abu Dhabi follow a similar regulatory framework. There are small nuances, but overall, what the regulators are looking for is the intention of providing safe and effective therapies. Patient safety and patient access are amongst the primary goals of the UAE.

When providing these regulatory frameworks, it is all about simplification. The UAE always aims to harmonize the best regulations from the US, UK, EU, Korea, Japan, and China and adopt them based on its evidence-based guidances. The plan is always looking forward to where we want to be in five years' time.

I advise new companies, biotechs, and healthcare providers to leverage the opportunity to involve MOHAP right from the beginning. If there is a new therapy being developed, MOHAP always encourages good communication highlighting the process involved, and milestones required to pass for successful approvals in UAE.

Q What would be some of the key considerations for a sponsor coming into the UAE and looking to conduct a cell/gene therapy clinical trial?

As: First and foremost, many people who come to the UAE with the intention of conducting a clinical trial assume that since they have a trial approved in their own country, they can automatically run one here. That is a real no-no in this region, though.

Things that work in the rest of the world may not work in the UAE. You must be conscious of the regulations in this part of the world. For one thing, people must be mindful of

DOI: 10.18609/cgti.2022.098

Shariah law compliance, which is inbuilt in the regulatory framework. This includes the intent to do no harm and to be halal. These are some of the concepts that outsiders may not know.

Secondly, many people bring the evidence of work that they have done elsewhere in the world that they think is applicable and acceptable here. In the UAE, there are certain intricacies involved around Shariah and acceptable practices, such as details of any animal studies and informed consents. Good consultants are an important key to facilitate the dialogue between the regulators and the company.

> "In the future, I believe the current focus for regenerative medicine of creating a balance between being progressive and being mindful will continue...In every situation, patient safety is critical."

When one is aware of the local customs and traditions in place, the task becomes easy. Awareness of the expectations of each stakeholder is an indispensable requirement in the region. There are a multitude of companies and healthcare facilities open to these types of collaborations. You can seek a local partner, hospital, or healthcare facility here to partner with, and bring forth the therapies or ideas that you would like to develop in/for the region. There are a good deal of clinical trials happening currently in this part of the world, including ones by ADSCC (Abu Dhabi Stem Cell Center) and Cleveland Abu Dhabi.

Q What might be some key regulatory and healthcare priorities or points of evolution in the region moving forward?

AS: In the future, I believe the current focus for regenerative medicine of creating a balance between being progressive and being mindful will continue. The essence of human dignity is of the utmost importance in this region. In every situation, patient safety is critical.

Providing access to world class healthcare solutions locally is high on the priority list here. There is a commitment to focus on preventive health issues, such as in breast cancer, and the UAE has created many avenues there, including mobile units for breast cancer screening, partnering with numerous hospitals who offer this service free of charge during the Breast Cancer Awareness Campaigns.

Diabetes is a common disease in UAE, too, and taxes have been levied on various sugary drinks to minimize consumption of these beverages. Alongside the therapies for cancer, rare diseases, and metabolic diseases, the focus is now moving towards prevention of lifestyle diseases. We are currently working on projects based on regenerative medicine in this space, but this is definitely going to be something to look out for in future.

The overall focus of the region will remain firmly on the longevity and health of the UAE population.

Q How do you see the UAE's CRO and CDMO services sector evolving further moving forward?

AS: There have been amendments to the regulatory framework, often in favor of new technology and new techniques for CROs and CDMOs based in the UAE.

There are a few existing CROs and CDMOs operating in the field of biosciences here. If you have a therapy, a prototype or an idea that you would like to bring to the UAE, you can bring in your own outfit, including lab services, or take the help of the facilities already set up here, through collaborations or through technology transfer. CROs and CDMOs are currently hiring, and there is a buzz of activity in this area. Being a relatively small country, I do not expect too many CROs and CDMOs to be here, but there will certainly be some facilities available with good quality management systems.

The UAE has laid down some of the strictest laws and regulations to adhere to the guidelines for human safety. Some of these laws are around evidence-based practice, training, licensure and approvals, and towards data protection. The breaching of any or some of these laws and regulations is a criminal offence. These directives and laws require us to take extra care surrounding each of these requirements such as the data management, and it is also the reason why we require the clinical or manufacturing services to be based in the UAE. Any company or entity that is interested in setting up operations in the UAE, and that might wish to act as a CRO or CDMO, must have a base here.

There are endless possibilities when you are based here in the region. UAE provides a great environment for the progress of biotherapies and regenerative medicine. I would conclude that UAE is definitely a place worth keeping an eye on if you are operating in the biotherapies space.

AFFILIATION

Asawari Bapat
Vice President Clinical and Regulatory Affairs
Questar Enterprises

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 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; externally peer reviewed.*

Submitted for peer review: *May 25 2022;* ***Revised manuscript received:*** *Jun 20 2022;* ***Publication date:*** *Jun 27 2022.*

DOI: 10.18609/cgti.2022.098

CELL & GENE THERAPY INSIGHTS

GLOBAL REGULATORY UPDATE

SPOTLIGHT

INTERVIEW

Trends in academic ATMP development & manufacture in Europe

David McCall, Editor, *Cell & Gene Therapy Insights*, talks to **Pauline Meij**, Head of the Center for Cell and Gene Therapy, and Qualified Person at the Leiden University Medical Center's GMP facility

PAULINE MEIJ is the head of the Center for Cell and Gene therapy (CCG) at the Leiden University Medical Center (LUMC). She is responsible for the production of ATMPs at the LUMC, Qualified Person for ATMPs and she is actively involved in the clinical translation of ATMPs. The research focus of Pauline Meij is on the clinical translation of cell and gene therapy products, the regulation involved, patient access and the role of academia in this. She was the lead author of the LERU ATMP briefing paper. Pauline Meij is a member of the ATMP expert group of the Dutch Medicines Evaluation Board and member of the ATMP working party of The Netherlands and Flemish Belgium.

Cell & Gene Therapy Insights 2022; 8(6), 725–729

DOI: 10.18609/cgti.2022.106

Q What are you working on right now?

PM: We are the center of cell and gene therapy for the Leiden University Medical Centre. Our core business is development and manufacture of advanced therapy medicinal products (ATMPs) for this academic center, but we also do some manufacturing for other centers.

We assist in the whole translation, regulatory, and quality elements of the new products that are developed by the different research departments in our center. When they want to go to the clinic, we help them with the translation and the manufacturing of the product.

Many different types of ATMP are developed and manufactured at our facility at the moment, including T cell products such as tumor-infiltrating lymphocyte products for malignancies, T cell receptor (TCR) gene transduced T cell products, and CAR-T cells. We are also currently generating our own GMP induced pluripotent stem cell (iPSC) line. Furthermore, we manufacture gene corrected stem cells, dendritic cells, and we work on an embryonic stem cell (ESC) derived product.

Q What key recent regulatory developments have affected ATMP manufacture in Europe, for you?

PM: At the Leiden University Medical Center, we think that patient access to ATMPs should be improved.

Compared to other medicinal products, we see a lot more academic-sponsored studies of ATMPs, and the products that are developed further by industry often come from academia. Academia plays a major role, and it is important that this connects to the regulatory side. Cooperation between regulatory offices, academia, and industry is important to bring this field further forward and create patient access to those products that are developed, but often remain within academia. For products that are on the market - or have been on the market and then subsequently withdrawn - there are many places where academia could play a major role. Over the last years, we have experienced an improved access to European Medicines Agency (EMA) and the national regulatory bodies for academia.

Q How is the point of care manufacturing picture developing in you view?

PM: Point of care manufacturing is important for ATMPs. It will be the future for at least a subset of these products. But it will be challenging.

We are now joining a point of care manufacturing study. It will be interesting to see how the process will progress with regards to requirements, infrastructure, different quality systems, responsibilities, and regulation.

"Over the last years, we have experienced an improved access to European Medicines Agency (EMA) and the national regulatory bodies for academia."

DOI: 10.18609/cgti.2022.106

At the least, the ATMP field needs specialist centers with their own GMP license and GMP quality systems.

Q What will be the likely impact on academia of current and likely future developments to the ATMP field? And how should academia prepare?

PM: At the moment, academia oversees the first phase of R&D and some products are developed further by industry. However, some of the industry products that reach the market are then withdrawn due to commercial reasons, and furthermore, not all the ATMPs developed in academia are of interest to industry - for example, those for ultra-rare diseases, or those with particularly complex manufacturing processes. Therefore, academia should take a responsibility for the further development of ATMPs and should consider even moving towards marketing authorization, in some cases.

We in academia should discuss this fact with regulators, industry, and all the stakeholders in the field. We should also listen to patients and how they see things.

Q How has your role as a Qualified Person (QP) evolved over recent years as the ATMP field continues to develop, and how might it evolve further moving forward?

PM: I started as a QP in 2011, for ATMP. In 2011, we encountered some hurdles with the regulations at the time. For example, fresh products had to be released without all the testing being in place yet, since this was a new paradigm – a personalized production for one patient and not an off-the-shelf product. We collaborated to solve problems like these. Eventually, the regulation was adapted to this paradigm, including the addition of GMP for ATMP guidance. However, not so much changed for us as QPs in that regard.

We manufacture many different products - ATMPs constitute a fairly broad area. This means knowledge must also be broad, and QPs need to fully understand their product. For example, QPs need to understand the possible effect of the number of non-specific T cells (or other impurities) in each specific product, whether it is autologous or allogeneic, and what all that means for the patient. We should realize it is different from a conventional medicinal product.

The role of the QP in point-of-care manufacture is again something we should prepare for moving forward. Specifically in academia, we now need to be releasing more products for clinical studies. And with regard to academia increasingly going for late product development / market authorization, individuals should be trained in realizing that there are some key differences in what you need to do.

Q What should phase-appropriate GMP look like in practice?

PM: Phase-appropriate GMP is a challenging subject. In the end the products you are administering to a patient in a Phase 1 clinical trial should be of the same basic quality as

the products during later phase clinical studies or the commercial end product that is on the market, although later phase products of course will have more development data available.

In multi-product facilities, like our facility, I also see organizational challenges in applying phase-appropriate GMP. So for me, I don't see a direct necessity for a phase-specific approach to GMP.

"What we have learned, especially with the speed of COVID vaccine development, is the importance of flexibility during product development and applying regulation."

Q There is a lot of talk of the 'new normal' in the wake of COVID-19 - can you define what GMP manufacturing of ATMPs in the 'new normal' will look like from your perspective?

PM: For us, there has not been a large amount of change in our daily work during, with the exception that we have the opportunities to do more on a remote basis. What we have learned, especially with the speed of COVID vaccine development, is the importance of flexibility during product development and applying regulation.

We should always have a critical look at the regulations that are there and whether they fit a purpose for the products we are developing and manufacturing - especially for ATMPs, as the diversity is enormous. Sometimes, certain preclinical studies are important to do, but at other times they will not teach you anything, or even give you 'false' expectations about safety. We should be able to be flexible and pragmatic, and discuss with regulators what is truly necessary to do in a development program. This will also speed up the whole process.

Q What are your key goals and priorities for your work over the next few years?

PM: We hope the products we develop reach the patients. I hope we achieve good results in clinical studies and start even more clinical studies with products we are currently developing. As I mentioned at the beginning, patient access is very important to me.

Especially in academia, we see that the regulatory expertise is lacking, as people are often not familiar with the whole process. Over the next few years, we want to be a regulatory expertise center and resource for academic and not-for-profit institutes. They can come to us and we can aid in the ATMP development process.

We need further harmonization in Europe, especially for multi-center clinical studies in different EU member states, which are currently difficult – hopefully, the Clinical Trials Information System (CTIS) will help in this. We also need to work on hospital exemption. We need to better define where the hospital exemption should apply and try to harmonize that between different countries.

And I hope we can improve the collaboration between all stakeholders in the field, to improve patient access to ATMPs, via academia and/or industry.

DOI: 10.18609/cgti.2022.106

AFFILIATION

Pauline Meij,
Head of the Center for Cell and Gene Therapy,
Qualified Person
Leiden University Medical Center's GMP facility

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 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.*

Submitted: *Jul 29 2022;* ***Revised manuscript received:*** *Jul 4 2022;* ***Publication date:*** *Jul 13 2022.*

JULY 2022 Volume 8, Issue 6

CELL & GENE THERAPY INSIGHTS

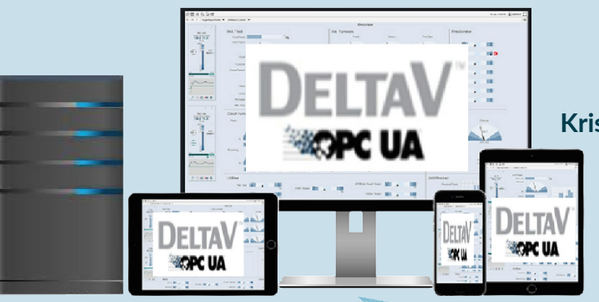
LATEST ARTICLES:

The digital revolution: technological innovations to enable automation in cell therapy manufacturing

Bruce Greenwald DeltaV Platform Development Manager, Emerson Automation Solutions
Sean Chang PhD, Manager, Early Innovation, Cell and Gene Therapy, Thermo Fisher Scientific
Krish Roy PhD, Director, NSF ERC for Cell Manufacturing Technologies and Marcus Center for Cell Manufacturing, Georgia Tech

The manufacturing process is complex, labor-intensive, and requires many open manipulations. It is also difficult to synchronize different instruments and products to make the workflow traceable and compliant with regulatory requirements. To solve these issues, a closed modular system can help minimize contamination and maintain flexibility. Most importantly, automating the process can reduce labor and human error. It is in this third aspect that digitalization plays a particularly vital role.

Cell & Gene Therapy Insights 2022; 8(6), 661; DOI: 10.18609/cgti.2022.099

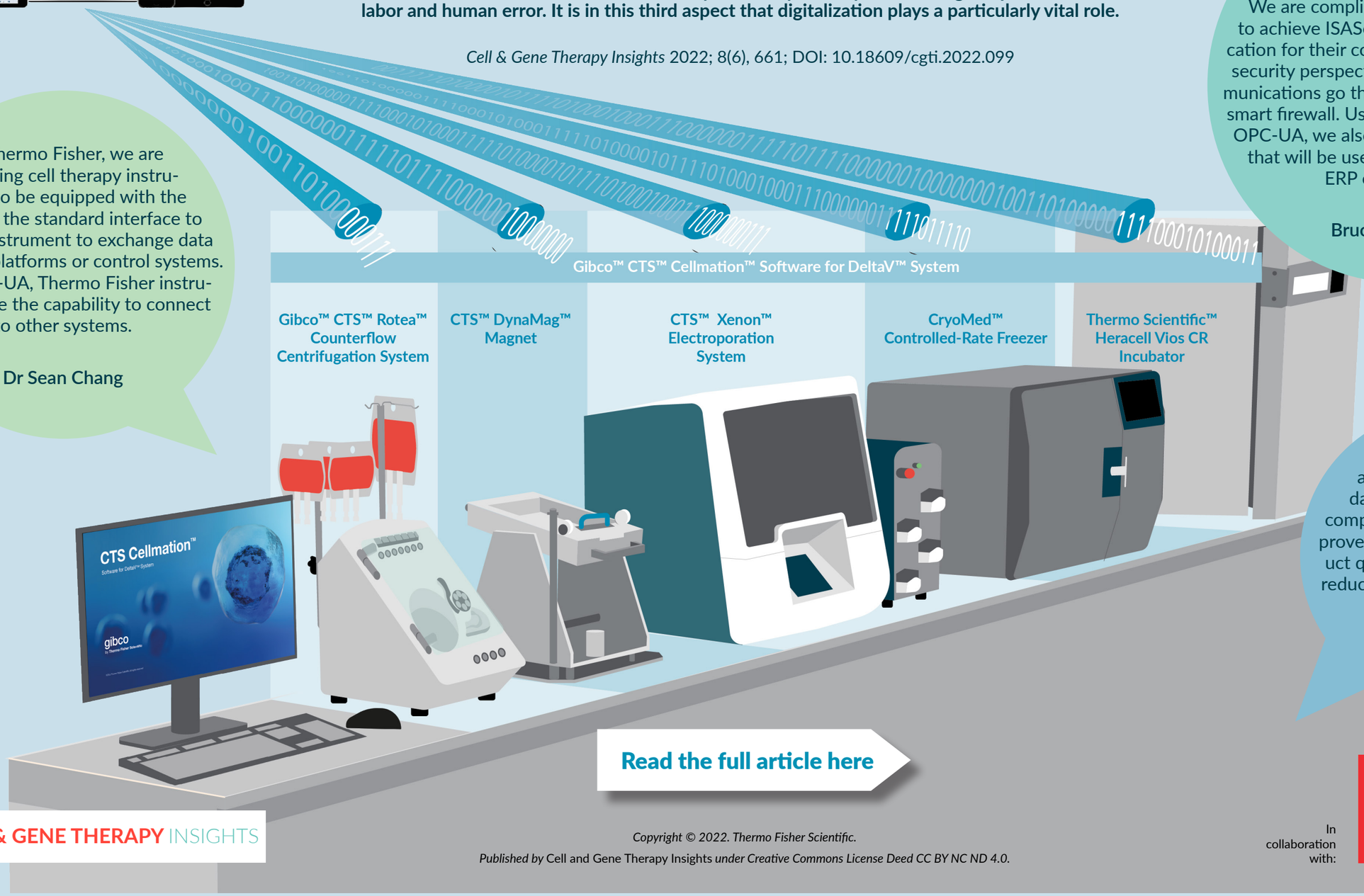


At Thermo Fisher, we are designing cell therapy instruments to be equipped with the OPC-UA, the standard interface to allow an instrument to exchange data with other platforms or control systems. With OPC-UA, Thermo Fisher instruments have the capability to connect to other systems.

Dr Sean Chang

DeltaV can provide a bubble around your entire control system. We are compliant and allow end users to achieve ISASecure SSA Level 1 certification for their control system from a cyber security perspective. The up and out communications go through our secure Emerson smart firewall. Using industry standards like OPC-UA, we also have web services tools that will be used for connecting to the ERP or MES layers.

Bruce Greenwald



Integrating process analytics, supply chain data, and cost modelling components would greatly improve the process and the product quality and reproducibility, reduce batch failures, and drive down cost.

Dr Krish Roy

Read the full article here

CELL & GENE THERAPY INSIGHTS

In collaboration with:
ThermoFisher SCIENTIFIC

INNOVATOR INSIGHT

Manufacturing considerations underpinning viral and non-viral platform selection

Elisa Manzotti speaks to Allison Hagerman, Aaron Noyes, Vladimir Slepushkin & Laurens Sierkstra

ALLISON HAGERMAN is a Professional Engineer focused on biotechnology, Ms Hagerman joined Oncolytics in 2010 and has been integral to the progress of its product development program ever since. Prior to being appointed as Vice President of Product Development, Ms Hagerman was the Director, Manufacturing and Engineering from 2013–2017 and Project Manager from 2010–2013, during which time she led the process performance qualification for pelareorep drug substance. Ms Hagerman is a Professional Engineer (P.Eng., APEGA) and Project Management Professional (PMP, PMI). She holds a Master of Biomedical Technology (MBT) degree from the University of Calgary, and BSc degrees in both Chemical Engineering and Biological Sciences. She is an accomplished equestrian and spends her spare time on horseback.

AARON NOYES is a Vice President of Integrated Drug Substance Development at Codiak BioSciences where he leads a team focused on developing scalable production processes for exosomes and robust technology to load varied payloads into exosomes. At the start of his industrial career, Aaron worked at Millipore before joining Wyeth Biopharma/Pfizer Biotech for 12 years where he developed purification processes and focused on scale-up of biologics, including mAbs, recombinant proteins, ADCs, vaccines, cell therapies, and viral vectors. Aaron received a BS in Biochemistry from the University of Massachusetts

at Amherst, a ME in Biotechnology Engineering from Tufts University and an Engineering Doctorate in Biochemical Engineering at University College London.

VLADIMIR SLEPUSHKIN is Global Head of Manufacturing at MedTherapy Biotechnology. He is leading all functions associated with manufacturing of CAR-T cells and viral vectors. Previously he was Executive Director of Vector Technology at Autolus Therapeutics, leading process development for manufacturing of lentivirus vectors in suspension cell culture, guiding assay development to support process development for lentiviral vectors, managing CMO for GMP vector production and T-cell processing. Before that, Dr Slepushkin was directing research vector core, and providing lentiviral, retroviral and AAV vectors for Kite Pharma. Vladimir proved successful in developing novel high-quality products by managing diverse technical groups and cross-functional teams, developing first-in-class clinical product from scratch, including facilities, equipment, manufacturing process, quality systems, regulatory CMC submissions and clinical trials design. He has proven expertise in technically understanding and leading the development and improvement of cell culture and purification processes, and operations and analytical methods, adhering to customer, regulatory, safety and environmental requirements and guidelines. Vladimir is experienced in identifying and resolving regulatory and manufacturing technical problems, as well as intellectual property assessment and licensing. He has authored 61 scientific papers in peer-reviewed journals and he's an author on 14 patents and patent applications.

LAURENS SIERKSTRA received his PhD in biotechnology in 1994 from the University of Utrecht after studying biology at the University of Leiden. He then joined Unilever as Project Manager and Unit Leader. In 2005, after the spinout of BAC BV from Unilever, he became CEO of BAC BV and set up the business in using single-domain antibodies for affinity purification, called CaptureSelect, which was sold in 2013 to Life Technologies. Since the acquisition by Thermo Fisher Scientific, he has been the business leader for the affinity purification business within the Bioproduction Division.

Cell & Gene Therapy Insights 2022; 8(6), 733–743

DOI: 10.18609/cgti.2022.111

With an ever-increasing range of viral and non-viral technologies available to advanced biotherapeutics developers, manufacturing considerations must play a key role in the decision-making process behind platform selection. These considerations include the current level of innovation in the bioprocessing toolkit and its corresponding capability to address the specific challenges facing individual technology areas.

In this article a panel of experts spanning the lentiviral vector (LVV), exosome, and oncolytic virus fields discuss the impact of manufacturing considerations on their respective platform selection and ongoing product/process development strategies, comparing the state of the art

in enabling technology in each application area, and discussing related challenges, needs, and opportunities.

Q Can you each briefly introduce us to your organization's current activities?

VS: MedTherapy is a startup company in the Boston area. The company is dedicated to providing services as a contract manufacturing organization (CMO) for the manufacturing of CAR T cells and lentiviral vectors.

Our main goal is to make manufacturing cost effective for people in developing countries. We consider the cost of goods when developing our manufacturing methods. One of the features that distinguishes us from many other CMOs is that our manufacturing facility is located in India, near New Delhi. This will allow us to lower prices due to a reduction in labor costs. We are still in the facility building phase, and starting next year we will be operational and looking for partners and clients.

AN: Codiak is a therapeutics company that started in Cambridge about 7 years ago, focused on demonstrating exosome therapeutics as effective immune-oncology drugs. Codiak's key technology is engineering exosomes to modify the tropism and deliver different payloads. We use these effective delivery vehicles in a way that takes advantage of the fact that they are immunologically silent.

We currently have three clinical candidates in or entering Phase 1 trials. One of them has an engineered surface Il-12 cytokine that allows for engagement with receptors on NK and T cells. Another takes advantage of the synthetic payload synthesis route for a selective cyclic dinucleotide STING agonist and combines that small molecule with an exosome to enable selective uptake in tumor-resident antigen presenting cells. Finally, we are working with anti-sense oligonucleotides attached to exosomes to downregulate various transcription factors in hepatocellular carcinoma. Other constructs in the pipeline include encapsulating AAV to enable re-dosing, and using exosomes with combinatorial ligands to enable vaccines.

LS: The Bioproduction division of Thermo Fisher Scientific is the global leading supplier of both upstream and downstream consumables, hardware, and single use products used in bioprocessing. My specific area is in affinity purification. We enable customers working on new therapeutics to come up with platform processes for purification, which will result in safe, affordable products.

Our pipeline is usually composed of all kinds of new modalities, including ongoing R&D programs to support lentiviral or exosome purification. Our main focus is for our customers to receive good platform purification solutions and associated analytics to be able to scale up their process in an affordable way.

AH: Oncolytics Biotech is working on a cancer therapeutic using a non-pathogenic virus, with the active ingredient being the double-stranded RNA virus itself.

That product is currently in Phase 2 trials in a number of oncology indications, most notably breast cancer. The team I lead is responsible for the process development, manufacture, analytical testing and clinical supply for that product.

Q Can you tell us about the key manufacturing-related considerations that impact strategic decision-making around initial platform selection and subsequent early development activities in your respective fields?

AN: The first thing we focused on for exosomes, which are a new modality, was reducing the risk. This means first reducing the risk of supply. We needed to have technology that can be scaled up to GMP manufacturing in a predictable way.

As a small company starting out, we did not have our own manufacturing facility, so we had to use a CMO. As we chose our CMO, it was important they already had equipment that we needed and trained operators already familiar with technology, in order to de-risk the production process.

The other key strategic piece pertains to regulatory risk. As we looked at exosomes, we wanted to make the process more acceptable to regulatory agencies, which involved taking steps such as using well-known cell lines, avoiding animal-derived components, and crafting release and characterization assays that build on the established state-of-the-art for recombinant protein production.

LS: For these early technologies, adding new components can complicate things, so de-risking those aspects is key. However, it can be good to utilize new technologies to deliver short-term improvements. That is where we sometimes help customers with their challenges, for example in purification, and we work with them to deliver a scalable solution.

VS: There are two viral vector platforms that can be used for CAR T cell transduction, either retroviral or lentiviral. The difference between these two platforms is connected to manufacturing in various aspects.

Lentiviral vectors are easy to make with relatively high titers for transient transfection, making it a very common platform. However, it can be difficult to make a stable cell line that would produce these vectors, which can limit large-scale manufacturing.

Retroviral vectors are made mostly using stable cell lines, making large-scale manufacturing easier. However, you cannot create high titer vectors with transient transfection for retroviral vectors. For early-stage development with varying vector design, it can be difficult as you need to make a stable cell line each time.

Q How would you sum up the current status of the bioprocessing toolkit in your respective fields? What have been the important recent advances, and also the important innovation needs?

DOI: 10.18609/cgti.2022.111

AH: Oncolytics' lead product is relatively simple by today's standards of viral and immuno-therapeutics. The toolkit we have available to us is fairly extensive, from old standbys to newer technology with more advanced controls for improved yields and outcomes.

From my perspective, the biggest recent advance is the widespread availability of single-use systems. This not only means single-use reactors, but also prepacked columns and single flow pass disposable items. These are appealing to CMOs because it limits their workload and provides ease of switching for varying client processes. If all these things are single-use systems, they tend to be accessible in a variety of locations at different facilities. This makes the process more flexible and adaptable for extension to other markets down the road.

In my experience, the most important challenge is limited facilities for live virus production. There is less innovation in the near-term in this area.

LS: We work on many different modalities at Thermo Fisher and every modality comes with its own challenges. For example, monoclonal antibodies have a different innovation need and drive than oncolytic viruses. Another example is lentivirus, as only a small subset of the material you produce can infect cells.

We work with companies that know their specific application, molecule, and challenges, to make those step changes in productivity that are often desperately needed.

AN: I echo the point that single-use disposable components are a key part of how we operate. For exosomes in particular, re-uptake of vesicles is a phenomenon by producer cells. Perfusion cell culture, wherein the released exosomes are rapidly separated from the cells, has been effective in terms of increasing titer. It however has introduced the challenge of separating 200 nm bio-nanoparticles from cells that are several μm in diameter. There is a need to grow the technology to do this.

More broadly we need to reach a critical mass in the industry to help drive innovation, learn from leaders, and enable enough large companies to share what they are doing in order to build into each other's advantage and thereby help the entire sector flourish.

Q For your specific class of molecules, what is the biggest challenge you see for achieving commercial production scales, specifically – or if production-scale has already been achieved, what would be the biggest improvements that would add the greatest amount of value to the manufacturing process?

LS: In this area, we have always been working on different new modalities and every modality has it specific unique requirements. For example, AAV started around 15–20 years ago, with people wondering what the platform system was going to be in terms of serotypes. The biggest step change was starting to make products for single serotype forms, to enable a scalable system. Later on, we launched a product that could do all serotypes as opposed to only one, which became the platform for AAV manufacturing independent upon serotype.

As a technology supplier, we moved towards focusing on what different types of modalities are being chosen. From our point of view, zooming in on the platforms that people will be adopting is one of the biggest challenges. Resolving this enables products which can be used to support that platform. The key step change is going from a plethora of different technologies, for example to purify products, to real platforms which can do that, which then streamlines and the use of a specific technology in early research into process development and finally into manufacturing for all new therapeutics derived from new modality platform.

AH: Scalability is a product of your process but also your materials. In addition to scaling up and out for larger volume production, we are also scaling up and out for later phase production, and eventually commercial production. This needs to be factored into planning as early as possible with your manufacturing partner, to avoid a situation where you are using reagents and materials that are suitable for early phase and not later phase.

Use of non-animal component-derived material and sourcing of materials that are fully cGMP suitable for later phase production will avoid the need for comparability efforts either in the clinic or in the manufacturing pipeline. Imposing or at least developing reagent specifications and controls early can help with scalability later.

VS: The greatest advantage for production at commercial scale is the development of stable cell lines for lentiviral vectors. Both lentiviral and AAV vectors are mostly manufactured by transient transfection. The main disadvantage of transient transfection is the need for a lot of plasmid DNA and expensive transfection reagents. Creating a stable cell line that does not require plasmid DNA to make vectors greatly improves scalability of the process.

The problem with this stable cell line is that some of the vector components are toxic to the cells, so you need to regulate expression. So far, several systems have been used with some success, but for lentiviral vectors, we are not yet ready to use this platform for commercial manufacturing.

AN: From my vantage point in exosome production, we run 500 L perfusion reactors, turning over a bioreactor volume a day. Over 20 days, we produce 10,000 L.

The production scale we are at, combined with the reasonable likelihood of doubling that scale, gives us ample material for commercial supply. The challenge now is ensuring consistency and safety of the product. One of the challenges in the bio-nanoparticle space is ensuring virus and adventitious agent safety. If there were inactivation technologies that were suitable for use with enveloped particles, that would be a huge advantage. That is one area we need advancements.

The other point speaks to comparability. The more complicated and the newer the modality gets, and the newer it is, the less understanding you start with. For the larger bio-nanoparticles, especially when they are relatively early in clinical progression, there is not a full sense of all the critical quality attributes (CQAs). It is important to define the likely CQAs early on and make the effort as a community to ensure CQAs are well understood to ensure comparability throughout process changes and batch.

Q What are the biggest challenges relating to the current toolkit – in particular, its scalability for commercial production when considering downstream processing and analytics?

DOI: 10.18609/cgti.2022.111

AH: In my experience, which is limited to production of an infectious viral vector itself, the downstream processing scalability has been relatively straightforward. There is certainly room for optimization, simplification, and improvement, but we are comfortable with the accessibility of the technology itself.

The more interesting challenge for our product type falls in the analytics. In any given situation, the variability in production is no higher than the variability in the analytical testing. There is room for improvement in understanding that range, the appropriateness of those ranges, and possibly looking to custom methods and consistency of outcomes. There is room for different manufacturers and analytical labs to support those types of activities to help these new molecules progress through the development pathway. The sooner we can start exploring those, the better.

VS: I agree that analytics present a more complex issue than downstream processing for lentiviral vectors. Downstream processing is relatively established with combinations of chromatography and tangential flow filtration (TFF). The only challenge in downstream processing is formulating the vector to avoid aggregation.

In terms of analytics, there are many challenges, for example variability in the titer determination. There is also no standard in the field that allows comparison of titer results between different companies. The results are often dependent on how the assay is performed. Another challenge is developing the potency assay, which can be difficult for these vectors, because they are used as an intermediate material to transduce T cells.

A third analytical challenge is the replication-competent lentivirus assay, as this assay is complicated, time-consuming, and expensive. In my view, it is not necessary, but the FDA and European agency still require this assay. It creates additional hardship and raises the price of the final product.

LS: The analytics bottleneck certainly applies when working on something relatively new. As a technology provider we always like to get into contact with customers who have specific issues, because there are many tools available within our company to help with these developments.

An example, which is close to our own purification products, is that when we develop a purification resin, those same ligands can be used for quantification and titer analysis, usually on any commercial analytical platform. Each analytical challenge can be overcome using the right tools.

Q Looking to the future, what would be the next-generation technologies for your specific platform areas that would represent a breakthrough?

VS: In terms of CAR T cells as a cell therapy product, next-generation technologies are being developed to shorten the time of manufacturing. Now, the time to manufacture T cells is between 7 and 10 days, and considering the time to test and release cells,

it often takes about a month from needle-to-needle for this product. That is challenging both in terms of pricing and for the patients, so it is critical to decrease it.

There are also developments in making allogenic CAR T cell products. Some companies are even trying to make lentiviral vectors that could be injected directly into patients without the necessity of making CAR T cells *ex vivo*. If this is successfully developed, it could be a huge advantage for the future.

AN: Single particle analysis would be a breakthrough, similar to how fluorescence-activated cell sorting has developed understanding of cell biology, allowing sorting for different markers. For exosomes, and this class of ~100 nm bio-nano particles, single-particle characterization would enable an understanding of the population you have and potentially enable the development of surrogates for potency. If you could subsequently sort those, that would be incredibly valuable because you could then directly connect potency to phenotypic properties of the particles.

AH: I agree with what's been said so far, and it touches on this concept of timeliness of information related to your production process. The quicker we can have readouts of the state of the process, whether that is the state of cell expansion, the infection process, or other elements depending on the molecule up for discussion, the quicker the overall production. Many of the analytical methods available at present are robust but time consuming, and only allow data gathering after a batch has completed.

The ability to get readouts mid-process that could be applied to decision making would provide an opportunity to optimize these biologics productions at exactly the right moment. For me, technology in this area that would be the most interesting development.

LS: In the purification and downstream area, one of the real breakthroughs would be if one could remove packed bed column technology. The volumes associated with new modalities are quite different than those in, for example, monoclonals or recombinant proteins, so that could make the area more amendable to this.

For example some new modalities could lend themselves to magnetic bead approaches like in cell therapy, where you move away from traditional purification steps.

Q What would be the key advances in innovation specifically for downstream processing and analytics?

AN: Robust particle sorting is technologically beyond the current technology. Affinity chromatography is a way to complement analytical characterization by sub-fractionating exosomes. Fusion of analytical techniques with the purification technology could be useful to drive potency higher or amplify selected properties.

Another unknown in analytics is what makes a potent particle. In viral vectors, where the potency per particle is relatively low, it is not always understood why this is. In exosomes, the reason behind the potency of the particles is also often unknown. Developing the characterization technology to enable that would be powerful.

DOI: 10.18609/cgti.2022.111

VS: One of the most important things in the lentiviral vector field is developing lentiviral vector standards that everyone can use in their lab, and qualify it there, using a titer assay.

Q What are the keys to successful collaboration between end users and bioprocess solution developers/providers, with a view to getting these new solutions introduced into processes?

AH: The key to any successful collaboration is clear communication. This means a clear understanding of both the requirements of the clients and the services available from the supplier.

Transparency around any roadblocks or bottlenecks leads to an efficient, smooth collaboration. If there is a circumstance where a group either is unfamiliar or uninterested in a certain scope of work, we can source the right partner for that collaboration and potentially pull teams together where possible. More generally, early conversations between stakeholders considering scope and scale allow providers to clearly see market needs and ensure they are solving a valuable unmet need.

LS: From our side, the focus is on openness and clarity. We have always been successful in working with customers to develop new areas. Our current product for AAV was fully developed together with a company in France and is now being used by most people working with and purifying AAV.

Collaboration requires openness, willingness, and the realization that certain advances will help the whole field. With these factors, there is no limit in terms of the products and areas that can be developed.

AN: Openness between companies like my own and vendors is happening. You need to have that trust to make breakthroughs. It has still been difficult to share externally, although this is changing as companies gain more confidence, and as technology advances. In the AAV field, the amount of collaboration is tremendous.

A successful collaboration requires openness and trust that allows you to use authentic materials, and transfer between sites. It is also important to build in time for iteration.

AFFILIATIONS

Allison Hagerman
Vice President of Product Development, Oncolytics Biotech

Aaron Noyes
Vice President of Integrated Drug Substance Development, Codiak Biosciences

Vladimir Slepushkin
Global Head of Manufacturing at MedTherapy Biotechnology

Laurens Sierkstra
Senior Director, Business Leader Purification at Thermo Fisher Scientific

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: *Allison Hagerman is an employee and stockholder of Oncolytics Biotech Inc. Aaron Noyes owns shares in Codiak BioSciences (CDAK) and has patent applications pending. He also holds published patents related to exosomes: W02022066928A3, W0202066898A2, W02022066934A2, W02021189047A3, W02021062290A1, W02021030777A1, CA3152478A1, W02020215010A1, W02020191369A1. Vladimir Slepushkin is an employee of MedTherapy Biotech, and a former employee of Autolus, Gilead and Novartis.*

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

ARTICLE & COPYRIGHT INFORMATION

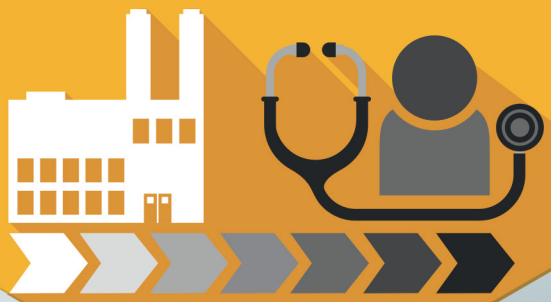
Article source: *This article is a transcript of a webinar, which can be found here.*

Webinar recorded: *May 10 2022;* ***Revised manuscript received:*** *Jul 12 2022;* ***Publication date:*** *Aug 5 2022.*

DOI: 10.18609/cgti.2022.111

CELL & GENE THERAPY INSIGHTS

Supply Chain Channel



Driving the digitization of cell & gene therapy supply chains

CELL & GENE THERAPY INSIGHTS

SUPPLY CHAIN CHANNEL:
Driving the digitization of cell & gene therapy supply chains

July 2022

Volume 8, Issue 6

COMMENTARY

Critical success factors to consider before digitizing a cell & gene therapy supply chain

August Zepka & Charles Wilfong

CELL & GENE THERAPY INSIGHTS

DRIVING THE DIGITIZATION OF CELL & GENE THERAPY SUPPLY CHAINS

CHANNEL CONTENT

COMMENTARY

Critical success factors to consider before digitizing a cell & gene therapy supply chain

August Zepka & Charles Wilfong

Digital supply chains are challenging to implement, especially in fast-paced and burgeoning industries. It is important to be thoughtful and intentional in determining key supply chain aspects, such as a delivery and operational culture, the roadmap, and a decision-making methodology; before initiating a transformation to digital capabilities. This article outlines some key elements and lessons learned for consideration that could make or break a digital transformation.

Cell & Gene Therapy Insights 2022; 8(6), 749–754

DOI: 10.18609/cgti.2022.115

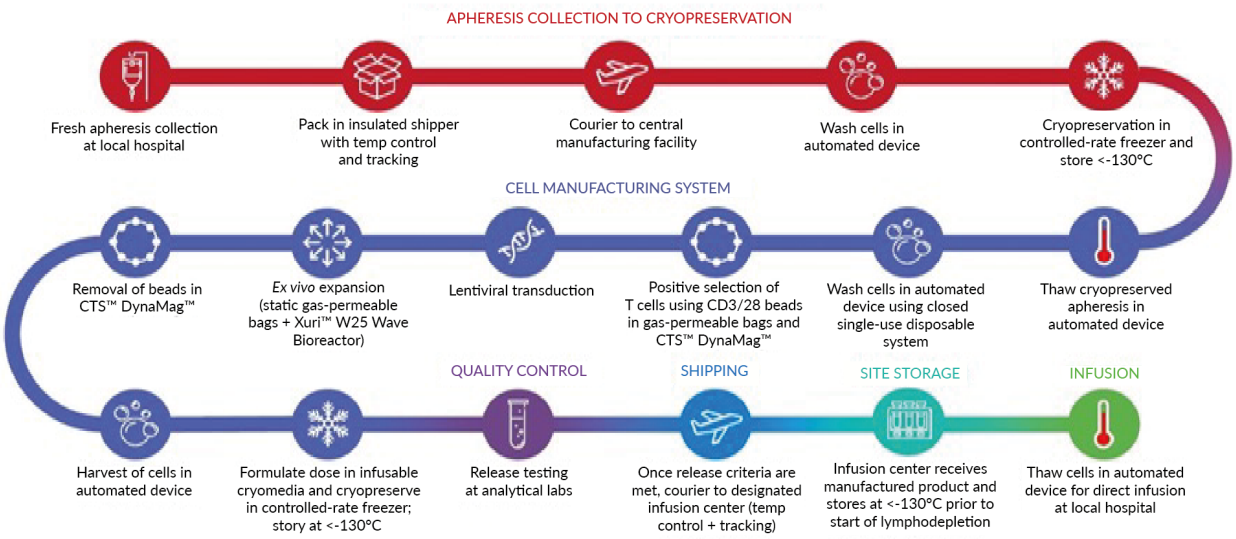
BACKGROUND

Planning, making, and delivering personalized autologous cell therapy products is complex and rapidly evolving. Digitizing the end-to-end supply chain offers real-time visibility into all aspects of manufacturing, which enables operational flexibility and unlocks efficiencies. Failure or lack of oversight during any step of the cell manufacture journey could impair the product and jeopardize timely patient treatment.

As an example, an autologous vein-to-vein cell manufacturing supply chain (Figure 1) encompasses cell collection from the patient, apheresis, and product administration. Throughout the process, cell storage,

FIGURE 1

Patient cell journey for autologous SPEAR T-cell products.



handling, and patient / product identity needs to be confirmed. This requires complex controls and digitization is key to achieving efficient scale and oversight.

"Early on in our development as a company, we recognized the importance of digitizing the patient journey," said John Lunger, Adaptimmune's Chief Patient Supply Officer. "While atypical for an early stage biotech to make such an infrastructure investment, we knew that managing the complex autologous manufacturing process would be impossible at even relatively small numbers without such capabilities."

Supply chain digitization fundamentally changed the way Adaptimmune operates. Digital capabilities improved the ability to understand capacity and demand, lowered cost of goods, formalized proper controls such as chain of custody and chain of identity, as well as provided the ability to adapt quickly to scheduling changes due to the urgency of patient treatment and care. The goal is to get the product to the patient as quickly and safely as possible.

Most organizations understand the benefits that a digital supply chain provides and want to make this transformation as well, and getting there can be challenging due to a wide variety of internal and external factors.

Some key external factors include lack of mature vendors and IT systems specifically designed for cell and gene manufacturing, unclear data standardization, bespoke system integrations and challenging pricing models for clinical-stage biotechnology companies. Although external factors are extremely important to understand and there are many challenges to overcome, this article will focus on the softer internal elements within an organization that can make or break a successful transformation to a digital supply chain.

CULTURE

Most start-up cell therapy companies can get by with manual processes due to less organizational complexity, small patient numbers in pilot trials, and the relative simplicity of the supply chain as typically outsourced to more established contract manufacture organizations. Interpersonal relationships among staff are enough to handle oversight, manufacture operations, compliance, and capacity needs. These manual processes do not easily scale and / or support cost efficiencies when multiple clinical trials across different product candidates are in play.

DOI: 10.18609/cgti.2022.115

Before initiating a digital transformation, a company should set aside time to align and agree on a target culture that best supports the journey from manual to digital process. Project management should not be confused with culture, and good project management cannot make up for poor culture. Culture cannot be formed organically. It needs to be established intentionally and thoughtfully by leadership, and continually reinforced throughout the organization. Formalizing a culture will shape behaviors and develop an ingrained understanding at all levels of the organization of how value is created for the company, patients, and partners through digitalization.

Considerations on culture include:

- Staff phenotypes – It is vital to hire and support staff who are resilient and can effectively deal with change, be willing to innovate while under pressure, understand the best balance of quality versus risk, and most importantly be supportive of each other. Phenotypes needed will evolve over time (some will disappear, new ones will be created), as manual processes give way to digital ways of working.
- Cross-functional teamwork – As organizations grow, departments get formed and functional heads put into place, which can easily lead to silo creation. Cross domain communication, alignment in execution and strong internal partnerships to achieve common deliverables across functional swim-lanes are critical. Trust, problem solving, willingness to disagree and commit, and compromise on methodology are principal elements to engrain into cross-functional operations.
- Achieving appropriate scale at the right time in the best way – Deep industry expertise is valuable, and often necessary to make efficient progress to digital. However, lifting and shifting playbooks / approaches from big pharma often conflicts with being nimble in resource constrained, timebound and cost-conscious smaller scale start-up and clinical-stage situations. Being too early in maturity can be frustrating, create unforeseen bureaucracy and stifle execution.
- Enterprise thinking – Not to be confused with cross-functional teamwork, understanding the what and the why of broader company aims is important to shape the 'how' of a digital eco-system. Independent functional strategies can easily create unnecessary complexity in methodology, increase cost and bureaucracy, cloud decision making and lengthen operational execution.
- Hands on mindset evolution – As manual processes evolve to digital processes, the work changes from data tracked in paper-based forms to more structured IT systems, which requires a different set of hands-on skills, outlook and experience. Being intentional in resourcing skills at the right time is key.
- Conflicting priorities / muti-tasking – In early-stage companies, staff usually wear multiple hats to fulfill the needs of a variety of roles. In a digital eco-system, some of these hats go away (become digital), while others evolve into deeper disciplines due to the demands of digitization.
- Process maturation – It is inevitable that digitalization drives formality on process, as functionality requirements and data flows need to be thoughtfully considered as a whole rather than piecemealed into a digital eco-system. It is important to decide how fast to mature process and how to build in flexibility where process cannot be matured easily. Digitizing too quickly could create bad digital processes.
- Change management should not be overly ad-hoc or over-engineered, yet needs to be formalized to ensure all parties understand what good end points look like.

ROADMAP TO STAND UP DIGITAL CAPABILITIES

Envisioning the end state early on and establishing the underlying delivery principles can

provide a common focus for the organization and a mutual understanding of the milestones to get there. Appropriate business needs and key milestone triggers should drive prioritization. Organizations must consider their unique business processes, identify the information capabilities that are needed to support those processes, and prioritize the implementation of those capabilities. It is important to understand and accept which processes are not really that unique. This will allow the organization to focus on the unique aspects of the business, and leverage what already exists for established processes.

The strategy should aim to establish flexible IT platforms and solutions which align to a company's short- and long-term goals. The strategy should account for supporting immediate needs with an ability to evolve rationally to future needs as well.

Some considerations when creating a roadmap:

- Process agility – Each process flow should be mapped out to define key data that needs to be managed across numerous internal and external systems, as well as the interactions between processes. Due to the evolving nature of cell manufacture, requirements may not be well understood so tolerance of less than perfect solutions in the beginning should be acceptable.
- External IT tools – IT systems used by external vendors such as contract manufacturers, logistics couriers and clinical sites will book-end requirements. These vendors deal with a variety of customer tools, so having a good understanding of the boundaries and limitations of their technical landscape and capabilities is essential.
- Iteration is your ally – Interim 'throw-away' solutions and continual use of manual process should be acceptable in the short term, where risk acceptance and scalability factors allow. Research emerging technology solutions because traditional tools may not be right sized for your organization and / or can be too expensive and complex to adapt to bespoke needs.
- Process maturity readiness – You need to ask yourself, 'Are we ready for the structure and discipline required to make the change'. As mentioned above, the transformation is a journey, it cannot be realized overnight; therefore prioritization is key.
- Timelines – Do not underestimate the time it takes to deliver. There are many moving parts to coordinate with making cell therapies in this rapidly evolving environment. In lieu, explicitly deciding on a phased versus big bang approach to deploying digital capabilities reduces risk on achieving immediate needs versus longer term goals. In addition, change management complexities needs to be a major consideration when determining the 'end state'.
- Decisions will evolve – There will always be constraints with both budget and people resources. In early start-up mode, things are usually fast-paced and each person has multiple jobs. Careful thought should go into decisions such as in-source versus out-source, buy versus build, and in-house versus cloud. These decisions should not be taken lightly, and will change over time as the organization matures and evolves.

DECISION MAKING & ENABLING MACHINERY

In many ways, digital transformation is about people and less about IT technology. Standing up technology does not guarantee a successful digital transformation. Making good decisions can help to reduce implementation risk and confusion among functional, project and enterprise goals. One of the most important mechanisms that fuels effective decision making is the underlying machinery that enables the decision process. Enabling machinery requires adequate formal structure to guide decision rights (who owns which decisions), how decisions get made, timing of decisions and why certain decisions are made (or not made). The appropriate balance between ad-hoc and formality is largely dependent upon the experience and maturity of the people involved. A successful

DOI: 10.18609/cgti.2022.115

supply chain transformation involves the collective effort from Business Resources, Information Technology, and Quality Oversight.

Some considerations on decision making structures:

- Effective decision making involves making sure that the organization is solving the right problems. Do not get caught in the trap of automating a poor process or implementing solutions that will make one person's job easier. The solutions must provide significant business value for the entire department or organization.

- New inexperienced workforce – There are very few deep experts in the cell therapy space. Everyone has their individual perspectives, and experience can be leveraged but new ways of thinking are welcome and needed. Be open to innovative ideas, as collectively we are all still learning together.

- Ways of working – Requires a shift in organizational behavior and talent management. This will involve retraining staff and adding additional skill sets to your workforce over time. Workforce talent is not always fungible in new situations; in that success in manual processes does not predict success in a digital eco-system. Maturity, experience, expertise, and attitude are key elements to be considered in digital staffing models. Digital operational management skills are challenging to measure, and essential to delivering consistent outcomes on time and on budget.

- Decision makers – Clearly define who are the decision makers. Be willing to listen to new ideas but in the end, decisions need to be made, understood, and clearly communicated with commitment and buy in across the organization. Value creation and enterprise thinking should be at the core of any decision, especially unpopular decisions.

SUMMARY

Over the last 5 years, Adaptimmune has implemented in-house bespoke solutions, larger traditional systems, and new IT tools specifically designed for cell manufacturing to create an integrated digital capability. No single IT system provides all the necessary features and functionality. In addition to culture, roadmap, and decision machinery, cyber-security, data protection regulation, business continuity, architectural fundamentals and disaster recovery should be considered primary requirements due to the importance of the cell therapies and the urgency of delivery of product for patients.

The cell manufacturing industry is maturing, and traditional IT vendors seem eager to work with manufacturers to re-configure their tools specifically to the unique challenges of the cell manufacturing market. Vendors can provide advice and IT solutions, but each company must be in control of their destiny. Leadership of the digital transformation is not something that can be easily outsourced, as each company is unique and will likely require some bespoke, home-grown solutions along the way.

There are many elements to a successful digital transformation, and at the center of it all is the people responsible for making it happen. The digital part is the means to the end. The transformation part is the challenge, and critical to get mostly right to create sustainable value.

AFFILIATIONS

August Zepka,
Senior Director Information Management, Adaptimmune

Charles Wilfong,
Vice President Information Management and Facilities, Adaptimmune

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: *Both authors are employed at, compensated by, and receive stock/options from Adaptimmune as their employer. The authors have no other conflicts of interest.*

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

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited.*

Submitted for peer review: *May 24 2022;* ***Revised manuscript received:*** *Jul 18 2022;* ***Publication date:*** *Jul 28 2022.*

DOI: 10.18609/cgti.2022.115