EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Quality Innovation Group (QIG)

Listen and Learn Focus Group (LLFG) on Personalised Medicines – meeting report

8 – 9 April 2025

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Introduction

The Quality Innovation Group (QIG) is a multi-disciplinary group that brings together expertise in both quality assessment and Good Manufacturing Practice (GMP) inspections, covering both chemical and biological medicinal products. Its formation in 2022 targeted one of the key goals of the EMA's Regulatory Science Strategy to 2025, and aims at advancing regulatory science by fostering research and innovation, as well as facilitating the seamless integration of cutting-edge scientific developments and emerging technologies into medicines development.

The QIG serves as the primary point of entry for developers to discuss innovative CMC approaches within its scope. Its goal is to contribute to the development of a forward-looking and predictive EU regulatory framework to enable implementation of innovative manufacturing technologies which will ultimately benefit patients across the EU. In addition, the QIG actively collaborates with other regional regulatory agencies to support the broader adoption and harmonisation of these technologies on a global scale.

The increasing understanding of interindividual variability between patients highlights the need for more personalised medicinal products, designed and manufactured specifically for small, well-defined patient subgroups or even for individual patients. This includes the development of medicinal products using the patients' own cells e.g. for bio-printing of tissues, or by introducing a therapeutic gene, or using tumour tissue to define patient specific neoantigens for immunotherapy. These so-called personalised medicines constitute a paradigm shift away from the traditional 'one size fits all' approach, towards innovative strategies, based on the understanding that each patient is biologically unique. The ultimate aim is to conceive individually tailored products that provide significant clinical benefit. While tailored manufacturing is well established in the manufacturing of consumer goods, the adoption of the individualised manufacturing in the pharmaceutical sector marks a major departure from traditional pharmaceutical manufacturing methods. Also, the current regulatory framework is primarily fitted to support the manufacturing of medicines at high-scale for large patient groups, rather than personalised therapies produced on a smaller, patient-specific scale.

In response, QIG organized a LLFG meeting to support stakeholders' developing personalised medicines on scientific and/or regulatory challenges they might be facing with the manufacturing and quality control of these medicinal products. These include but are not limited to: manufacturing of small batches, small numbers of batches or even n=1 batches, platform technologies or 3D printing/3D bioprinting for manufacturing of personalised medicines. Also, rapid analytical methods (e.g. for sterility or potency testing) needed for personalised medicines with a short shelf life or where clinical considerations necessitate rapid release were proposed to be discussed.

The focus of the meeting was on quality aspects. Non-clinical and clinical aspects were outside of the scope of this meeting.

Legal and regulatory aspects were also outside of the scope of this meeting.

Stakeholders were invited to submit abstracts from real, mock or generic case studies of personalised medicines manufactured for small, individual groups or for individual patients. These case studies were intended to illustrate the scientific and/or regulatory challenges encountered during the pharmaceutical development, manufacturing and quality control, along with their proposed solutions. The focus was on highly personalised approaches in manufacturing, for example:

1. Manufacturing of autologous cell-based products (which may include genetic modification) using a manufacturing process that foresees individual adaption of critical process parameters,

aiming to meet critically defined product quality attributes that have been correlated to better patient outcomes.

2. Manufacture of personalised or individualised medicines on the same manufacturing platform ('one patient/group of patients-one product').
3. Individualised neoantigen-based immunotherapies. The bioinformatic aspects of identifying patient specific tumour neoantigens have been highlighted as a specific challenge to be considered.
4. 3D Printing or 3D bioprinting manufacturing.

The event was attended by 155 participants from industry, academia and regulatory authorities, including representatives from the European Commission Joint Research Centre, EDQM, US FDA, PMDA and Swissmedic.

The meeting comprised the following sessions:

Tuesday, 8th April 2025

1. Setting the scene: Personalised Medicines, QIG
2. Session 1
   - 2.1. Artificial Intelligence-driven, Decentralized Production for Advanced Therapies in the Hospital, AIDPATH
   - 2.2. Advancing ATMP Manufacturing: Scientific Challenges and AI-Driven Solutions, PDA
   - 2.3. Personalised T cell therapies, including QC testing of small volume products and appropriate potency testing strategies, Leiden Medical Centre
   - 2.4. Next Generation Sequencing for Individualized Therapies, Roche
   - 2.5. An innovative, fully-synthetic DNA platform for next generation Cancer immunotherapy, Neomatrix
   - 2.6. Real-time Release Testing by In-line Soft Sensors for mRNA-LNP Drug Product, Moderna
   - 2.7. Panel discussion
   - 2.8. Closure of the day

Wednesday, 9th April 2025

3. Session 2
   - 3.1. 3D Printing Implementation in Hospitals and Pharmacies: Use of commercialised pharma-inks, Gustave Roussy and FABRX
   - 3.2. How to safely implement 3D printing processes to produce personalized solid oral forms with decentralized production (Point of Care (POC) settings), NwEUam
   - 3.3. Manufacturing Process of Antisense Oligonucleotides for N-of-1, Medicines Made to Measure
   - 3.4. 4.4. Accelerating validation and adoption of ARMMs for innovative therapies, NIMBL, NIST and BioMérieux
   - 3.5. Panel discussion

4. Conclusions and closure of meeting

This report includes the abstracts as provided by the speakers (reflecting their view), and a summary of the discussions held at the LLFG including views from stakeholders and/or regulators.

1. Current scientific understanding and regulatory perspective on Personalised Medicines

There is currently no globally harmonised legal definition of personalised medicine[1]. Within the European Union, the term is often used interchangeably with precision medicine or stratified medicine, referring to approaches that tailor treatment based on an individual's genetic, molecular, and lifestyle profile. The EU's Personalised Medicine Action Plan seeks to integrate genomics, biotechnology, and health data to deliver more targeted and effective therapies. At the international level, the International Council for Harmonisation (ICH) addresses key components of personalised medicine—such as biomarkers, genomic testing, and targeted therapies—through various guidelines. Notably, ICH E15 covers pharmacogenomics, while ICH E2E focuses on the use of biomarkers in drug development. These frameworks are critical for ensuring the safety and efficacy of personalised treatments across borders. The World Health Organization (WHO) also supports precision medicine through its global digital health strategy (2020–2025), which emphasizes capacity-building and the development of guidance to support personalised care worldwide. Such global efforts aim to make medical innovation more inclusive and accessible to all.

The fundamental shift from a 'one-drug-fits-all' model to individualised treatment is the essence of personalised medicine. This approach offers the promise of improved clinical outcomes, reduced side effects, and more efficient use of healthcare resources by focusing on what works best for each individual patient. Central to this model is advanced diagnostics. The use of genetic, proteomic, and metabolomic biomarkers allows for highly precise disease identification. This enables clinicians to choose therapies that are most likely to be effective for a specific patient profile. Multidimensional datasets, like those from next-generation sequencing, can even become part of the manufacturing process in personalised therapies. This underscores the need for platforms that can manage diverse data inputs while maintaining consistency and confidentiality.

In the absence of standardised legal or scientific definition, the terms precision medicine, personalised medicine and individualised medicine are frequently used interchangeably[2,3]. Clarifying these distinctions is important to ensure that all parties share a common understanding during discussion. Within this context, medicinal products and therapies could be categorised according to their degree of customisation, giving rise to three distinct concepts:

- **Precision medicine (low customisation),**
- **Personalised medicine (moderate customisation),** and
- **Individualised medicine (high customisation).**

[1] Galasso, I., et al. Different names for the same thing? Novelty, expectations, and performative nominalism in personalized and precision medicine. Soc Theory Health 22, 139–155 (2024). https://doi.org/10.1057/s41285-024-00203-8.

[2] Martínez-Jiménez JE et al. A review of precision medicine in developing pharmaceutical products: Perspectives and opportunities. Int J Pharm. 2025;670:125070. https://doi.org/10.1016/j.ijpharm.2024.125070.

[3] Brew-Sam N et al. The current understanding of precision medicine and personalised medicine in selected research disciplines: study protocol of a systematic concept analysis. BMJ Open. 2022; 12(9): e060326. doi: 10.1136/bmjopen-2021-060326.

Based on the scientific publications[2,3] the three groups may be interpreted as outlined below. As mentioned previously, this reflects the current scientific discourse in the field but does not represent legally binding definitions from a regulatory perspective.

Precision medicine, also known as targeted medicine, takes a population-based approach. Treatments are designed for groups of patients who share specific genetic traits or biomarkers. For instance, cancer therapies developed for patients with HER2 overexpression, or defined genetic mutations fall under this category.

Personalised medicine offers a deeper level of customisation by tailoring therapies to subgroups based on individual genetic profiles and/or lifestyle factors. Examples include selecting a diabetes treatment aligned with a patient's genetic makeup or administering autologous CAR-T cell therapy using a patient's own cells.

Individualised medicine represents the highest level of customisation, offering one-to-one therapies developed for a single patient. Examples include cancer immunotherapies based on the unique genetic sequence of a patient's tumour, patient-specific TCR-T cell therapies or, induvial 3D-printed tablets.

Each of these innovations represents a significant advancement in designing and delivering treatments tailored to the unique needs of individual patients. As the degree of customisation increases, so do the challenges in development and regulatory approval. However, these challenges have to be balanced against the potential for significantly increased patient benefit.

To support these innovations, manufacturing processes must evolve. Advanced manufacturing approaches enable precision, scalability, and adaptability, key elements for delivering personalised treatments efficiently and safely. Lastly, regulatory frameworks are evolving, with new and upcoming guidelines addressing advanced therapies, mRNA vaccines and immunotherapies, oligonucleotides, or phage therapy. These will be crucial in ensuring that innovation is met with appropriate quality, safety, and efficacy standards.

In conclusion, the future of personalised medicine holds immense potential, but it also requires cross-sector collaboration, robust data infrastructures, and adaptive regulatory frameworks.

2. Session 1 summaries as provided by the presenters

2.1. 'Artificial Intelligence-driven, Decentralised Production for Advanced Therapies in the Hospital', AIDPATH.

AIDPATH (Artificial Intelligence-driven, Decentralised Production for Advanced Therapies in the Hospital) is an EU-funded project aiming to improve the manufacturing of CAR-T cell therapies by enabling decentralised, hospital-based production that is both scalable and personalized. The project aims to address key barriers to wider clinical implementation of autologous CAR-T therapies, including high costs, long production times, and the need for highly specialized centralized facilities.

At the heart of AIDPATH is a high-automation manufacturing process that integrates fluidic and robotic operations with real-time monitoring of critical process parameters (CPPs). The system includes embedded single-use sensors that capture high-frequency data on glucose, lactate, pH, dissolved oxygen and carbon dioxide, temperature, and other metabolic and environmental markers. These real-time data streams feed into both at-line and in-line analytics to support continuous monitoring, quality control, and adaptive manufacturing.

The AIDPATH platform is built on a flexible, modular, and manufacturer-agnostic architecture, meaning it is not tied to any specific equipment provider and can integrate diverse components tailored to each

clinical site's infrastructure. This modularity is crucial for decentralized deployment in hospitals across Europe, supporting local GMP-compliant production of patient-specific CAR-T cell therapies.

A cornerstone of the platform is its AI-powered digital twin, a dynamic, mathematical model of the CAR-T cell expansion process. Trained on historical data from bioreactors and validated with high-frequency sensor input, the digital twin simulates and forecasts CAR-T cell growth in real time. This enables a shift from fixed-duration expansion protocols to a patient-specific, adaptive manufacturing strategy, ensuring that harvesting occurs precisely when the cell population meets therapeutic thresholds for each individual.

Another unique innovation in AIDPATH is the incorporation of metabolomic profiling, allowing for a deeper understanding of T cell biology during the manufacturing process. By analyzing metabolic markers at different stages of T cell selection and expansion, the system can identify signatures associated with exhaustion or long-term persistence. In the future, this might allow the process to be adjusted in real time to favor T cell phenotypes with improved in vivo performance, increasing the overall potency and durability of the final CAR-T product.

To support continuous optimization, AIDPATH includes a secure, integrated data platform (LogiqSuite) that connects manufacturing, clinical, and patient-reported data. The data platform couples production data directly to patient outcome data. This creates a feedback loop with de-identified privacy-unenriched data for continual learning in the AI cases. These AI cases are used to refine future manufacturing strategies. The system also supports advanced features such as hospital resource management, production scheduling, and clinical decision support.

Moreover, personalised risk-benefit based therapy improvement could be added in the future. These approaches require regulatory frameworks that can accommodate continual learning AI systems, adaptive control strategies, and decentralized manufacturing processes. While the idea of a regulatory sandbox is gaining traction in some sectors, it is not yet a feasible option in this context. Therefore, a close and sustained collaboration with regulatory authorities is essential to ensure that innovative models can be safely and effectively translated into clinical practice.

2.2. 'Advancing ATMP Manufacturing: Scientific Challenges and AI-Driven Solutions', PDA.

In the development of ATMPs, one of the main challenges is to control the variability of the starting material and biological manufacturing processes. This variability affects the robustness, sustainability and predictability of the product, so it is very important to develop tools that allow better control and adaptation of the manufacturing process. By understanding the elements of variability early enough, we can focus better on the most critical parameters and make more robust cost-effective manufacturing strategies.

AI can be a very useful tool to overcome this challenge, supporting us with predictive models, early manufacturing quality control and clinical translational (patient subgroup identification/ treatment window based on patient signature) investigations. However, for AI to work properly, it is necessary to have strong and well-planned data architecture. This means data must be clean, organized, and collected in the right way from the beginning, following data integrity guidelines. Also, early engagement of data scientists and SMEs at onset of the projects is essential. If the data is not well structured or lacks important information (i.e. out of specification data is also valuable data), even the most advanced AI will not give meaningful results.

One of our biggest concerns is that data is very often compartmentalized in data silos. Pharma and biotech industry usually keep their data isolated, without being connected or integrated. This creates

data silos, and it is difficult to get complete control of the process, particularly in the field of ATMPs, where holistic understanding across multiple disciplines is a must to understand often highly complex diseases or treatments.

One solution that we propose is to foster partnership (i.e. not only between departments in the same company, but also between the industry and regulatory authorities). EMA has already published the "*Reflection Paper on AI"*, which is an excellent first step. However, we believe that more partnerships to build more detailed guidelines and practical frameworks are still needed across the different aspects of product life cycle (starting material, control strategy, process improvement, potency bridging and patient clinical response) to help implement AI in an integrated unbiased and efficient way. This includes how to validate and train/test AI models, how to adapt them over time (i.e. detect, monitor and correct data drifts) and how to make sure data is shared in a responsible but useful way.

Finally, if we want to really use the potential of AI in ATMPs, the regulatory environment must grow at the same pace as AI technology. This is not something one company or institution can do alone, it will require collaboration between regulators, industry, and technology experts. We need to build together a future where data is not kept in silos but shared with responsibility to support science, innovation, and better treatments. This is how we can support ATMPs like Cell Therapy to reduce manufacturing costs and subsequently reach more patients.

2.3. 'Personalised T cell therapies, including QC testing of small volume products and appropriate potency testing strategies', Leiden University Medical Centre.

T Cell Receptor (TCR)-T cell therapies are highly individualized therapies. Potential TCR targets can represent any tumour-associated peptide that is presented by HLA. Contrary to CAR-T cells, TCR-T cells are HLA-restricted: the TCR recognizes the HLA presenting the tumour-associated peptide as a single complex. Rare HLA types presenting rare tumour-associated molecules render some targets truly unique (N=1), with unique patient specific batches, and subsequent challenges to manufacturing development.

Manufacturing of TCR-T cells requires a gene insertion, which can be performed either through lentiviral transduction or by non-viral CRISPR/Cas9-based gene editing using a double-stranded (ds) DNA repair template. The viral vector or dsDNA template are individualized starting materials that are unique for each patient. A major scientific challenge is the requirement of exhaustive quality control (QC) testing of these starting materials. Small scale and flexible production of starting materials is a prerequisite for the economic feasibility of individualized therapies. However, for exhaustive QC testing large quantities of the starting materials are needed. Moreover, some QC tests with long lead times can be incompatible with clinical timelines due to limited life expectancy of patients.

A potential solution is to balance quality management activities using a risk-based approach. Exhaustive QC testing of starting materials is especially important for products that serve a large population (risk to many), whereas the balance tilts for individualized therapies (risk to few): limited QC testing may increase uncertainties about starting material quality, but might still result in a favourable benefit/risk ratio for the individual, in certain clinical settings, depending on the availability of alternative treatment options. It is proposed to identify QC tests for QA that have a low risk/occurrence rate and balance the benefits of these tests against timeline and economic feasibility of the therapy development (i.e. how long does a test take and how much material does it require for how much *additional* risk reduction?). Tests with a low added benefit, or a high cost-to-risk-reduction ratio (e.g. large quantities of material spent for a small additional risk reduction, or on mitigating a highly improbable event) are subsequently nominated for alternative mitigation strategies or surrogate

measures, where possible, or may be considered for exemption with proper justification. An example of such a test would be replication-competent lentivirus testing, which in the case outlined is incompatible with timelines and requirements for large volumes of viral vector material.

Summary of Perspective:

- **Economic feasibility** is a real risk, limiting patient access to potentially curative therapies
- Risk is highest for personalised therapies: manufacturing and development costs per patient is higher compared to manufacturing for large groups
- **Unavailability of a treatment could be a risk to the patient**
- **Assess safety with availability in mind:** the risk-benefit scale tilts differently for N=1 or N=very few patients. Concept of 'Risk to One' vs. 'Risk to Many'
- **Some risks are more relevant than others** – focus mitigation on relevant risks
- **De-risk using Quality by Design** and platform validation – more emphasis on production method/controlling the process, instead of individual batch qualification can reduce QC costs per batch without compromising quality

2.4. 'Next Generation Sequencing for Individualized Therapies', Roche.

The Roche presentation introduced the context of personalized therapies and Next Generation Sequencing (NGS) including an overview of Ex Vivo CAR T Cell Therapies and individualized neoantigen specific therapies, and potential applications for NGS as a powerful multi-attribute analytical tool. The typical workflow of a NGS method, as well as End-to-end NGS QC metrics and the question of industry-wide reference standards were discussed. A general framework for NGS validation was introduced, followed by two short case studies, NGS for Nucleic Acid Materials analytics as well as NGS for adventitious virus testing.

For regulatory challenges, four topics were discussed:

- **Risk-Based GxP Regulations for various NGS applications**

  Depending on the intended use of the NGS data, a variable level of control and validation is required. The evaluation of the control level should be phase appropriate, and the applicable GxP framework would depend on the decision that is taken based on NGS data. Nonetheless, careful and tight control needs to be kept on the sampling, handling, sample preparation and throughout the workflow with complete traceability between samples throughout the final manufacturing process and administration of the product. For NGS used to determine potential viral contaminants, on the other hand, the same framework applies as for any other QC release testing.

- **The Validation Framework for NGS QC Release Testing**

  The regulatory and quality frameworks need to keep pace with the diversity of technical approaches and rapid evolution of NGS technology. Where available and appropriate, relevant guidelines and requirements should be leveraged and it is noted that interpretation of ICHQ14 and ICHQ2 (R2) requirements is key for setting right CQAs based on the specific NGS application. It is important to note that the NGS assay and data analysis pipelines require an inter-dependent validation process along with the sequencing platform. Therefore, leveraging appropriate QC metrics and reference controls as early as possible in the product life cycle can better inform and enable robust validations of NGS based assays as programs mature.

- **Guidance on Appropriate NGS Assay Sensitivity Specifications**

  Because NGS methods may have different method sensitivity when switching from a conventional method, NGS assay sensitivity may not match expected or previous results from conventional methods. Use of an appropriate thresholding specification for impurities testing by NGS should be considered depending on assessed risks, also when used for virus testing to avoid false positives and false negatives. The presenter mentioned that, in the case of an unexpected signal, there is high level guidance in Ph. Eur. 2.6.41 on an investigation process to verify if the NGS signal is a false-positive result before additional testing using orthogonal methods. In this GxP sensitive area further clarification of regulatory expectations and also for notifications to authorities, would be desirable.

- **Use of NGS for the Detection of Viral Extraneous Agents**

  For this QC-like setting, it is very positive that per ICH Q5A (R2), NGS can replace conventional virus detection assay(s) without a head-to-head comparison as long as the method is suitable for its intended purpose. Still, the use of analytical reference materials as an alternative to WHO International Reference Panel reference materials should be acceptable based, maintaining similar characteristics of the panel. In targeted approaches alternative panels are also allowed based on risk assessment outcome and the specific NGS technology application. As for the use of controls in the Routine Assay: For transcriptomics approaches, the use of synthetic RNAs and a defined number of virus-infected cells as a reference standard. Nevertheless, the latest is currently not available commercially.

2.5. 'An innovative, fully-synthetic DNA platform for next generation cancer immunotherapy', Neomatrix.

Neomatrix is an advanced biotechnological platform aimed at developing next-generation cancer immunotherapy through a fully synthetic DNA approach. This novel technology outlines a comprehensive 6-week process from patient sample collection to personalized immunotherapy delivery.

The manufacturing begins with the identification of the tumour neoantigens by standardized sample collection, ensuring high-quality tissue and blood samples for genetic sequencing. This involves DNA and RNA extraction from blood and FFPE tissue, with quality controls for tumour content and output requirements for sequencing depth. The sequencing process enables identification of tumour-specific mutations used to design Neoantigen Cancer Vaccines (NCVs). Neoantigen selection is managed by proprietary software, which chooses 20 high-affinity neoantigens based on MHC class I and II binding predictions and mRNA expression data. The chosen neoantigens are then used to assemble personalized immunotherapy encoded in synthetic DNA.

Neomatrix's Neo-Lin synthesis employs an entirely enzymatic, plasmid-free process, avoiding bacterial contamination and antibiotic resistance. The synthesis achieves high fidelity and is suited for complex DNA sequences. Manufacturing is carried out in a UK-based GMP-certified facility using ISO 7 clean rooms and single-use systems. Batch sizes are flexible, ranging from 50 mg to 10 g, ensuring rapid and tailored production. Following synthesis, the Fill and Finish phase is conducted in the Netherlands. This includes sterile filtration, filling, validation of release tests, and logistics coordination. The final drug product is distributed across Europe and claimed to be evaluated under stringent quality controls such as sterility, identity, purity, endotoxin levels, and container closure integrity.

The delivery of the cancer immunotherapy drug product is utilised by Electro-Gene-Transfer (EGT), a method that transiently permeabilizes the cell membrane to enable DNA entry, leading to antigen

expression and immune activation. EGT is already applied in applications like electro-chemotherapy and supported by devices available across Europe.

According to the company, regulatory and scientific challenges are addressed, including defining GMP boundaries, optimizing logistics, and shortening release times. During the presentation, questions were raised regarding AI/ML tools like the applied algorithm-neoepitope selection software and whether external quality accreditation is required. Additionally, discussions focused on the level of detail needed in DNA topology proof and detection of residual synthetic enzymes in the final product. The potency assay is another critical element, correlating in vitro DNA expression (mRNA or protein) with immune response in vivo was considered important to substantiate the relevance of the set specifications. Since each immunotherapy is unique and lacks a universal tag to monitor plasmid derived protein levels, expression is confirmed via quantitative RT-PCR. The company proposes adopting RNA-based assays to streamline batch validations.

The company claimed that stability studies show the DNA immunotherapy is robust, maintaining potency after storage at -20°C and even under stress conditions (up to 65°C for 20 days). The proposed product's shelf-life would be >6 months, and logistics support includes freeze-thaw validation and rapid sterility testing. Each batch contains 70 vials, with detailed allocations for patient doses, backups, retention, testing, and stability trials.

In conclusion, Neomatrix claimed to present a scalable, rapid, and safe solution for individualized cancer immunotherapy.

2.6. 'Real-time Release Testing by In-line Soft Sensors for mRNA-LNP Drug Product', Moderna.

The presentation showcased a Process Analytical Technology (PAT) approach using soft sensors to enable Real-Time Release Testing (RTRT) for mRNA-LNP Drug Product, focusing on Moderna's individualized neoantigen therapeutics platform. This approach is designed to address critical challenges in the production of mRNA-LNP therapeutics, such as the quality control (QC) burden and the tight timelines inherent in scaled-out, small-batch manufacturing processes of personalized medicines. Traditional off-line testing methods, such as osmolality measurements, require use of limited material as well as being time-consuming, creating bottlenecks in the manufacturing workflow. By integrating soft sensors, this approach aims to replace these traditional methods with non-invasive, real-time alternatives that improve both efficiency and scalability.

The concept of soft sensors is rooted in their ability to predict key quality attributes—such as osmolality—using in-line measurable variables like refractive index (RI) and UV absorbance. These sensors rely on statistical models that align with the definitions outlined in ICH Q13, allowing them to either replace or supplement physical measurements. The approach represents a significant shift toward data-driven decision-making in pharmaceutical manufacturing. To develop robust soft sensor models, a comprehensive Design of Experiments (DoE) using mRNA-LNP components was performed revealing strong correlations between RI, osmolality, and critical formulation components such as sugar and LNP content. By combining RI and UV absorbance data, accurate osmolality predictions were achieved, highlighting the potential of these soft sensors to provide reliable, real-time quality data.

The implementation of the presented PAT approach was aligned with industry standards, including validation protocols based on ASTM E2617-10, ensure both qualitative and quantitative reliability of the soft sensors. The strategy emphasized seamless process integration, lifecycle management, and scalability, all of which are essential for modern pharmaceutical manufacturing. These considerations

were designed to improve the speed and efficiency of QC testing but also to support the broader adoption of Industry 4.0 principles, such as digital integration, automation, and advanced analytics.

In the context of mRNA-LNP drug as personalized medicine the impact of this approach can be significant for the manufacturing of products, where speed and adaptability are critical. By significantly reducing QC time and minimizing the use of material for testing, the soft sensor-based PAT framework enables faster and more cost-effective production. The integration of digital tools and data-driven methodologies supports the transition toward a more efficient, and scalable manufacturing process, also addressing future demands for high-quality, personalized therapeutics.

2.7. Panel discussion (day 1)

The Listen and Learn Focus Group (LLFG) was highly informative and provided examples of innovative developments by industry/academic stakeholders, as well as the scientific and regulatory challenges associated with the manufacture of personalised medicines. Presentations from industry and academic experts on day 1 highlighted a broad range of case studies and emerging technologies, including advanced therapy medicinal products (ATMPs), the use of artificial intelligence (AI), patient specific identification of tumour-neoantigens and next-generation sequencing.

As personalised and especially individualised medicines often originate from academic research and/or start-ups with strong academic affiliation, there is a clear need to enhance the communication of fundamental regulatory concepts to audiences less familiar with regulatory frameworks. A shared understanding of key regulatory/scientific concepts, such as consistent manufacturing or product comparability, and the use of common language between regulators and developers is essential. Early clarification of these concepts facilitates more robust and efficient development and regulatory compliance. It also supports better project design and increases the likelihood of successful progression toward market approval.

The following points summarise the key insights and outcomes from the panel discussion with stakeholders and regulators. While not presented in chronological order, they reflect the main themes and findings:

- Industry representatives encouraged regulators to consider the critical manufacturing and regulatory challenges with the manufacturing of individualised CAR-TCR-T cell products and other ATMPs. These challenges include the implementation of adaptive manufacturing, the use of AI tools and digital twins, decentralised manufacture, and the integration of data from multiple sources. As these areas are still evolving it is crucial for both developers and regulators to keep pace with advancements and maintain ongoing dialogue to effectively address these challenges.
- In this context, regulators emphasised that when applicants propose novel manufacturing approaches involving complex regulatory issues and seek additional regulatory flexibility, it is important to demonstrate that these innovations offer clear benefits to patients beyond existing approaches. This expectation is also described in the CHMP Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need (EMA/CHMP/BWP/QWP/IWG/694114/2019).
- Developers were encouraged to engage in scientific advice meetings and other regulatory early interactions like ITF meetings to foster an open exchange of ideas. Such ongoing dialogue enables regulators to identify priorities for developing additional regulatory tools when necessary, helping to ensure that safe and efficacious innovative therapies reach patients.

- The AIDPATH consortium suggested that a regulatory sandbox could be a valuable mechanism for exploring future regulatory pathways. Regulators noted that while a regulatory sandbox might be considered in future EU legislation, it remains important to work within the current regulatory framework. A number of flexibilities already exist under current legislation, and developers are encouraged to make full use of these available tools.
- Regulators acknowledged the specific challenges posed by validation of dynamic, AI-controlled manufacturing processes. They also highlighted that such data-rich approaches are well-suited to quality-by-design (QbD) and design space methodologies. For instance, if outer process parameter ranges are well-defined, it is feasible to adapt manufacturing processes on a batch-by-batch basis to accommodate patient-specific factors. From a regulatory standpoint, it is possible to design appropriate validation protocols to support personalised medicines, even when novel manufacturing technologies are involved. In cases where AI tools or algorithm-based controls are used, it must still be clearly demonstrated that the final product meets quality standards to ensure safety and efficacy. For example, where metabolic parameters are used for process control it must be shown that they are relevant for ensuring the quality of the final product.
- Available guidance for personalised medicine, such as autologous ATMPs, generally addresses key aspects in active substance manufacturing, finished product manufacturing, and quality development. However, supplementary guidance is needed to address the unique challenges posed by highly individualised products. These include:
  - Establishing the principles for demonstrating product consistency, despite patient-specific variability;
  - Developing suitable potency assays;
  - Designing identity tests that are suitable for drug product release and allow for meaningful analysis, given the individualised nature of the product.
- In cases where the individualisation extends to the starting material used in the manufacturing of the drug product, such as a viral vector coding for a patient-specific TCR manufactured exclusively for a single patient, regulatory flexibility may be warranted. Specifically, the use of prior knowledge (e.g. data from related products), in combination with thorough characterisation and a robust risk assessment, could justify a reduction in the release testing panel such that certain analytical tests do not need to be performed on every batch. For example, the requirement to test for replication-competent Lentivirus (RCL) in every vector batch was highlighted as an area requiring flexibility in the context of personalised TCR-T cell therapies, given the small production scale and the short time to treatment. The fact that each vector batch is manufactured at a small scale for exclusive use in a single drug product batch should be taken into account when determining the extent of required analytical testing of the vector starting material.

  The challenges associated with developing a suitable potency assay for individualised products were acknowledged. Regulators are open to alternative approaches to potency testing. However, developers are expected to demonstrate that their control strategy, e.g. including a surrogate test, is sufficiently robust to ensure each batch has the required biological activity.
- Developers highlighted the need for further regulatory guidance on the requirements and methodologies for validating the use of AI tools in a GMP-compliant setting. Some of these concerns are expected to be addressed in the upcoming EU GMP Annex 22. Regulators emphasised, however, that overly prescriptive guidance on validation of AI tools might inadvertently hinder innovation. Therefore, any future guidance should retain a degree of flexibility

to accommodate evolving technologies and developments. It was also noted that the existing EU regulatory framework already provides a range of tools and flexibilities, and the lack of dedicated AI-specific guidance should not be viewed as a barrier to the adoption of appropriate AI-solutions within the GMP-setting.

- With regards to NGS, the implementation of industry wide standards for validation of both wet lab and bioinformatics pipelines such as the use of natural and in-silico generated reference FASTQ files has been discussed and recognised as a valuable resource for developers.
- The definition of standardised parameters and specifications for NGS accuracy, such as specific thresholds, depth of sequencing, specific library prep, database and bioinformatic pipeline, number of reads, etc., was discussed. However, the establishment of universal benchmarks was considered less feasible, as these criteria are highly dependent on the NGS-platform, workflow (wet-lab and bioinformatic), and the type of sample. Therefore, a specific validation according to the specific intended use of the NGS application would be a better option.
- In line with this, the need for distinct definitions and requirements for GxP in the context of NGS usage has been indicated.
- In general, it was agreed that when NGS is used for generation of an individualised cancer immunotherapy, both the NGS-bioinformatics and the bioinformatics used for defining the cancer neoepitopes are part of the manufacturing process. In this context, the applicability and need of GMP requirements was discussed, along with the question on whether oversight should remain within the responsibility of the QP, who would be responsible for qualifying this relevant part and/or vendor for the Drug Product manufacturing process.
- For individualised cancer immunotherapy, NGS defines the composition of the active substance, making it crucial for ensuring product quality. Depending on the type of product and manufacturing process, NGS aspects may need to be conducted under GMP or under the principles of GMP. In either case traceability remains essential to ensure the correct patient sequence is used in personalised medicines.

3. Session 2 summaries as provided by the presenters

3.1. '3D Printing Implementation in Hospitals and Pharmacies: Use of commercialised pharma-inks', Gustave Roussy and FABRX.

Context and Rationale

The limitations of standard pharmaceutical manufacturing models to address the growing need for personalised therapies, particularly in vulnerable populations (e.g. paediatrics, rare diseases), was highlighted. The application of 3D printing (3DP) technology in clinical and pharmacy settings was presented, focusing on the preparation of patient-specific oral dosage forms using semi-solid extrusion and pharma-inks.

Technical Overview of 3D Printing Process

An overview of semi-solid extrusion technology using pharma-inks (formulations combining APIs with excipients) was given, including Critical Process Parameters (CPPs) such as rheology, extrusion speed, temperature control, and printed dosage form geometry.

Quality by Design (QbD) principles were applied in formulation development to define critical quality attributes (CQAs), critical material attributes (CMAs), and CPPs.

The capabilities of 3D printing were outlined:

- Dosing flexibility
- On-demand small batch production
- Enhanced safety and ergonomics (reduced operator exposure)

Regulatory Considerations

Regulatory gap exists regarding:

- The status / classification of pharma-inks
- In-process controls during decentralised production
- The qualification in non-GMP settings (e.g. hospital or community pharmacies)

Proposed solutions regulatory model:

- Develop a monograph for pharma-inks (similar to ATMPs or radiopharmaceuticals)
- Standardise validation requirements for site-specific 3DP manufacturing
- Define adequate requirements for traceability, equipment qualification (Installation, Operational and Performance Qualification (IQ/OQ/PQ), and batch release.

Case Studies

Two clinical case studies were presented: Cyclophosphamide (paediatric oncology) and Minoxidil (alopecia treatment).

Case Study 1: Cyclophosphamide

Clinical Need: Off-label use in paediatric oncology (neuroblastoma, nephroblastoma) with dose requirements from 5–40 mg.

Challenges with current preparations:

- Oral solution: poor stability
- Dose Accuracy: tablets unsuitable for dose splitting and paediatric use
- Compounding: time-consuming and variable

3DP solution: Development of chewable/dispersible printed dosage forms tailored by body surface area (BSA), with enhanced chemical stability and rapid dispersion in 5 mL water. Process includes pharma-ink preparation under ISO 7 conditions and controlled extrusion via 20G nozzle.

Case Study 2: Minoxidil

Clinical Need: Widely prescribed orally for alopecia, but no authorised oral formulation available in Spain.

Challenges and need for automated compounding:

- Manual capsule filling is labour-intensive, error-prone, and presents exposure risks
- Need for dose flexibility and combinability with other APIs

3DP solution: Automated capsule production using M3DIMAKER software and printer, with inline pressure and mass uniformity control. Enables rapid and reproducible preparation of personalised therapies in community pharmacies.

Path Forward and Industrialisation Strategy

To facilitate broad access, the project proposes two different pathways:

Route A: Continue with full in-hospital/pharmacy manufacturing under national frameworks (requires EU harmonisation).

Route B: Centralised production of pharma-ink / cartridges and decentralised 3DP, supported by a clear regulatory status for pharma-inks.

Conclusion

3D printing of medicines is already being used in pharmacies under compounding regulations. However, scaling the technology requires decentralizing manufacturing, posing several challenges, including cross-border distribution of pharmaceutical inks. Standardised "pharma-inks" are essential for safety, efficacy, and economic viability. Regulatory guidelines may be needed to clarify the standards for pharma-inks, and requirements for application of GMP, in-line quality control, and distribution.

3.2. 'How to safely implement 3D printing processes to produce personalized solid oral forms with decentralized production (Point of Care (POC) settings', NwEUam

3D printing comprises different technologies and this presentation focused on semisolid extrusion (SSE) and fused-deposition modeling (FDM). Regulatory questions to be addressed include regulation of ink manufacture and commercialisation, the printers and printing process, and the printing forms.

Two clinical cases, both for paediatric patients, were selected to illustrate the current status (both are immediate release forms according to the European Pharmacopoeia Guidelines):

- SSE paste with sildenafil citrate
- FDM filament with hydrocortisone

Inks Manufacturing Process

In the case of SSE, pharmacists can either prepare paste locally as a magistral preparation or, possibly in future, buy intermediate product (pre-filled cartridge) from a pharmaceutical company (GMP standard production). In the case of FDM, intermediate product (drug-loaded filaments) may be produced by a pharmaceutical company (GMP standard production).

For clinical use, the standards that the "inks" and final printed forms (compounding) must meet need to be clarified to ensure safety and regulatory compliance. It is also necessary to address questions regarding the transportation and stability of the intermediate manufacturing product.

Printing Process

For both technologies, printers can be placed at Point of Care which may be hospital pharmacies, community pharmacies or a compounding centre.

Both pharma-inks are printed at different temperatures using a pharmaceutical 3D printer. After the selection of printer parameters (e.g. nozzle diameter, nozzle temperature, bed temperature, speed)

and the 3D shape, the material is deposited layer-by-layer, ensuring precise structure formation. The pharma-ink with the same composition could be used to print batches with multiple different doses.

The short time between production and administration will limit time for end testing and/or QP certification. Some suppliers have integrated a balance into the building platform, which could help ensure mass uniformity. If integrated tools within the printer are insufficient to verify the quality of the final form, external tools should be considered. The types of tools needed should take into account hospital pharmacies (which have certain analytical tools) and community pharmacies (which have much fewer tools). If process validation is performed, the minimum testing (e.g. mass uniformity) which is sufficient for each individual batch needs to be defined.

As mentioned above, 3DP in a POC setting can be done as a magistral preparation. However, it is foreseeable that not every pharmacy will have its own 3D printer and that a certain degree of regional centralisation takes place. This raises the question what level of GMP adherence is necessary and which level of supervision is mandatory.

In order to allow for flexibility and efficient decentralised production potential solutions to guarantee safe and effective use and implementation of this promising technique might be:

1. Guidelines regarding the status of intermediates inks
2. Implementation of suitable Process Analytical Techniques (PAT) enabling real time release of the end product at the Point of Care.

3.3. 'Manufacturing Process of Antisense Oligonucleotides for N-of-1', Medicines Made to Measure (MMM)

The presentation discussed a standardized approach for the manufacturing of personalised therapeutic splice switching antisense oligonucleotides (ASOs). For MMM, the focus lies on ASOs applied to treat ultra-rare neurological diseases in an N-of-1 setting. They argued that if this new approach is successful for this setting, it can in the future also be modified to meet the needs of different settings.

The manufacturing of synthetic oligonucleotide drug substances traditionally follows the same set of unit operations. These are: solid phase synthesis, cleavage and deprotection, purification of the full-length oligonucleotide and packaging in a primary container. In the classical pharmaceutical setting, these unit operations are always optimized and scaled up to commercial scale before validating the manufacturing process.

The N-of-1 setting differs, as it will always remain on a very small scale. On top of that, fast development and manufacturing time is required, because the treatment is developed for a single individual, for whom the treatment needs to be available in a timeframe that they still benefit from the treatment. For progressive diseases, neurons are continuously and irreversibly lost due to the disease progression.

To tackle this problem, MMM proposes standardizing the modifications of the ASO to streamline the process. For ultra-rare neurological diseases, they propose using the same modifications as the commercially approved ASO Nusinersen, as well as successful N-of-1 ASOs i.e. Milasen, Atipeksen and Zebronkysen. These modifications are 2'-ethoxymethyl (MOE), phosphorothioate (PS), 5'-methylcytosine and 5'-methyluracil as illustrated in Figure 1.

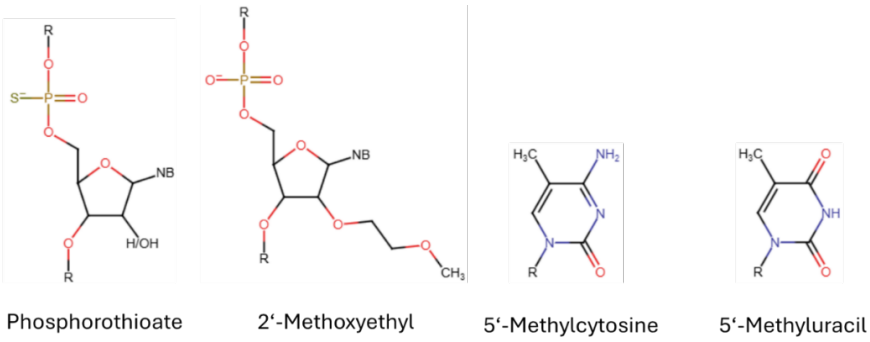

Figure 1: Illustration of chemical modifications

By using these same modifications, a standardized manufacturing process can be made, where the only parameter that changes is the sequence of the bases in the ASO. With this approach, MMM proposed a platform validation can be performed rather than validation of all unit operations for one specific drug substance. The platform validation would consist of validating that the outcome of the unit operations lies in a well-defined range for a variety of oligonucleotide sequences.

Once this validation of the standardized process has been performed, product-specific validation is no longer required when an N-of-1 drug substance is manufactured.

As part of this platform validation, the necessity of some quality control tests can be omitted for the platform. Examples of these tests are heavy metal tests, or residual solvent testing when water is the only used solvent used for the purification steps. When the content of these impurities is below detection limit for all the validation samples, it can be argued that they are not required for release testing of oligonucleotides.

3.4. 'Accelerating validation and adoption of ARMMs for innovative therapies', NIMBL, NIST and BioMérieux.

The use of Alternative and Rapid Microbiological Methods (ARMMs) in biopharmaceutical manufacturing, especially for certain cell and gene therapies (CAGT), creates advantages over compendial methods in that they can enable faster product release, improved process monitoring, and more comprehensive quality assurance.

The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) attempted to understand the successes and challenges around ARMM adoption through surveys, interviews, and a facilitated Active Listening Meeting between industry and FDA representatives. It was observed that many organizations have successfully implemented ARMMs in approved manufacturing processes (60% of the organizations are currently using ARMMs for release testing for at least one product and 30% plan to implement ARMMs in 1-2 years), suggesting an absence of significant regulatory obstacles to implementation. A common theme across all success stories is that technology maturity and vendor support are necessary, but not sufficient for adoption. Successful deployment also requires organizational adoption readiness, a strong business case, and regulatory coordination often including early engagement with Health Authorities.

The National Institute of Standards and Technology (NIST) Rapid Microbial Testing Methods (RMTM) Consortium convenes experts to identify and address measurement challenges and standards needs related to the use of ARMMs for cell and gene therapies, with an emphasis on molecular ARMMs such as polymerase chain reaction and next generation sequencing (NGS). The Consortium has developed approaches to quantify microbial cell reference materials for properties relevant to molecular ARMMs, such as total cells and total genome copies. The Consortium is also running interlaboratory studies to

develop community datasets that survey ARMMs capabilities, demonstrate a common test sample of 10 to 100 colony forming units (CFU) of bacteria in a background of human T-cells, and evaluate fitness for purpose of a sequencing database and bioinformatics pipeline for use of NGS as an ARMM for cell and gene therapies. These efforts aim to build measurement tools and strategies that support the adoption of ARMMs.

With respect to the regulatory framework, the presentation highlighted the recent and ongoing changes at the pharmacopoeias level to facilitate the use of ARMMs, especially for controlling microbiological contamination in CAGT products and short-lived products.

The following aspects were identified as key to accelerating adoption of ARMMs**:**

1. *Clarifying supplier and user responsibilities for analytical validation*

In this aspect, the revision of Ph. Eur. 5.1.6 Alternative Methods for Control of Microbiological Quality is encouraged. Indeed, amongst reasons for delaying the implementation of ARMMs, the fact that primary validations are redone multiple times by multiple users on same technology has been outlined by several surveys.

2. *Promoting centralized regulatory review of Primary Validation to harmonize data evaluation and limit geographical differences*

In this aspect, EDQM discussions around a certification approach for primary validation data is encouraged.

3. *Raising awareness on analytical validation approaches.*

In this aspect, the publication of additional validation examples by EDQM is encouraged.

4. *In Europe, efforts should focus on streamlining the validation process (leveraging centralized evaluation of primary validation data generated by suppliers) to allow users to focus on product specific aspects.*

3.5. Panel discussion (day 2)

The meeting was very informative and contributed to a deeper understanding of stakeholder innovative product developments, as well as the scientific and regulatory challenges associated with the manufacture of personalised medicines. Presentations from industry and academic experts on day 2 focused on 3D printing, antisense oligonucleotides, and rapid microbiological methods.

3D printing

The two presentations on 3D Printing (3DP) outlined the different applications of this technology to provide personalised solutions for dose flexibility and multidrug combinations. Examples were given of current application of the technology in paediatric care and manufacture of formulations not commercially available.

Challenges were shared from the perspective of point of care (where technology is currently mostly implemented) users, academic developers, and equipment suppliers.

The use of Quality by Design (QbD) principles in development of formulations (pharma ink) thorough characterization, and in development of the printing process through establishment of a design space, was emphasized in both presentations. Indeed, a good understanding of the properties of the raw materials, critical process parameters and the finished product critical quality attributes and their interrelationships was pointed out as the starting point of manufacturing process qualification.

Key discussion points included:

- The properties of active substance(s), excipients, and manufacturing process that are critical to product quality, and relevant to performance and manufacturability, were discussed. Some properties were specifically pointed out in the context of 3DP, such as preparation flexibility, rigidity and imprimability (or printability), characterized by rheological studies and texture analysis.
- During the Q&A and panel discussion, the importance of solid-state characterization and stability of the pharma ink were highlighted in view of the potential impact of the ink preparation and printing process on these attributes, and on related properties (e.g. dissolution, PK profile). The impact will depend on the nature of the active substance (and its Biopharmaceutical Classification System (BCS) class), the printing technique (e.g. semi-solid extrusion SSE, fused deposition modelling FDM, etc.) and the printer. The active substance can be subject to different stress depending on the technique used. This, in turn, can have an impact on the impurity profile according to the active substance structure and properties.
- The presenters were asked to elaborate on the performance of the 3DP technology in terms of accuracy. A higher level of dose accuracy and precision was claimed with this technology compared to more traditional solid dosage form manufacturing processes, based on results gathered in several investigational studies. The QIG indicated that this kind of results, if published, could feed risk assessments, be leveraged to justify surrogate-based control strategies, and promote acceptance of the technology by regulatory authorities.
- Questions were raised regarding the proposed approach to qualification of equipment and validation of the process. The validation of the ink manufacturing was indicated as being quite challenging, and the need for a proper pharma ink qualification was emphasized. For the printing step, both presenters proposed an approach similar to ATMPs, by printing a number of confirmatory batches designed and quality tested to verify the printing boundaries (including range of doses) and reproducibility. Validation should be carried out at the level of the ink manufacturer/printer supplier with the technology transferred to the end user. Like for other pharmaceutical equipment, the importance to carry out Installation, Operational and Performance Qualification (IQ/OQ/PQ) to identify the process critical steps (including hardware and software), and to perform some functional testing at the printing site was highlighted (factory / site acceptance testing (FAT/SAT)). These activities can be supported by the printer supplier. Initial and periodic training of the user covering e.g. handling of the software, workflow from prescription, selection of the pharma ink, selection of the printing recipe, maintenance of traceability, etc should be implemented.
- The QIG reiterated the added value of formulation and process design and full validation in an industrial environment, complemented by the manufacture of qualification/verification batches on site.
- Presenters also mentioned the availability of different operating modalities, accessible with different login profiles (restricted in the software settings): a mode where the user can implement changes in terms of process parameters and/or quality controls for research and process optimisation purposes, and another mode where the user sticks to prescriptions, validated recipes and procedures (SOPs). Any use is recorded. This locked modality is aimed at securing the use in the point of care facility. In any case, the higher the flexibility foreseen by the end user, the higher the requirements for QC capacity and GMP compliance, based on risk assessment.
- In terms of control strategy, the QIG noted the need for a different approach for in-process quality control and for release of the printed product. Indeed, in most applications, small batch sizes are

produced, therefore limiting the testing capacity. The use of non-destructive techniques such as NIR and Raman spectroscopy during the manufacturing process was mentioned in the presentations. However, it was acknowledged that the implementation of PAT tools is not straightforward due to the significant development, validation and maintenance work required for chemometric methods, for which industrial companies are in a better position to implement those than point of care facilities. In this context, the importance of the collaboration between the users and the printer suppliers, and the possibility to integrate those tools in the printer, was emphasized. This could facilitate the use of real-time release testing (RTRT) approaches for the finished product.

- The regulators also noted the presenters request for harmonisation in the Quality Control/ Release tests required. To cope with the specific characteristics of the printed products, the compendial tests usually performed on solid dosage forms may need an adaptation, e.g. friability and hardness suited for compressed/tableted products. In this context, the presenters suggested the development of specific Ph. Eur. monographs which could serve as a useful guide on the tests expected to be performed at the level of the ink and the tests to be performed on the printed dosage form.
- Presenters were asked how to deal with errors or equipment malfunctioning during routine manufacturing, and how these may be picked up through quality control. They indicated that in addition to sensors e.g. for temperature control, mass control or extrusion pressure, alarms are put in place to identify any deviation from validated parameters and stop the process. Furthermore, the printers have systems of audit trail that allow evaluating the actions adopted for batch release decisions.
- Presenters were also questioned on the risk for cross-contamination. They indicated that currently, there is no quality control system on the printers for detection of product residues. This could be foreseen in the future. Printers are designed in such a way that every piece of the equipment can be removed after printing and cleaned. Validation of cleaning, SOPs in place, and use of disposable materials in contact with the formulation, were defined by stakeholders as appropriate risk minimization measures.
- The panel discussion highlighted the need for further reflection on the specific responsibilities between the manufacturer of the pharma ink, the supplier of the printer and the end user to ensure that the equipment functions as expected and is correctly maintained, that the printer is used properly, that batch release is performed in compliance with regulatory requirements, and that a medication of the expected and consistent quality is dispensed to the patient. The need to have contracts between each party was also mentioned for example for qualification, maintenance, training etc.
- In view of the applications and use cases presented, it is understood that different manufacturing routes, involving 3DP technology, are envisaged. In the presenters' view, the main envisioned routes are: 1) the compounding route and 2) the decentralised route. These routes could likely run in parallel, the compounding route in the short term for rare diseases applications, multidrug combinations (polypill) or dose adaptations, and the registration route in the far to medium term for larger groups of patients. Presenters acknowledged that implementing 3DP in a locked mode, according to validated recipes and ranges, should cover a large extent of clinical needs in daily practice.
- Both presentations highlighted similar challenges in supplying the pharma ink across multiple territories in EU to manufacture personalised medicines. The lack of regulatory status for the

pharma ink was pointed out, whether it should be considered an intermediate product or a finished product, and the consequence to consider the final users, e.g. hospital pharmacies, as finished product manufacturers as a result of the strict application of current legislation.

- Regulators highlighted that the decentralised manufacturing is not allowed for 3DP under the current EU legislation. However, the need for further reflection on what could be done under the current regulatory framework is acknowledged. In this context, the importance of securing as much as possible the use of the technology by the end users to avoid use beyond what has been validated by the manufacturer of the ink and the supplier of the printer, was underlined.

Antisense oligonucleotides

The antisense oligonucleotide (ASO) case study presented proposed a platform approach for ASO manufacturing using similar chemistry which are intended for the treatment of ultra-rare life-threatening neurological diseases via the intrathecal route, most of them for children.

Key discussion points included:

- Pending availability of an EU regulatory framework for platform technologies, platform approaches for oligonucleotides could be considered for different aspects. An example may be to establish critical process parameters (CPPs), manufacturing set points, and proven acceptable ranges (PARs) for the manufacturing process. Another aspect could be elements of the analytical control strategy or stability approaches using prior knowledge. It was discussed that the definition and the boundaries of the platform and its related manufacturing processes and control methods are key to allow a platform process validation approach instead of product-specific process validation.
- It was recognised that a lot of information on potential oligonucleotide impurities and degradation pathways is available in the public domain. For purity testing, the use of generic published analytical methods (e.g. IP-RP-HPLC/MS) also used for the control of approved products may be an option for stakeholders developing N-of-1 oligonucleotide medicines. However, the question remains if and at what timepoint method optimisation or development of product specific methods is needed.
- Approaches for stability testing were also discussed. The presenter indicated that up to now stability programs with a considerable number of batches for different oligonucleotides sequences have been initiated for the case study presented. For such N-of-1 stability programs the omission of microbial purity is reasonable. It is also reasonable that only one batch (e.g. a batch used for toxicological testing) is included in such stability programs.
- It was also suggested by industry stakeholders that the nature of solid phase oligonucleotide synthesis and its intensive use for approved products i.e. an existing technology and framework, may allow establishing a platform for the use in small patient populations without repeating all studies (e.g. manufacturing development, process validation, and stability) for each oligonucleotide sequence.
- It was agreed by QIG and industry stakeholders that benefit-risk considerations such as those described in the 'EMA Prime Toolbox Guidance' may be helpful for stakeholders developing N-of-1 oligonucleotide programmes.
- The participants also discussed how to allow for limited release testing for attributes where sufficient previous data (prior knowledge) are available (e.g. residual solvents). It was agreed by the QIG that such an approach may be reasonable when adequately justified. The QIG

mentioned that changing the chemistry or basic principles of the manufacturing process e.g. for purification would require additional studies and/or justification when the claim of a platform has been made.

- The need of interaction and co-operation of different stakeholders active in the field of personalised oligonucleotides to move the topic forward was mentioned. The QIG acknowledged this initiative and offered further support on any scientific challenges encountered.
- GMP aspects for the presented case study were also discussed. GMP inspectors pointed out that although clinical trials consist of different phases (I/ II and III), there is in general no difference in GMP requirements for investigational medicinal products (IMP's) during the different clinical trial phases for ASO. Terms such as GMP-like, which were used by some stakeholders, should be avoided as it is either GMP or it is not GMP. The basic rule is that the quality of the product for the person involved in the trial should be in line with GMP and suitable and therefore cannot depend on the phase or the number of people involved in the trial. However, it's clear that knowledge can be different and grows during the trials which has an impact on GMP aspects like specifications settings, knowledge of parameters, validation and qualification efforts, etc.
- It was recognized that the number of batches used for the treatment of one or a very small number of patients is extremely small and often only one batch is needed. However, there could be cases where additional batches are needed years after. In that case, for consistency reasons the same manufacturing process as for the initial batch should be applied to avoid the need for additional comparability studies to demonstrate comparable quality of the batches.
- Finally, it was acknowledged that the EMA 'Draft guideline on development and manufacture of oligonucleotides' (EMA/CHMP/CVMP/QWP/262313/2024) already addresses in a dedicated section some aspects relevant for personalised medicines e.g. on characterisation of the impurity profile.

Rapid microbiological methods

The significant efforts made in standardising and comparing various alternative and rapid microbiological methods (ARMM) was acknowledged. These efforts provide valuable insights into identifying the most suitable ARMM for different use cases.

Key discussion points included:

- Industry representatives shared insights on the challenges and lessons learned in demonstrating comparability between rapid microbiological methods and compendial methods. Regulators highlighted the flexibility offered by the current Ph. Eur. Chapter 5.1.6, Alternative Methods for Control of Microbiological Quality. This chapter allows for primary validation to be conducted by the supplier, with the user responsible for verifying the method's suitability for their specific application. Importantly, this Ph. Eur. chapter does not require the user to repeat all the validation studies already performed by the supplier.
- The proposed EDQM certification procedure for rapid microbial methods was also discussed. While intended to support Member States, participants mentioned that this approach, once established, could facilitate broader global acceptance of these rapid methods.
- Regulators questioned whether NGS is sufficiently rapid to support batch release of cell-based medicinal products that require administration within 24 to 48 hours. Industry representatives

noted that while sequencing data can be generated in as little as four hours. The total turnaround time, including sample preparation and data analysis, makes it challenging to have results available within 24 hours. However, further optimisation may reduce this timeframe in the future.

- A key challenge discussed was the risk of false positive results due to the high sensitivity of NGS methods. Replacing an approved method with NGS may lead to the detection of signals that were not previously observed using current methods. Concerns about false positive results were highlighted as an issue hindering widespread adoption. Additionally, current databases may be biased, with overrepresentation of certain species and underrepresentation of others, potentially skewing results. To address these issues, efforts should focus on developing more balanced databases and understanding background positive signals from materials and reagents. This will support the establishment of appropriate criteria for interpreting positive signals and ensure correct interpretation of results.
- During the panel discussion, regulators emphasized that the selection of microorganisms plays a crucial role for both generic validation and product-specific suitability testing. In addition to adequate consideration of aerobic and anaerobic species, true slow-growers such as C. acnes and other challenging species must also be included in the studies. These are important aspects to generate a sufficient database to determine relevant method parameters such as LOD, specificity and the minimum incubation period.
- The discussion also addressed the need for standardisation and the availability of reference materials. ARMMs are expected to play an increasingly important role in enabling faster product release, not only for those products requiring immediate administration, but potentially across a broader range of applications.

4. Conclusions and next steps

The QIG LLFG provided a good forum to learn from our industry and academia stakeholders about the challenges that lie ahead for the development of personalised medicines.

The QIG will use the information gathered to inform its future priorities and consider which additional actions are necessary to facilitate the development and registration of personalised medicines.

The below conclusions were reached:

- **Adaptive regulatory framework**: QIG recognised that manufacturing and control of personalised ATMPs sometimes require adaptations that, although may not be explicit in the available set of guidelines, could still be implemented if appropriately justified. It was emphasised, however, that when novel manufacturing and control approaches that raise complex regulatory issues and request additional regulatory flexibility are used, it is important to justify that these innovations offer clear benefits to patients beyond existing approaches. For instance, a risk-based strategy for release testing of N=1 products would need a clear justification based on, e.g. prior knowledge, extensive product and process characterisation and a risk assessment. For some parameters (e. potency or identity), implementation of appropriate surrogate tests could be a better option than reduced testing. In this regard, stakeholders were recommended to initiate early interactions with regulators, for example via QIG 1:1 meeting, Innovation Task Force meeting and/or scientific advice/protocol assistance requests.
- **AI-guidance**: The need for further regulatory guidance on the requirements and methodologies for validating AI tools in a GMP-compliant setting was also highlighted. Stakeholders were informed

that some of these concerns are expected to be addressed in the upcoming EU GMP Annex 22. It was also noted that the existing EU regulatory framework already provides tools and flexibilities and that the lack of dedicated AI-specific guidance should not be viewed as a barrier to the adoption of appropriate AI-solutions within the GMP-setting.

- **NGS**: The use of NGS implies three main parts: 1) wet-lab, 2) bioinformatic analysis and 3) expert assessment. Also, the use of NGS implies the possibility to apply many different paths to arrive to the same result. That means workflows in the wet-lab or in the bioinformatics cannot be standardised by regulators. The best approach is that regulators describe the general content of a workflow to leave enough room for innovation but at the same time have some general lines to follow. Therefore, any process and product that uses NGS as part of their development or manufacturing process needs to be assessed on a case-by-case basis. The assessment should be conducted by a multidisciplinary group of experts comprising at least 3 profiles: NGS wet-lab expert, NGS bioinformatic expert, and a regulator assessor expert in the field where the product is indented to be used (clinical expert) e.g. cancer expert, and/or in the part of the process where NGS will be applied (Quality expert) e.g. viral safety.

  Regulatory guidelines should define controls for validation and running controls, rather than trying to define certain thresholds (e.g. depth of sequence, read number, coverage...). Such controls allow regulators/technical expert teams to verify if the workflow design fits the goal, if the goal was reached and if the process (development/manufacturing) is reproducible.

  Considering the above, the proposed next steps with regards to NGS are as follows:

  - Use and evaluate the already written guidelines ICHQ5A (R2) and Ph. Eur. 2.6.41 to verify if any additional guideline/recommendation needs to be developed by EMA.
  - Strengthen EU regulators training on NGS

- **ASO:**
  - Use and evaluate the already written guidelines ICHQ5A (R2) and Ph. Eur. 2.6.41 to verify if any additional guideline/recommendation needs to be developed by EMA.
  - Strengthen EU regulators training on NGS.
  - The EMA has published a 'Draft guideline on development and manufacture of oligonucleotides' (EMA/CHMP/CVMP/QWP/262313/2024). This guideline already addresses in a dedicated section some aspects relevant for personalised medicines. The public consultation phase has been finalised, and the stakeholders' comments will be evaluated by the guideline drafting group members. A final guideline is expected in 2026.
  - The use and administration of personalised antisense oligonucleotides is strongly connected with prior knowledge and platform technology approaches. However, the term 'platform' is not yet defined by the current EU pharma legislation. The EU legislative provisions for 'platforms' for human medicinal products are being drafted by the European Commission as part of the on-going reform of the EU pharma legislation and it is anticipated the forthcoming legislation will provide a definition for platforms for the purposes of an associated EU registration.
  - The need for interaction and co-operation of different stakeholders active in the fields of personalised oligonucleotides to move the topic forward mentioned by stakeholders is strongly supported. Ways of interaction with EMA are described in the final paragraph of this section.

- **3D printing:**

- QIG considers 3DP an important emerging manufacturing technology. Regulators acknowledge the advantages of an automated and highly standardised production with qualified printers, and the value of GMP manufactured pharma inks and validated printing processes. The QIG appreciates the efforts that are being made to secure as much as possible the use of this innovative technology and acknowledges that risk-based considerations will be critical to facilitate its implementation.
- The QIG also recognises the current challenges on 3DP highlighted by stakeholders. Regulators understand that certain envisioned routes for manufacture and supply do not fully fit the current EU regulatory framework. It is anticipated that the decentralised manufacturing approach is mentioned in the revision of the pharmaceutical legislation under discussion. In the meantime, potential regulatory pathways within the current EU pharmaceutical legislation may be identified and established. Further discussions on the appropriate way forward are required. QIG will continue working on this topic to develop guidance for stakeholders focused on quality and manufacturing requirements to support the use of 3DP, including the regulatory status of the pharma ink.
- To stimulate efforts for harmonisation in terms of quality control tests to be performed on 3D printed products, regulators encourage stakeholders to liaise with their National Pharmacopoeial Authorities to submit their requests to EDQM for adapted pharmaceutical technical procedures and/or specific Ph. Eur. monographs.
- Stakeholders are also invited to consider the publication of their findings on the performance of the 3DP technology in terms of dose accuracy and precision. This could promote acceptance of the technology by the regulatory authorities.

- **ARMMs:** the discussions underscored the importance of continued collaboration between industry and regulators to refine validation strategies, improve data interpretation, and support the adoption of innovative rapid microbiological methods. These efforts are essential to supporting timely and reliable release of advanced therapies to patients.

Finally, whereas these joint LLFG meetings are considered of high value to have open discussions with all stakeholders and share information, the QIG invites individual organizations that want to discuss confidential details with the QIG to apply for a 1:1 meeting with the QIG (early discussion) or apply for scientific advice requesting QIG involvement (written feedback). For details on how to get in touch with the QIG, please consult its webpage.

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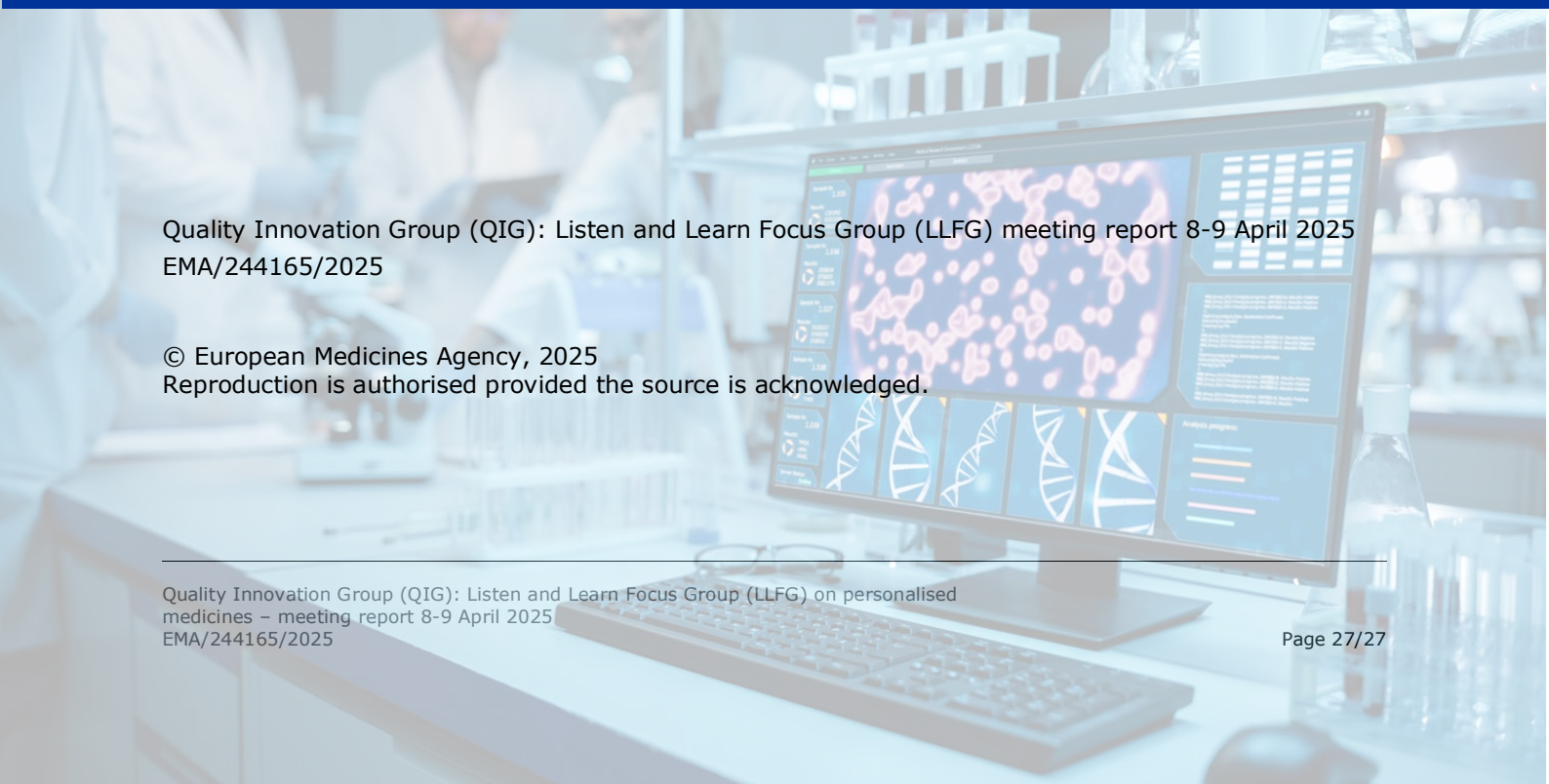

Quality Innovation Group (QIG): Listen and Learn Focus Group (LLFG) meeting report 8-9 April 2025
EMA/244165/2025