EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Quality Innovation Group (QIG)

4th Listen and Learn Focus Group (LLFG) meeting report

19 – 20 November 2024

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Introduction

The use of prior knowledge for the development of manufacturing processes for a very similar product/process within an organization has increased in recent years and has facilitated the development of manufacturing platform technologies.

To have a better understanding of stakeholders' thinking on the use of manufacturing platform technologies and to open the dialogue, the QIG organised a dedicated Listen and Learn Focus Group (LLFG) meeting on this topic. The aim was to discuss case studies for active substances, finished products of both chemical and biological medicines (including vaccines and ATMPs) where prior knowledge has been used to substantiate the information on a potential manufacturing platform in future marketing authorisation applications. The aim was to reflect on the platform utility and the appropriate level of scientific data maturity, respectively. The meeting aimed to also identify general scientific challenges with the use of platforms and possible solutions.

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.

The publication of the EC Proposal for a Directive repealing directive 2001/83/EC and directive 2009/35/EC[1] and the subsequent EP resolution texts that include a legislative proposal and definitions for 'platforms', 'platform technologies' and a 'platform technology master file' were noted. It was however not the scope of this QIG LLFG meeting to reflect on these or other legal aspects and definitions or to pre-empt in any way the final legislative definition of a 'platform'. Therefore, potential regulatory e.g. Marketing Authorisation (MA) cross-referencing/legislative issues were outside of the scope of the meeting.

Instead, the meeting featured case studies on different technologies and approaches prepared by industry and academic stakeholders.

The event was attended by approximately 140 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, 19th November 2024

1. Introduction to QIG, meeting scope and objectives of the 4th LLFG meeting
2. Use of Prior Knowledge and Platform Approaches: an EU Regulatory Perspective
3. Session 1
    - 3.1. Platforms technologies are critical to accelerating vaccine development, CEPI
    - 3.2. mRNA-lipid nanoparticle (LNP) platform technology to support specification setting and determination of product shelf life, Moderna
    - 3.3. Platforms for medicinal products manufactured using prior knowledge, investigational medicinal products' (IMPs) considerations, ISPE

[1] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52023PC0192

3.4. Multiple antigen presenting system (MAPS) technology, a cutting-edge platform manufacturing, PDA

3.5. Viralgen - Platform strategy, Viralgen

3.6. Optimising development of gene therapies for rare genetic diseases, Fondazione Telethon ETS

3.7. Prime editing: Platform technologies, Prime Medicines

3.8. Panel discussion

3.9. Closure of the day

Wednesday, 20th November 2024

4. Session 2

4.1. an EFPIA/VE perspective (Continuous Direct Compression (CDC) platform focus), EFPIA/VE

4.2. Application of a platform approach to oligonucleotide drug substance development, EPOC

4.3. Strategy for implementation of a platform approach for synthetic oligonucleotides, BioSpring.

4.4. Statistical approaches to develop data-driven prior knowledge into a platform, CMC Statistical Network Europe

4.5. Panel discussion

4.6. General sum up

5. Next steps and closure of the 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. It is acknowledged that some comments relating to potential future regulatory/legislative provisions were brought forward by some stakeholders but given that these were outside of the scope of the meeting they are either not covered in this report or only included as part of the record of stakeholders' comments.

1. Introduction to QIG, meeting scope and objectives of LLFG

The Quality Innovation Group (QIG) is a multi-disciplinary group comprising quality assessment and GMP inspection expertise, both for chemical and biological medicinal products, established in 2022 to deliver on key goals of the EMA's Regulatory Science Strategy to 2025 (e.g. enabling and leveraging research and innovation in regulatory science and catalysing the integration of innovative science and technology into medicines development).

The QIG is the point of entry for developers to discuss innovative CMC approaches under scope. Its goal is to ensure that the EU has a predictive regulatory framework to enable implementation of innovative technologies which will ultimately benefit patients in the EU. QIG also collaborates with other regional regulatory agencies to enable widespread implementation of these technologies.

The QIG priority topics in 2024 were process models and platform technologies. This meeting was focused on platform technologies. As indicated above, the objective of this LLFG was to consider the scientific challenges associated with the extensive use of prior knowledge such that a coherent body of prior knowledge data can be ring-fenced as a 'platform' for the active substance (or complex starting material that might be an active substance, in its own right, in another product e.g. lentivirus vector or CRISPR/Cas9 & sgRNA for CAR-T cell therapy, monoclonal antibody for an antibody- drug conjugate) and/ or finished product manufacturing process in a MA.

For the purposes of this LLFG, the term 'platforms' refers to manufacturing technologies that comprise the entire active substance and/ or finished product manufacturing process (end-to-end) and information in the MAs, for either chemical or biological molecules. Platform approaches for analytical procedures only were not considered to be in scope of this meeting.

Three scenarios were foreseen for discussion:

1. Platform for medicinal products manufactured using prior knowledge, such as common manufacturing platform approaches (multiple MAs).
2. Platform for medicinal products against agents which are or have a potential to cause serious cross-border threats to health e.g. pandemic/pandemic preparedness (one MA).
3. Platforms for the manufacture of personalised or individualised medicines ('one patient/group of patients-one product', one MA) e.g. covering different ultra-rare orphan indications.

Stakeholders were invited to submit abstracts from real or fictitious/generic case studies to be presented at the LLFG meeting outlining examples of platform technologies compliant with any of the three categories above and focusing on the scientific challenges and data required to verify the proposed 'platform'.

2. Use of prior knowledge and platform approaches: an EU regulatory perspective

Prior knowledge includes a company's knowledge and data from development and manufacturing (e.g. experience based on similar compounds, products and processes) as well as reference to scientific and technical publications or application of established scientific principles. References to prior knowledge and/or platform approaches appear throughout ICH guidelines Q8 - Q14 and in various EMA guidelines. For reference, the EMA organised a workshop on the use of prior knowledge and its use in regulatory applications in 2017. The workshop report is published here.

Prior knowledge is also essential to enhance the development of medicines that target an unmet medical need with the aim to help patients to benefit from these therapies as early as possible. This is achieved by optimising the medicines' development plans and speeding up their evaluation. This approach is described in detail 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'.

Examples where prior knowledge has been used in the submission were mentioned in the presentation. These examples included seasonal influenza vaccines strain updates, COVID mRNA vaccines variant updates, several CHMP approved products and clinical trial applications for several synthetic oligonucleotides (where prior knowledge approaches have been used to justify proposed re-test period/shelf-life).

A case study from a marketing authorisation application where the control strategy for the Protein A chromatography step in the manufacturing of a monoclonal antibody was based fully on prior knowledge and no product specific data were required for this specific manufacturing step was presented.

It was noted that the ICH Q11 glossary includes a definition for Platform Manufacturing ("The approach of developing a production strategy for a new drug starting from manufacturing processes similar to those used by the same applicant to manufacture other drugs of the same type (e.g., as in the production of monoclonal antibodies using predefined host cell, cell culture, and purification processes, for which there already exists considerable experience))". In this regard, it was recognised that in Europe, the concept of veterinary vaccine platform technologies and vaccine platform technology master file (vPTMF) has already been established in the legal framework (relevant for veterinary vaccines) and the first certification of a vPTMF has been issued by EMA in November 2024. However, 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 thus far have been considered by the European Parliament.

As part of the on-going discussions, the need for a definition of the term 'platform' has been recognised, and proposals for such a definition have been published recently. However, as stated above, it was not the intention of this QIG LLFG meeting to reflect on the legal proposals and definitions or to pre-empt the final legislative definition of a 'platform'.

It was noted that during stakeholder interactions with EMA during the last 5 years (2017-2023), 29 uses of platforms were identified from scientific advice procedures, innovation task force (ITF) and company meetings. It became obvious that companies and regulators do not always have the same understanding of what a platform is since it is currently understood as a very broad concept, i.e. "Leveraging prior knowledge, data extrapolation and shared data packages to develop multiple (personalised) medicinal products by reducing development time and costs, while safeguarding products' quality and patient safety".

Therefore, in order to hear stakeholders' views and progress this topic further, stakeholders were given the possibility to present case studies and discuss their views as part of the panel discussions. Panel discussions focused on:

i) Platform definition

- Differences between a platform and prior knowledge
- End to end (E2E) considerations for platforms
- What are the minimum data required to show that a platform is established?
- Defining the fixed components and pre-defined intentionally variable components of a platform
- Format and location of platform data in the dossier

ii) Applicability of the platform for different products

- Will the 'fixed' components comprise data which are identical for each product, or could there be minor differences?
- How to justify cross-referencing of data across linked MAs?
- Approaches to demonstrate that a new product is part of the platform

iii) Lifecycle management

- Platform lifecycle maintenance and how will it link to multiple products with their own lifecycles?
- Reproducibility for linked products (including future products).
- Introduction of changes/improvements in the platform.

iv) Platform based on several products for ultra-rare diseases

- Approaches to validate a platform-based manufacturing process based on the data of different products manufactured with it, prior to one of these are approved as medicinal product.

Summaries of these discussions are captured in Section 5 of the report. The sections below, 3 and 4, contain the summaries of the stakeholders' case studies, as provided by the presenters. They do not constitute QIG or EMA views.

3. Session 1 summaries as provided by the presenters

3.1. 'Platforms technologies are critical to accelerating vaccine development', CEPI.

Summary

CEPI has started a Regulatory Innovations Consortium with experts from industry, most of whom led vaccine development during the COVID-19 pandemic. The goal of the Consortium is to leverage regulatory innovations to accelerate vaccine development. Use of Platforms is one of the Consortium's highest priorities.

Problem Statement

There is a lack of awareness and alignment on basic principles for using platforms to accelerate vaccine development and authorization

Solution

CEPI proposes building a platform integration framework to create awareness and alignment, starting with foundational principles such as definitions, categorization, prior knowledge, and differentiated investment

Key Definitions

Modality refers to the structure of a product's active substance.

A *Platform* follows a specific, well-defined process using specific platform technologies, equipment, analytical methods, formulations and a specific Quality Management System to make products with uniform specifications and highly predictable characteristics.

Platform Technologies are well-understood, reproducible and antigen agnostic technologies, which can include a nucleic acid sequence, molecular structure, mechanism of action, delivery method, vector, specific process (e.g. fermentation or purification), analytics or a combination of any such technologies that the sponsor demonstrates (1) is incorporated in or used by a product and is essential to the structure or function of such product; (2) can be adapted for, incorporated into, or used by, more than one product sharing common procedural elements; and (3) facilitates the manufacture or development of more than one product through a standardized production or manufacturing process or processes.

Benefits of Platforms

The benefits of platforms increase with experience, leading to higher potential for positive benefit-risk assessments, regulatory prioritization during pandemics, and leveraging prior knowledge to accelerate development. Platforms could progress from Potential to Designated to Established over time.

A *Potential Platform* is a manufacturing process, specifications, equipment and Quality Management System that uses platform technologies and **can potentially be used** for the manufacture of more than one product through a standardized process but has not yet been validated, licensed by a WHO Listed Authority and used.

A *Designated Platform* is a platform that meets the following eligibility factors for granting the designation: (1) it is incorporated in, or used by, **a product that is approved** by a WHO Listed Authority (WLA); (2) preliminary evidence demonstrates that the platform has the potential to be incorporated in, or used by, more than one vaccine without an adverse effect on quality, manufacturing, or safety; and (3) data or information indicates that incorporation or use of the platform has a reasonable likelihood to bring significant efficiencies to the vaccine development or manufacturing process and to the regulatory review process.

An *Established Platform* is a designated platform that has been demonstrated for use in **two or more products** through validation, licensure by a WHO Listed Authority, and use.

Prior Knowledge

Leveraging prior knowledge, including non-clinical, clinical, and CMC data, can facilitate dossier preparation and drive decision-making in a Public Health Emergency.

Regional Manufacturing

Establishing regional vaccine manufacturing and supply chain networks is critical for vaccine equity and health security.

3.2. 'mRNA-LNP platform technology to support specification setting and determination of product shelf life', Moderna.

mRNA-LNP technology is well suited as a platform for medicinal products, affording the opportunity to leverage shared scientific principles and manufacturing processes between products to enhance development efficiency and streamline regulatory evaluation. Existing mRNA-based medicines registered in the European Union, including vaccines intended to prevent disease associated with COVID-19 and respiratory syncytial virus (RSV), demonstrate the potential of mRNA-LNP technology for medicinal products. Commonalities between these registered products, such as lipid composition, manufacturing processes, and analytical methodologies, highlight the feasibility of a platform approach, standardizing the development of mRNA-based medicines by focusing on shared aspects of product design and manufacturing.

Regulator expectations towards product-specific data required at the time of filing of initial marketing authorisation applications can pose challenges in product development, as often only limited development, clinical, and commercial experience are available. This is particularly challenging in the determination of batch release specifications and shelf-life, where the extent of the data for each individual medicinal product may constrain the utility of the statistical analyses ideally included in these assessments and justifications. This may also lead to inconsistent conclusions between products or an increased post-approval lifecycle management burden as analyses and conclusions are iteratively refined as additional product-specific data become available. Including applicable supportive data and knowledge from clinical experience, manufacturing history, and stability studies across products as a

platform approach in the development of new mRNA-based medicines can help overcome this challenge.

By considering the features which may be common between different mRNA-based medicines, the potential to build platform understanding of specifications and shelf life across the development of multiple products is apparent. Nevertheless, the applicability of platform knowledge and conclusions to a new product in development must be suitably assessed and scientifically justified. For example, not all attributes or their specifications may be universally applicable between products, particularly when products differ in function or therapeutic application. The utility of the platform approach can be maximised by allowing sufficient flexibility for sponsors to determine and provide scientific rationale to justify the elements of the platform which are supportive for the new product. This ensures the platform remains broadly applicable and based on scientific principles, while accommodating product-specific nuances. Ongoing lifecycle management of the platform dataset would include incorporate new data and account for evolving scientific understanding, ensuring the platform remains robust and adaptable.

Basing conclusions on deeper platform experience, more robust statistical analyses, and justified for new products by a focused set of key confirmatory product-specific data elements, can accelerate the development and review of new products, incentivise optimization and harmonization between products, and build greater public confidence in the quality and safety of new products. For regulators, the greater predictability in the content and conclusions of new MAAs, supported by well-understood and justified scientific principles, would increase the efficiency of review and reduce resource requirements.

3.3. Platforms for medicinal products manufactured using prior knowledge, investigational medicinal product (IMP) considerations, ISPE.

This presentation discussed, within the context of a forthcoming ISPE guideline, a platform approach for mRNA Investigational Medicinal Products based on application of prior knowledge supported by Quality by Design (QbD) principles.

The following were the key topics:

- **Platform Technology and Methods:** Platform technology is a strategic approach applied to similar products using consistent principles and methods. Definitions from Biophorum, ICH Q11, and EMA's guidelines were included. The definition from Biophorum was analysed by ISPE/BioNTech and leveraged as a suitable approach for the intended application to mRNA IMPs.
- **mRNA Manufacturing:** The presentation covered mRNA platform manufacturing. It briefly touched on "platform methods", identifying them as DNA Template, drug substance (DS) Platform, drug product (DP) Manufacturing, and Analytical Platform. It emphasized the use of QbD principles for IMPs and focused on discussing the approach for the DP platform method.
- **Case Studies and Data Sets:** A case study was presented to highlight approaches to develop similar compounds, focusing on dosage forms, quality attributes, process parameters, and control strategies. The LNP particle size across formulations was used to show the consistency across formulations. A minimum data set for mRNA/LNPs was proposed to confirm dosage form-specific elements. Phase-appropriate knowledge management based on Quality Risk Management (QRM), with increasing reliance on experiments across clinical trial phases, was suggested as a suitable and pragmatic approach to support the platform approach.

- **Challenges and Knowledge Management:** Key challenges include determining batch numbers especially for IMP in early Phases Clinical Trials, assessing mathematical models for design space robustness, and limited regulatory guidance specifically available for IMPs.

3.4. MAPS technology, a cutting-edge platform manufacturing, PDA.

This case study presented by GSK on behalf of the Parenteral Drug Association (PDA) related to the MAPS (Multiple Antigen Presenting System) Technology, a novel vaccine platform, especially appropriated for highly multivalent vaccines directed against *Streptococcus pneumoniae*. MAPS technology relies on high-affinity interactions between a biotinylated polysaccharide (PS) and rhizavidin-fused pathogen-specific proteins.

The Polysaccharide (PS) component of MAPS was used to illustrate the benefit of the platform knowledge for Process Evaluation (PE), with potential support for Process Performance Qualification (PPQ).

Due to the peculiar PSs chemical structural features and related prior knowledge, the PS manufacturing process can be platformized, and the same process understanding strategies can be applied when additional pneumococcal serotypes emergence trigger the development of next-generation vaccines, or to other emerging pathogens.

In the case study, GSK proposed to group PSs based on similarity of chemical behaviour during specific process conditions and PS structure. For each group, a leading serotype would be identified, i.e. a serotype that based on its properties (e.g., structure, sensitivity to hydrolysis, size, viscosity), would be the most at risk of failing to meet the acceptance criteria for quality or performance attributes for a given unit operation. For a lead serotype, it was proposed to consider process evaluation including full exploration of process parameters criticality and ranges. For the other serotypes in the group, it was proposed to focus process evaluation on extremes of process variables under the premise that the extremes are fully representative of intermediate conditions (bracketing approach).

The current grouping strategy is grounded on prior knowledge, structural information, and experimental data. However, moving forward, modelling approaches can be used to support grouping strategy and definition of lead-serotypes.

Platform knowledge, resulting from evolving experience on the process performance, could be used to inform modelling strategies for further optimization such as simplification of the experimental plan for process evaluation and onwards.

Leveraging the definition of fixed and adjustable parameters, a top line proposal for eCTD structure and content was presented where fixed parameters were proposed to be included in an eCTD section applicable to multiple serotypes, while adjustable parameters were proposed to be included in the eCTD sections specific to the impacted serotypes or group of serotypes. Platform development was proposed to be described in 3.2.S.2.6 while validation results, including the matrix approach, if any in 3.2.S.2.5 Process Validation and/or Evaluation. This strategy is expected to facilitate the distinction between platform-related and serotype-specific information, and to reduce the workload associated with file preparation, review and approval.

The strategy for MAPS filing will be assessed based on the progress of ICH M4Q(R2) and possible implementation of the Platform Technology Master Files (PTMFs) concept in the European Pharmaceutical Legislation as well as its associated regulatory framework i.e., initial registration and lifecycle management (LCM) activities.

The presentation concluded by highlighting the importance to enabling platform approaches and its data usage (i.e., prior knowledge) in regulatory applications, the importance to consider the approval of the platforms and not only products; as well as the benefit of platform use for life cycle management activities, where dedicated Post Approval Change Management Protocol (PACMP) can be used as an alternative of traditional variation submissions.

The stakeholder recommended the Agency to develop a guidance to standardise terminology and methodology for platform technologies, to enable platform approaches and its data usage (i.e., prior knowledge) in regulatory applications as this will accelerate the development of new medicines and vaccines for the benefit of patients.

Moving forward, *in silico* approaches for rapid product development and manufacturing, and effective use of platform prior knowledge to streamline Process evaluation and PPQ approach should be possible.

3.5. Viralgen - Platform strategy, Viralgen.

Viralgen Vector Core, S.L.U. (Viralgen) is a contract development and manufacturing organization (CDMO) specializing in the production of Advanced Therapy Medicinal Products (ATMPs). Its main product is a sterile suspension of adeno-associated viruses (AAVs) for human use, designed to deliver therapeutic genes between inverted terminal repeat (ITR) sequences. Viralgen employs technology that enables the manufacturing of various AAV serotypes with specific genes of interest (GOI).

Viralgen's platform views the transgene as a unique element and the capsid as a common structural component within each serotype, sharing consistent physicochemical characteristics. Its manufacturing process relies on a Pro10™ cell line derived from HEK-293, a single master/working cell bank used across all programs. This system integrates standard plasmids (Rep/Cap and helper) with the GOI specific to the target disease. Consistent raw materials, in-process controls (IPC), release specifications, and same equipment for the USP and DSP process, such as single-use bioreactors and same chromatographic skid with uniform parameters ensure reduced variability and streamlined production.

To date, Viralgen has produced >100 GMP batches across various AAV serotypes. These products share quality attributes that enable the assessment of limits, ranges, and critical process parameters. Viralgen employs a Quality by Design approach to establish process and product control strategies, leveraging historical data to standardise processes and reduce reliance on product-specific experiments.

Gene therapies typically require very limited doses, often a single administration. Combined with the focus on rare diseases or low-dose conditions, this creates challenges in developing robust and cost-effective manufacturing processes. Viralgen’s standardised platform accelerates development, ensures consistent quality, and reduces costs, making these therapies more accessible.

In Viralgen’s experience one of the main challenges in gene therapy is the lack of specific regulatory guidance to set meaningful acceptance criteria for AAV products, especially in the absence of enough product specific data. Regulatory agencies like FDA require batch acceptance criteria already in early clinical phases, particularly for residual impurities. In Viralgen’s view setting such criteria with limited data is complex, not only due to a lack of product knowledge, but due to the product complexity related to gene therapies.

Viralgen’s strategy is to use historical process performance data from products within the same serotype (+/- 6 sigma) alongside product safety and efficacy criteria. Products within the same serotype exhibit similar behaviours, enabling the grouping of GMP batch data to establish initial specifications. This approach has been approved by EMA, FDA, HC, and MHRA for four different

programs for early clinical phases. Viralgen aims to apply similar strategy and leverage knowledge based on a rational supportive by data in later clinical and commercial phases, reducing process validation activities, accelerating development, and ensuring high-quality treatments for unmet medical needs.

The use of data generated from similar products by CDMOs would be able to accelerate commercialization processes, especially in those cases where prior knowledge or exclusivity of the process does not allow for conclusive data. The use of data generated from similar products manufactured under a single process could help to gain deeper and safer knowledge than the exclusive production of each drug. The existence of confidential Master File type documents would help the development of these concepts.

3.6. Optimising development of gene therapies for rare genetic diseases, Fondazione Telethon ETS.

Fondazione Telethon, a not-for-profit organization developing ATMPs for rare genetic diseases and member of the EU-funded JOIN4ATMP consortium aiming to accelerate ATMP development and adoption across Europe – and in collaboration on platform concepts applied to ATMPs with T2Evolve, a EU-funded project focused on immunotherapy using genetically engineered immune cells – are exploring the parallel-sequential development of ex-vivo lentiviral vector transduced CD34+ stem cell gene therapies utilizing a platform concept to reduce the overall development burden for rare and ultra-rare diseases. The approach is initially targeting three different lysosomal storage disorders whilst maintaining the same mechanism of disease correction. The drug products all utilise the same promoter and vector backbone, highly similar manufacturing processes, primary packaging and product control strategies. The main variable is the therapeutic transgene for each different disease.

To establish a platform in this setting, it is considered appropriate to generate a full CMC data package on the first drug product to pass through each developmental study ("lead product") and then to perform significantly reduced confirmatory (e.g., reduced number of time points, reduced analytical panel) or additive studies for subsequent products ("platform products") based on the prior knowledge available and to address missing knowledge related to disease or transgene specific attributes without complete repetition.

Key considerations for platform development:

- The underpinning scope is to optimise the development of ATMPs and ease the burden of clinical translation in the early phases of development whilst safeguarding patient safety and ensuring the most direct path to marketing authorisation (MA).
- The resulting ATMPs are envisaged to be standalone drug products pursuing individual Marketing Authorisation Applications (MAAs).
- A matrix design of studies can ensure the generation of robust and exhaustive "platform" data packages from very early development stages to avoid the necessity of repeating studies at a later stage, jeopardizing MA achievement.
- It is considered that there is little to no opportunity for platform approaches based on identical end-to-end process and controls without adaptation. Modular approaches to manufacturing processes and CMC controls should be envisaged, defining components in the process that can be identified as modules constituting plug-and-play elements that could be cross-referenced across multiple programs with the importance placed on the inputs and outputs and an appropriately understood design space from modules rather than fixed parameters.

- Data from both development stage and authorised ATMPs should be leveraged when defining platform modules. The programs collectively contribute generated data to the consolidation or adaptation of the process/drug product design space within the modular platform framework.
- An a priori definition of the quantum of data to justify specific modules/components as a "platform" cannot be defined. Such definition would follow a case-by-case and risk evaluation-based process, also considering the intended use of the platform and clinical risk/benefit evaluation.
- As a developer that continues to seek alliances with industrial partners to out-license and advance ATMP development programs, the platform concept must safeguard the possibility to leverage data packages that constitute the transversal totality of data across sponsors to enable maximised efficiency to all associated development programs.

3.7. Prime editing platform technologies, Prime Medicine.

Prime editing is a genome editing technology designed to enable precise, programmable "search-and-replace" modifications of DNA without introducing double-strand breaks or requiring donor DNA. Briefly, a Prime Editor complex targets specific DNA sequences via a prime editing guide RNA (pegRNA) with both "search" and "replace" sequences, nicks one strand, and uses a reverse transcriptase domain to incorporate corrective genetic sequences. The repair is precise, with minimal off-target effects, and avoids undesirable bystander edits. The Prime Editing platform enables the correction of various mutation types, including point mutations, insertions, and deletions, making it applicable to a wide range of genetic diseases.

This presentation described the potential of Prime Editing to bring personalised therapies to patients suffering from genetic conditions. The case study focused on applying Prime Editing to Chronic Granulomatous Disease (CGD), a life-threatening genetic disorder caused by multiple mutations in multiple genes (e.g., NCF1 and CYBB). Prime Medicine's lead program, PM359, is a prime edited, ex vivo hematopoietic stem cell (HSC) therapy. Prime Editing is used to correct the causative mutation of in the NCF1 gene encoding p47 protein, and the corrected HSCs are then reintroduced to the same patient.

Prime Medicine has developed CMC platforms to support the PM359 program with the goal of leveraging modularity to accelerate development of future drug candidates that target other causative mutations of CGD. This modular CMC approach also de-risks the manufacturing process, quality, regulatory, clinical and analytical strategies. By leveraging shared components (i.e., pegRNAs, nicking guide RNAs (ngRNAs), Prime Editor mRNA) across different therapeutic programs and utilizing consistent manufacturing processes for those shared components, the Prime Editing platform has the potential to allow for rapid adaptation to new targets (causative mutations). The manufacturing strategy for ex vivo HSC therapies also exemplify this modularity. Processes like cell enrichment, electroporation, and cryopreservation are consistent across cell therapy programs, with minimal modifications needed for different mutations. Analytical assays, raw materials, stability programs and manufacturing steps can be standardised, potentially reducing the need for extensive re-validation for future drug candidates. This efficiency could reduce the time and resources required for both development work and regulatory review. In addition, modular platforms may be particularly valuable for rare diseases, where patient populations are limited, and conventional drug development approaches are both time consuming and cost-prohibitive.

The presentation concluded with an example of how CMC platforms and CMC data can be leveraged from an initial drug development program across new iterations of development programs that target other causative mutations of a rare genetic disease, ultimately streamlining the development

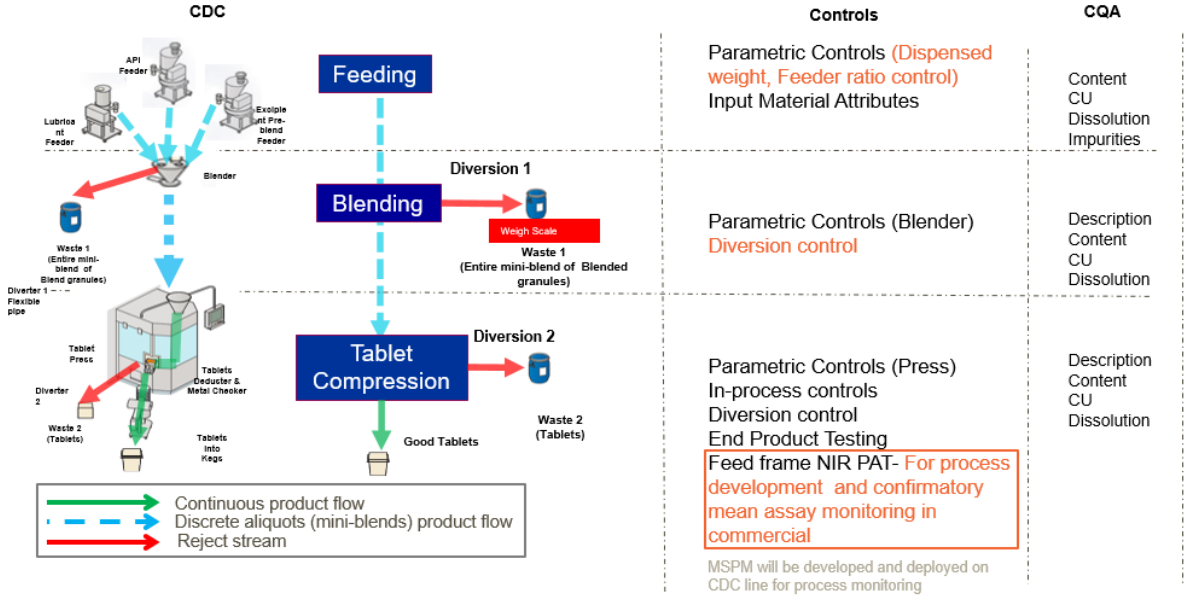
paradigm. In summary, the prime editing modular platform approach has the potential to greatly accelerate patients' access to this class of gene therapy medicines and improve patients' quality of life.

4. Session 2 summaries as provided by the presenters

4.1. An EFPIA/VE perspective (Continuous Direct Compression (CDC) platform focus), EFPIA/VE.

A case study was presented by EFPIA and Vaccines Europe (VE) on the use of prior knowledge via the GSK and Pfizer's examples of a Continuous Direct Compression (CDC) Tablet Manufacturing platform, which is used as a common manufacturing platform for multiple MAs and their medicinal products.

Figure 1. Continuous Direct Compression (CDC) Flow (Source: EFPIA)



It has been presented that although the CDC platform is well established for the manufacture of tablets, it has some industrialisation challenges which can be overcome through the use of prior knowledge in order to deploy the platform and how this can further enable industrialisation and lifecycle maintenance of the CDC and other manufacturing platforms.

It was noted that critical to the platform deployment is prior knowledge of the platform. This is used to inform a general approach to control strategy, product specific process validation and cleaning, troubleshooting of any issues or defects observed. The determination of the general limitations of the platform is ensuring that the platform can be deployed confidently within known boundaries.

For drug substance and product meeting pre-defined criteria, critical to the rapid and effective industrialisation is a streamlined approach to development focused on verification of the prior knowledge and its applicability to the new drug substance and product. Whilst it is already possible to re-use development data from existing products in a new MAA, it is currently not clear how best to structure this in the context of the current CTD. Companies are also concerned about expectations to re-assess data from earlier files and the implications for either reproducing unnecessary development data or the implications of adopting a streamlined development approach leveraging prior knowledge which is subsequently seen as deficient leading to significant additional development work and delays impacting patient access.

EFPIA/VE also presented their position that the below key guiding principles can enable the deployment of platforms and the use of prior-knowledge through the development of a world-leading regulatory tool (i.e., *Platform Technology Master File, s*ee * Expanding Master Files for human medicinal products in the EU/EEA). Since many of these are related to the future regulatory/ legislative framework that will apply to platform provisions and are outside of the scope of this meeting, they are not reproduced here but are detailed in the document linked to the text.

4.2. Application of a platform approach to oligonucleotide drug substance development, EPOC.

EPOC's presentation discussed a generic modular approach to platform strategies for synthetic oligonucleotide drug substances and the opportunities associated with the application of platform knowledge[2]. In addition to the general concept, a case study from Ionis Pharmaceuticals was presented to demonstrate how application of platform data may be used to streamline and expedite the development of therapeutic antisense oligonucleotides (ASOs).

Synthetic therapeutic oligonucleotides are commonly manufactured using the same basic unit operations i.e., solid phase synthesis, cleavage, purification, and isolation. Information gained from this work has led to a strong understanding of oligonucleotide chemistry and how the various processing steps impact associated quality attributes.

This understanding coupled to the platform nature of the manufacturing processes allows for prior knowledge built from decades of process development to be immediately and directly applied to new compounds.

EPOC's experience is that prior knowledge is already used in development, characterization, and validation of oligonucleotide manufacturing processes. Specifically, prior knowledge is commonly used in risk assessments and to define control strategies for the manufacture of oligonucleotide drug substances.

The applicability of prior knowledge is most apparent for an oligonucleotide platform where the scope of the platform is defined as a group of synthetic oligonucleotides of identical length, synthesized using the identical process and equipment, starting materials, reactants, reagents, and solvents. The primary difference being the sequence. Such a definition of an end-to-end platform may be unnecessarily restrictive.

EPOC emphasized that more flexibility can be gained by applying a modular approach, that aims at identifying the specific platform knowledge that is applicable to a new molecule entering the platform. A key tool to enable such a modular approach is a quality risk assessment (QRA). QRAs are conducted to determine how well the new compound fits within the existing platform but also to identify those areas that require more process development because the existing platform knowledge might not be applicable. Such an approach can enable the identification of platform unit operations and non-platform unit operations.

EPOC proposed that once a unit operation is validated for a platform, it is expected that the unit operation remains in a validated state for new oligonucleotides entering the platform. Applicability of the platform data could be confirmed with a single product-specific validation batch.

[2] Altevogt, D.; Cedillo, I.; Curtis, C.; Diorazio, L. J.; Faber, J.; Jones, M. T.; Telford, A.; Turner, G.; Wetter, C. Platform Strategies for Synthetic Oligonucleotide Drug Substances. *Org. Process Res. Dev.* **2023**, *27* (12), 2211– 2222, DOI: 10.1021/acs.oprd.3c00303

Case Study

Most ASOs, including all of the MOE gapmer ASOs manufactured at Ionis, are synthesized by the same 4-step elongation cycle, repeated for each new nucleobase added to the sequence until the full sequence has been synthesized. Ionis possesses a significant amount of prior knowledge and platform data for MOE gapmers synthesised in this manner and wished to leverage it to reduce development requirements for four ultra rare disease programs to treat severe neurologic diseases.

Each of the four programs has a development timeline between 18 – 36 months until filing of a marketing application, EU patient populations between 200 – 1000, and a maximum annual API supply requirement of 0.7 kg, whereas the minimum operational batch size produces 2.4 kg, resulting in significant waste. Further, due to the short development timelines and the four programs overlapping, Ionis would have difficulty completing the compound-specific development work normally required.

Therefore, Ionis requested Scientific Advice with BfArM to:

1. Use prior knowledge and platform data to establish the critical process parameters (CPPs), manufacturing set points, and proven acceptable ranges (PARs) for the manufacturing process (i.e. to not complete compound-specific development work for each program and instead utilize the best practice synthesis method optimised at Ionis over many years; the same synthesis method already being used for an approved commercial program).
2. Manufacture one single, combined registration stability and process validation batch prior to submitting the marketing application.

Ionis felt the proposals were justified based on the significant amount of prior knowledge and platform experience detailed, including significant process validation and commercial manufacturing experience with the same process.

BfArM deemed the proposed approaches acceptable, pending marketing application review, and work is underway per the agreed to plan.

Next, Ionis and EPOC would like to expand the use of a platform approach to larger scale programs, particularly for steps that are known not to be sequence specific. Another potential next step is to apply the platform approach to newer chemistries. For example, there are a number of oligonucleotide development companies that are building up a fair amount of experience with ligands and for siRNA manufacturing and other similar processes, for which a similar platform approach can likely be applied once sufficient knowledge and data are available.

Although oligonucleotides lend themselves well to a platform approach due to the consistency of the manufacturing process, some challenges to applying a platform approach successfully and wholistically have been identified and are as follows:

1. How best to evolve the platform as new knowledge is gained

   The preference from a pharma company perspective would be that the initial bounds of a platform are not constraining and can be adjusted with proper justification if within a reasonable scope of an originally established platform
2. Identifying an approach for utilizing platform knowledge to reduce requirements for post-approval change variations
3. "Platform" is a broad term with no clear definition
4. Regulatory uncertainty

The benefit of utilizing a platform approach is reduced if there is no harmonization among agencies to allow the approach

EPOC and Ionis appreciate the opportunity to present thoughts on applicability of a platform approach as well as a relevant case study and look forward to continued dialogue between industry and EMA to further advance acceptability of a platform approach in marketing applications.

4.3. Strategy for implementation of a platform approach for synthetic oligonucleotides, BioSpring.

As a CDMO for more than 25 years, BioSpring has significant experience in the manufacture of oligonucleotides for pharmaceutical and biotechnology companies. This knowledge is routinely implemented in the design, scale-up and validation of manufacturing processes.

BioSpring proposes an accelerated development strategy that utilizes product specific platform knowledge accumulated within the organization. Using this knowledge and confirming its outcome by data collected from traditionally validated manufacturing processes of representative compounds will allow the implementation of an overall process control strategy applicable to all members of the corresponding specific family of oligonucleotides.

The proposed platform approach consists of three steps:

1. Define the family of oligonucleotides based on their sequence, with same manufacturing process, CQAs, CPPs, CMAs, and risk assessments,
2. Set acceptance criteria for a new compound to be part of the family using statistical tools,
3. Apply platform knowledge to supplement sequence specific data, thereby facilitating and streamlining validation efforts and regulatory submissions.

This approach benefits patients, as it provides a faster development pathway with potentially reduced numbers of validation batches, resulting in a faster access to new medicines.

Using platform data for control strategy provides a more robust design space, based on cumulated prior knowledge. The inclusion of approved platform data would streamline the regulatory review process for approval of a new member of the platform.

In a case study, BioSpring applied the platform approach using a defined oligonucleotide family in which members share identical starting materials and CMAs, 80% identical sequence, the same CQAs and the same manufacturing process applying similar CPPs. Subsequently, the membership of a new sequence to the family was confirmed using statistical tools. A qualified small-scale model for all unit operations was used to show that using the defined family process parameters will lead to a product meeting the predefined quality attributes. A predetermined succession of Design of Experiments for the new sequence can be used to confirm the responses fit within the expected values for the family. Having confirmed family membership of a new compound, platform data could accelerate the development of drug substances with potentially the execution of only one PPQ batch for process verification.

However, challenges remain to overcome:

A suitable amount of data is needed to support a family and platform data might contain product specific data from different sponsors, raising concerns regarding data ownership.

The criteria defining a platform must be robust enough that changes of the platform processes will not affect individual family members.

The appropriate regulatory strategy to use platform data should allow sharing the extensive experience held at a CDMO with authorities while respecting the intellectual property of all stakeholders and supporting life cycle management of the platform process.

The potential submission of a Platform Technology Master File is a key element to support a single platform of a CDMO, supporting multiple applicants.

It could capture the platform data describing an oligonucleotide family and would allow a streamlined review process for marketing authorization of a new member resulting in faster patient availability.

As guidelines for Platform Technologies are developed, CDMOs should be considered as important stakeholders.

4.4. Statistical approaches to develop data-driven prior knowledge into a platform, CMC Statistical Network Europe.

The presentation delved into the statistical methodologies used to integrate prior knowledge into a platform to enhance drug product development. Statistical approaches to prior knowledge as a platform can be used to combine data into a single model where the parameter effects are considered to be exchangeable with the new product.

The content reflects their personal opinions and not those of their employers.

Executive Summary

The presentation emphasised the importance of leveraging prior knowledge to streamline development, enhance product understanding, increase process confidence and improve quality.

By using statistical methodologies such as frequentist, machine learning, and Bayesian approaches, prior knowledge can be integrated into data-driven models that are mathematically validated and quality-checked and could be used as a platform-model.

Key Messages

- *Statistical Methods for Prior Knowledge Integration:*

1. The presentation highlighted the frequentist, machine learning and Bayesian statistical methods to integrate historical data as prior knowledge platforms.
2. Frequentist methods involved collating data from new and historical studies, modelling them, and testing evidence to pool model parameters.
3. Machine learning methods involved splitting prior data into training and test sets, modelling them, and validating the model on new data sets.
4. Bayesian methods involved creating prior distributions for each model parameter and applying a range of techniques to combine the prior data knowledge with new study data to form posterior distributions.
5. The importance was emphasized of statistically planning the data collection, robust model fitting and evaluation necessary for reliable predictions. The examples shared on empirical models can be generalised to non-empirical models.

- *Benefits of Data-Driven Approaches:*

1. Data-driven approaches to prior knowledge can lead to more efficient drug product development and faster market access to medical products for patients.

2. These approaches enhance knowledge for new projects with limited product-specific knowledge during early development.
3. They drive greater consistency and efficiency in development strategies by generating cross-product usable platforms.

- *Case Studies:*

1. Examples were shown, combining development data with final processes for monoclonal antibody projects and immediate release oral solid dose forms.
2. These case studies highlight the practical benefits of using prior knowledge models to set up risk assessments, improve FMEAs, and reduce experiment design resources.
3. Tools were highlighted to assess the statistical validity of combining the prior data knowledge with the new products data.
4. The statistical validation provides a quantitative evidence-based approach, from the submission applicant to the regulator, of the value proposition delivered via a data-driven prior knowledge platform.

Conclusion

The presentation concluded by emphasising the imperative for regulatory adaptation to integrate data-driven prior knowledge into development processes. It proposes that prior data can be combined into a platform when input parameters have similar effects on a response, then various statistical approaches can be used to assess the evidence of suitable performance.

5. Summary of the panel discussions

The panel discussions focused on three main areas: platform definition, applicability of the platform to different products, and lifecycle management. Consideration was also given to platforms based on several products for ultrarare diseases.

i) Platform definition

It was recognised that the term 'platform' will continue to be used for a variety of approaches. In the EU the future legislative framework will define what can be submitted under a potential platform registration scheme and where this does not accommodate all scenarios, prior knowledge can still be leveraged in applications.

Questions discussed:

- *What is, for you, the difference between a platform and (prior) knowledge and understanding of a manufacturing technology (with or without modelling)?*
- *To what extent do you consider that Platforms need to be E2E?*
- *Can any stakeholders give their view on what are the minimum data required to show that their platform is established (i.e. data required to corroborate your proposed 'platform'), in terms of data source (will you use development product data only? /only use data from authorised products?/ what literature data might be relevant?/ will modelling data be used?) and amount of data (e.g. number of products)*
- *Please comment on how you would define the fixed components and pre-defined intentionally variable components of your platform, and what would be the minimum data set for each of them.*

Summary of the responses:

It was noted that there were different views among stakeholders on what constitutes a platform:

- *Some stakeholders consider that platforms and prior knowledge are the same and are interchangeable terms.*
- *Other stakeholders recognised that there is a close link between prior knowledge and platform but made the distinction that prior knowledge is used to define a platform. They considered the platform a modality to express and demonstrate the prior knowledge of a specific manufacturing process that has been acquired, or in other words, a platform could be seen as a body of prior knowledge that is registered in an MA/PTMF (with open and closed parts).*
- *Some considered that prior knowledge might also be defined as retrospective data, while platform approaches can comprise both retrospective and prospective data packages.*
- *It was noted that approximately 35% of attendees indicated that they had already tried to use prior knowledge for MAA and/or clinical trial applications in the EU and quoted positive experience.*
- *-Some stakeholders proposed to set out rules to limit a platform to a family/class that is included or excluded and include pre-agreed acceptance/inclusion criteria as to how it can be applied to future products or post-approval changes for the same product. It was also proposed that a platform with linked products in one therapeutic area may facilitate for example, greater predictability of the impact of impurities in new products being considered within the platform.*
- *Some stakeholders considered a platform to be broader, while others suggested the use of a platform to register some kind of design space.*
- *Others suggested that a platform can be described as a mathematical model applicable to different products.*

Regardless of the lack of an agreed definition, it was clear that scientific-based approaches are needed to bridge different products and scales so that the common data can be used for one platform.

Overall, it was recognised that a platform approach can provide a streamlined development and validation approach to accelerate the availability of innovative medicines to the patient based on a more robust control strategy established across an entire family of products instead of a single product.

Some stakeholders made proposals for definitions for 'platform', 'platform technology' or 'platform method' (see for example summaries from CEPI and ISPE above) or even suggested that a platform should follow a modular approach. However, whereas the proposals were noted, no discussion on the definitions per se took place as legal definitions were considered to be out of the meeting scope.

Another aspect raised is the balance needed between flexibility in the platform definition and its potential efficiency:

- A constrained platform definition with clear "on platform" vs. "off platform" criteria may simplify decision making on the relevance of platform knowledge but could result in many highly similar platforms; this would hinder the accumulation of deep platform knowledge and understanding, and disincentivize ongoing improvement of the platform.
- On the contrary, a very flexible definition may undermine potential efficiencies in product development and evaluation, where each platform element may need to be considered 'case-

by-case', thereby taking away the advantage of the platform to be agile and reduce the amount of data need to support the platform.

The importance of incorporating process development data into the platform and not limiting it to data from authorised products, was mentioned. The minimum data set is generally expected to be commensurate to the development stage of the platform and to the product indication (e.g. for ultrarare diseases there might not be information from authorised products at all). Having access to a useful mathematical model can add robustness to specific components of the platform e.g. establishing appropriate specifications and shelf-life.

In general, it was agreed that risk assessments are needed to define the minimum dataset of prior knowledge which can be leveraged in the context of a platform approach.

Some stakeholders proposed that for the use of the same platform technology, applicants should always:

- justify the applicability of the authorised platform for any new products (in MAAs and CTAs)
- specify where the common (and/or product specific) platform information is located
- minimise the amount of de nuovo data that regulators need to assess for new products

In this regard, some stakeholders requested that future regulatory guidance specifies the amount of data needed to justify a platform (e.g. data from a single approved product may not justify a platform) and the level of information required in MA dossiers. A challenging aspect to consider regarding the use of data from early clinical programs raised by regulators, is that the safety and efficacy of those products is not known. For example, if those products do not progress because of a safety issue, one can question whether/ what would be appropriate to leverage from the associated prior knowledge.

Applicants should provide data to demonstrate that the product fits into the proposed platform. When their inclusion is based on a risk assessment, bridging data are expected to show that the product is compatible with the platform. It was recognised that the minimum number of products and number of batches of these products to define each platform differs. It should be up to the applicants to justify the number of products and batches put forward based on the type of product, the development phase of the product, the developer experience with the manufacturing platform process and the related knowledge. As regulators and stakeholders gain further experience, regulators might be able to issue more specific recommendations, but at this point in time it would be too early and potentially block innovation.

Stakeholders were also requested to reflect on the number of products that could be linked to a given platform, also considering the product class and the prevalence of the indication. In this regard it was recognised that the more data used to support its establishment, the more robust the platform would be. QIG noted that such matrix approaches, as proposed in some presentations, have already been applied for vaccine updates e.g. for polysaccharide vaccines, when new serotypes have been incorporated. Participants were asked what the extra benefit from using a platform approach on top of the matrixing approach would be for such vaccines. It was claimed that a platform would streamline registration of subsequent products.

It was noted that the benefit/risk profile of the product also dictates where more limited/different (e.g. more developmental) data sets could be accepted e.g. for a rare disease product with high unmet medical versus prophylactic vaccines, where more mature data would be expected.

Overall, it was concluded that applicants should define a balance and evaluate whether it is worth opting for a platform registration scheme (which might be available for certain products in the future) if only a small portion of the manufacturing process is amenable to a platform, rather than referencing

prior knowledge in the dossier as it is currently done. It was noted that stakeholders' views might be different on that point.

To make use of a platform approach, a clear definition is needed. Applicants need to define which parts of their process constitute a platform within the constraints of the (future) legal definitions, and as needed, justify which parts are fixed and which are variable. In addition, it was noted that an end-to-end approach for the clinical trial phase may be challenging.

With regards to clinical trials, it was noted that prior knowledge is systematically used by companies to develop new products and therefore, to support clinical trial applications for IMPs.

Several stakeholders supported the concept of a "Platform Master File" (as proposed by the European Parliament) that captures the prior knowledge to support the marketing approval of new family members. Although such regulatory/legal matters were outside of the meeting remit, several stakeholders raised the importance of considering CDMOs as important stakeholders in any future PTMF discussions to permit sharing of data sets with regulatory agencies, while respecting the intellectual property of all stakeholders. Sharing proprietary platform data from multiple MAHs for CDMOs to obtain a platform requires agreements between the involved companies.

Some stakeholders also stressed the benefit of sharing platform knowledge and making it publicly available for example by industry consortia.

With regards to the definition of fixed components and pre-defined intentionally variable components, it was noted that these would specifically depend on the platform claim being made. Generally, fixed components comprise scientific principles and platform data, and variable components comprise product specific data (e.g. length and sequence of the targeted mRNA, process parameters that can be adjusted to cope with specific polysaccharide properties of the MAPS). It was claimed that flexibility in the definition of the platform is needed to maximise potential utilization.

ii. Applicability of the platform for different products

Questions raised:

- *Examples presented included mRNA, oligonucleotides, continuous direct compression, MAPS (vaccines), AAV vectors, ATMPs. Will the 'fixed' components comprise data which are identical for each product, or could there be minor differences? Please discuss and justify your proposal.*
- *It would be helpful if you discuss how you will demonstrate that a new product is part of the platform. For example, how does sequence length etc impact on CQAs if you want to leverage specifications and stability from other products.*
    - *Would it be appropriate/realistic to expect a protocol in the initial MAA for demonstrating that a new product is part of the platform?*
    - *Would you already be able to identify in that protocol what the extent of any minor differences will be in subsequent MAAs?*
- *How do stakeholders plan to show in the context of use of a platform for any subsequent/follow-on product that there is no impact to safety/efficacy?*
- *In view of autologous products, what impact has the autologous source of a starting material with respect to different underlying diseases?*

Summary of the responses:

Some presenters indicated that based on the current knowledge of their product/process they had decided to pursue standalone MAA and not considered defining a platform. Other presenters advocated

a platform approach as it can set the scene for future products and avoid re-submission and re-assessment of the same information in different MAAs. Regardless, it was noted that a company's approach on that point may change in the future when more information/data are gathered.

It was noted that the ability to leverage chemistry manufacturing and controls (CMC) data throughout the development phase, and ultimately the MAA for each product, requires consideration from an early stage of development to ensure that the minimum dataset is available to support each standalone product dossier.

Some stakeholders claimed that existing knowledge is fully leveraged to develop platform control strategies, which are then applicable to new products that are intended to be added to the platform. In the presence of reliable data, this alleviates the need to demonstrate this same level of detail for every new product going forward and expanded operational flexibility (i.e. total line throughput and batch size flexibility). They claimed that such an approach is foundational to the platform technology and is following general regulatory requirements. However, the need to have enhanced product-specific data was also highlighted. For example:

- Accelerated stability testing to quickly generate data predictive of long-term stability should be generated and compared to the stability profile predicted by cross-product analysis of the expanded platform data set; this can bridge between the platform approach and product-specific data expectations for both new applications and used for lifecycle updates to the platform.
- Real-Time stability data can supplement the limited product-specific stability data available at submission to confirm and validate accelerated testing results and model-based predictions as data become available.

There was also a proposal to conduct an early assessment of the feasibility of linking proposed new candidates to a platform, followed by confirmation of this by executing a limited/defined number of Design of Experiments (DoEs) to show compatibility with platform data.

Although such regulatory issues were not in scope of the discussion, with regards to the submission of the documentation there was a stakeholder's proposal to include:

- - eCTD platform sections applicable to multiple products to document fixed parameters (e.g. serotypes: common raw materials as well as process steps, equipment & parameters, reagents …), and
- - eCTD sections specific to one product (e.g. serotype) to document adjustable parameters (including serotype specific -to adjust according to serotype's properties- process parameters)

It was acknowledged that the approach would depend on the design and definition of the platform. Some participants suggested that the platform itself might be kept restricted to certain elements (i.e. not end-to-end) that would remain consistent in all linked products such that there would be no need to update the platform or withdraw certain products from the platform. The usefulness of such type of platform, however, would be restricted and challenging (see discussion above regarding platform definition).

It was pointed out that there is a need to have a good understanding of how the product fits in the platform and which bridging data are needed to justify the addition of a new product. The applicant should justify the number of batches needed to demonstrate that the new product is part of the platform; the use of mathematical models in demonstrating and justifying this is generally supported by regulators. Developers are encouraged to discuss their experience and views among themselves and publish them to disseminate the experience gained especially for specific product classes. This can

substantially progress the depth of knowledge available to support platform approaches for all stakeholders and assessors.

During the discussion some reflections on how platform data should be managed in order to understand the impact across different programs and developers were also shared. If there is an issue, the other developments would need to be evaluated, and some might need to be put on hold.

There was a proposal to base product specifications on anonymised data from other products. However, it was noted that this might have some limitations. For example, if an impurity is present and neither regulators nor applicants have access to data from the other products, they don't know the safety of those products, or if the patient population they intended to treat with this new product is different, one cannot confirm that the use of that anonymised data for the applied product is acceptable. It was also noted that the impact of the manufacturing scale on the product quality should also be considered.

In response to the applicability of the platform to different products, one company stated that at the time of the clinical trial for the first product they would establish a comprehensive CMC package. It would not be possible to leverage much data as they would have limited experience at that time. However, later (for example when they develop a product for a different mutation in a different gene), the company would not intend to change the manufacturing process, the IPCs, etc and therefore they would aim to demonstrate consistency and comparability of critical drug substance/drug product attributes between the first product and the new product under development. They would try to leverage platform analytical assays with product specific qualification and reduce some assays (e.g. impurity assay) where possible, by leveraging process development data.

There was a proposal to define inclusion and exclusion criteria when defining a platform. If one of the products does not fulfil the inclusion criteria it should not be included.

iii. Lifecycle management

Questions raised:

- Please discuss how the platform will remain reproducible for linked products (including future products) even during their lifecycle i.e. there is reasonable certainty that the 'platform' can link to multiple products.
- How do you see that changes/improvements can be introduced in the platform for all products that are manufactured on it.
- What are the challenges/issues with defining and maintaining your platform?

Summary of the responses:

In general, participants recognised that continued development and innovation in manufacturing technologies and science (e.g. mRNA-LNP) require thoughtful lifecycle management of established platforms based on current state of the art understanding. The need to keep collecting post-marketing data was acknowledged in terms of:

- Real-World Evidence: Collect and analyse real-world evidence from post-market surveillance to continuously validate and update shelf life and specifications, for example.
- Continued Verification: In both individualised and non-individualised contexts, ongoing verification of the appropriateness of the platform must be performed to confirm appropriateness of the limited product-specific or patient-specific data included in the review of the initial MAA.

Stakeholders suggested that a platform master file (PTMF) as mentioned above, if included in the future pharma legislation proposal, could be introduced as part of the original MAA or post-approval.

Stakeholders indicated that the platform must be robust and defined to such an extent that lifecycle changes/revisions of platform elements are possible (e.g., as a result of additional process knowledge gained), as there is a need to keep the dossier up to date, and lifecycle changes should not:

- Negatively impact the risk/benefit profile of the medicinal product already approved under the concerned platform approach
- lead to linked products dropping out of the platform, and
- it was proposed that resulting changes could still be considered under a continued platform verification strategy/approach and be documented accordingly

The majority of participants were of the view that certain aspects of the platform (e.g. manufacturing processes, elements of the equipment, control strategy) can change over time, like for traditional manufacturing processes. Therefore, if a platform approach is pursued, the platform itself may need to evolve and improve over time and the regulatory framework needs to allow updates. In this regard, it was also noted that there can be a scenario where a product originally included in a platform may no longer fit into the updated platform and, therefore, might need to be excluded from it. This might trigger the consideration of development of a separate platform, covering new family-products. With regards to the lifecycle management and maintenance of the platform applicability to all concerned products whilst still evolving, stakeholders expressed the value of EU's grouping and work-sharing procedures, albeit it was recognised that dossiers can be updated without the need to register a platform.

In response to the question on the use of protocols, stakeholders indicated that they would consider the use of Post Approval Change Management Protocol (PACMP) to implement changes in addition to traditional variations.

There were some proposals from stakeholders to develop a platform master file in the EU with open and restricted parts as they exist now for active substance master files (ASMFs). However, as indicated above, these legal aspects were not within the scope of the meeting as they are outside QIG remit and have therefore not been discussed.

iv. Platform based on several products for ultra rare diseases

- *Would you consider it acceptable to validate a platform-based manufacturing process based on the data of different products manufactured with it, prior to one of these are approved as medicinal product?*

The use of prior knowledge and platform manufacturing approaches for the development of medicinal products for ultrarare diseases, especially for early phase trials, can be considered useful in the context of the limited product-specific knowledge and the very limited batches available for small patient populations. It was claimed that prior knowledge can be used to reduce development time and costs and therefore accelerate access for patients, while avoiding repetition and the unnecessary conduct of animal studies, enhance process knowledge and increase the development success rate, while safeguarding products' quality and patient safety. This was seen as key to the sustainable development of medicines for ultra-rare diseases.

In relation to this, one of the presented case studies included an example of the use of prior knowledge accumulated on AAVs to design a strategy on how to set acceptance criteria in early clinical phases, which is based on the production system data collected from different products. It was proposed that

this approach could be used for later clinical and commercial phases to reduce the process validation activities; with the potential to offer treatment to patients in areas of unmet medical needs, reduce development timelines and enhance product accessibility and affordability.

A conceptual connection to individualised/personalised medicines was also raised. Considerations around i) the core data set needed at initial MAA to appropriately reach a benefit-risk conclusion for a product (e.g. mRNAs) not yet designed or characterized, ii) how the quality of an individualised medicine is continuously confirmed, as patient-specific manufacturing continues, and iii) how the development and potential marketing authorization of individualised (mRNA-LNP medicines) can be used to pressure test the application of platform concepts between non-individualised products, and vice versa, were raised.

6. Conclusions and next steps

Stakeholders welcomed the on-going efforts of the EMA QIG to support innovation in manufacturing and quality. This 4th LLFG meeting provided a valuable opportunity to hear industry's and academia's views and proposals with regards to the use of manufacturing platform technologies and to hold an open dialogue on this topic. Overall:

- The use of prior knowledge and platforms is seen as fundamental to streamline development programs and facilitate early access to new medicines for patients. Prior knowledge was seen as the basis for establishing a platform manufacturing approach.
- During the meeting it was noted that there are different interpretations among stakeholders on what constitutes a platform. QIG acknowledges this term will probably continue to be used with the broadest interpretation, but in the EU, it is anticipated the forthcoming legislation will provide a definition for platforms for the purposes of an associated EU registration.
- For end-to-end manufacturing platforms, stakeholders highlighted that some platforms might need a combination of fixed platform-specific and flexible components to be realised.
- Some attendees proposed a modular approach in addition to the end-to-end approach in which the platform would consists of individual manufacturing steps (modules) that could be cross-referenced across multiple programs, for example generation of a critical starting material e.g. viral vectors for ex vivo gene therapy or sgRNA used in gene editing approaches).
- During the meeting a general desire from stakeholders for flexibility with regards to platform implementation was raised e.g. they considered that although, ideally, one approved product should be available to approve a platform, this should not be considered a pre-requisite; developmental data, should be acceptable. Especially, in view of rare diseases, there is a need to find a balance between how much data and from how many products there are data. In this regard, it was noted by stakeholders that the minimum data required to demonstrate a platform could be based on developmental data, clinical trial data, modelling/ theoretical data and/or data from approved products. The relevance and adequacy of the supporting data should be justified.
- Several stakeholders stated their preference for the implementation of a PTMF, although this may involve data sharing. The need to consider the value that a mechanism to (confidentially) access CDMO data in accelerating product development was stressed by industry stakeholders. However, this is a legal aspect which is outside the remit of QIG.
- Lifecycle management for platform and associated products was discussed and needs further consideration e.g. is the platform only presenting development data and be static or it will define processes/ parameters which will change.

- As next steps, the QIG will use the information gathered to inform its future discussions and consider which additional actions are necessary to facilitate the implementation of manufacturing platforms once the updated pharma legislation is available, while facilitating the use of prior knowledge based on experience with a specific manufacturing platform within the current pharma legislation. Stakeholders are welcome to share any additional quality considerations they may have with QIG and request a 1:1 meeting with QIG to discuss further case-studies in more detail.

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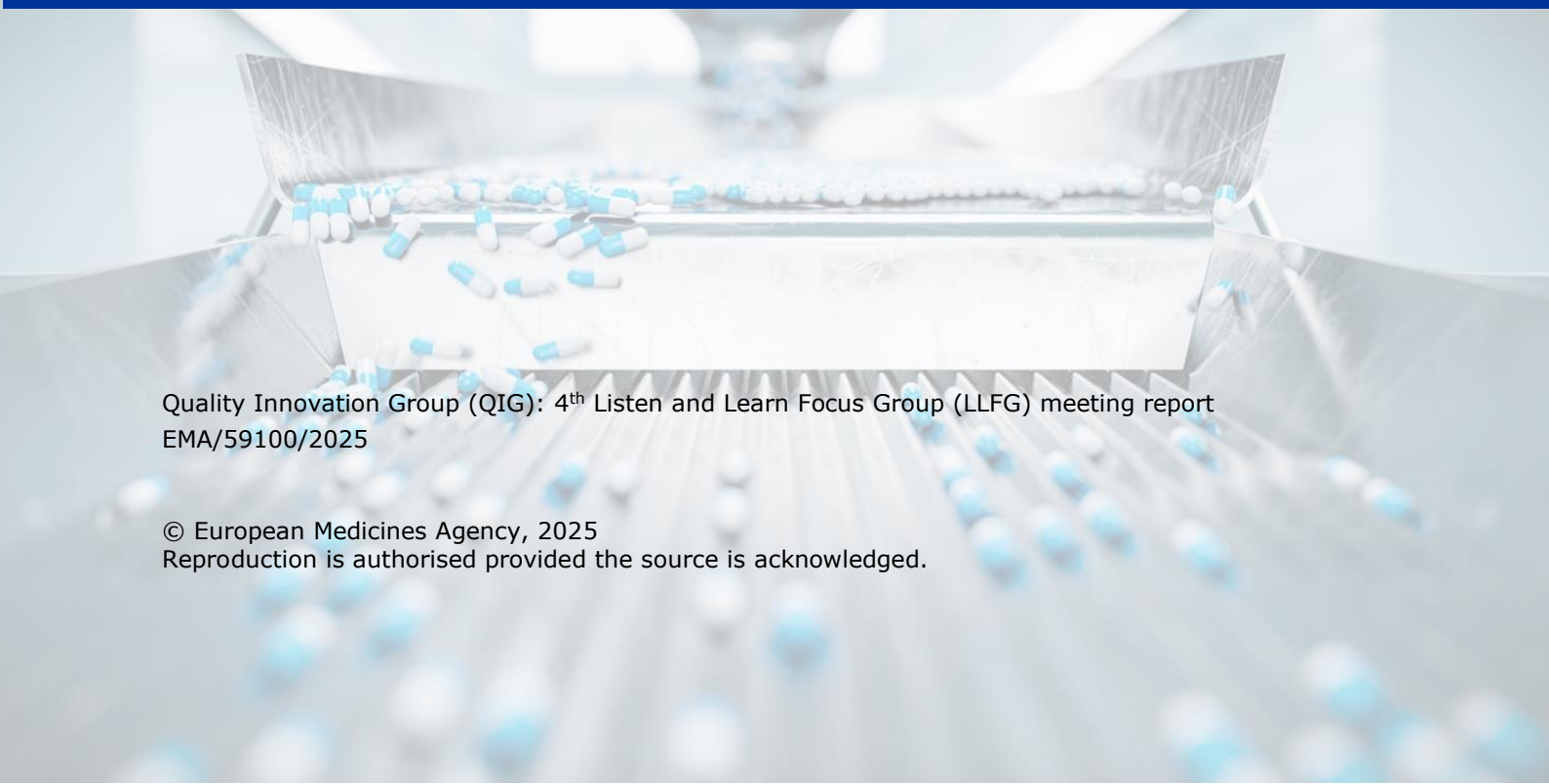

Quality Innovation Group (QIG): 4th Listen and Learn Focus Group (LLFG) meeting report
EMA/59100/2025