EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Quality Innovation Group (QIG)

Listen and Learn Focus Group (LLFG) meeting report

- Continuous manufacturing
- Decentralised manufacturing

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Meeting Report

Listen and Learn Focus Group (LLFG) meeting Quality Innovation Group (QIG)

13th March 2023, Virtual

Introduction

The Listen and Lean Focus Group (LLFG) meetings are part of the Quality Innovation Group (QIG) horizon scanning activities and are meant as proactive discussions with stakeholders on forthcoming innovative technologies in drug manufacturing and/or facilities design. The objective is to understand the challenges they face, and proactively formulate appropriate regulatory responses to these as they mature (e.g., developing position papers, Q&A documents, etc.) to support their development and implementation, and ensure EU harmonization as well as seek global alignment.

The QIG selected some priority topics for 2023, taking into account the background information available (i.e., EMA Regulatory Science Strategy to 2025, stakeholder`s responses to the QIG survey published in December 2021, an overview of ITF meetings with CMC discussions between 2019-2021, and relevant information from the NCAs) (2023 work plan for the Quality Innovation Group (QIG) - Consolidated workplan (europa.eu)). Although some challenges have been identified from interactions with industry and literature review further dialogue with stakeholders was required to fully understand the specific CMC and GMP challenges they face.

The QIG organized the first LLFG meeting on 13th March 2023 focusing on two of its priority topics for 2023, namely continuous manufacturing (CM) of biologicals or end-to-end CM (all product classes) and decentralized manufacturing (DM).

A call for abstracts from stakeholders for the proposed two topics was launched at the end of 2022 to identify specific focus areas for these priority topics to be discussed during the meeting. The QIG considered all abstracts submitted by industry and academia and selected four to be presented by stakeholders during the LLFG. The aim of these presentations was to describe the proposed technologies and their maturity and to point out stakeholders' perceived scientific and regulatory challenges with the current EU regulatory framework.

The event was attended by QIG members and secretariat, 49 industry participants, 10 academics, 42 regulators from the national competent authorities, as well as partner international regulatory authorities, namely US FDA and PMDA representatives.

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The meeting was organised in the following sessions:

1. QIG structure and operation
2. Session 1 on Continuous Manufacturing
    I. QIG presentation on current regulatory requirements
    II. Presentation on CM of biologicals "time-to-results" analytics challenge, Merck
    III. Presentation on Enabling implementation of CM through process models: a vaccine platform example, GSK
    IV. Plenary discussion on CM
3. Session 2 on Decentralized Manufacturing
    I. QIG presentation on current regulatory requirements
    II. Presentation on DM solution for autologous ATMPs, Tigen Pharma
    III. Presentation on DM individual manufacturing units, MSD
    IV. Plenary discussion on DM
4. General discussion and sum up

The next sections of this report summarise the discussion and key points raised by industry and academia stakeholders during each of the sessions of the LLFG. The stakeholders' identified challenges and proposed solutions for the two technologies are also highlighted in the conclusion section of this report. While it is emphasised these are the views expressed by stakeholders, the QIG took note of these and outlined some areas for future follow-up as presented in section 5 of the report.

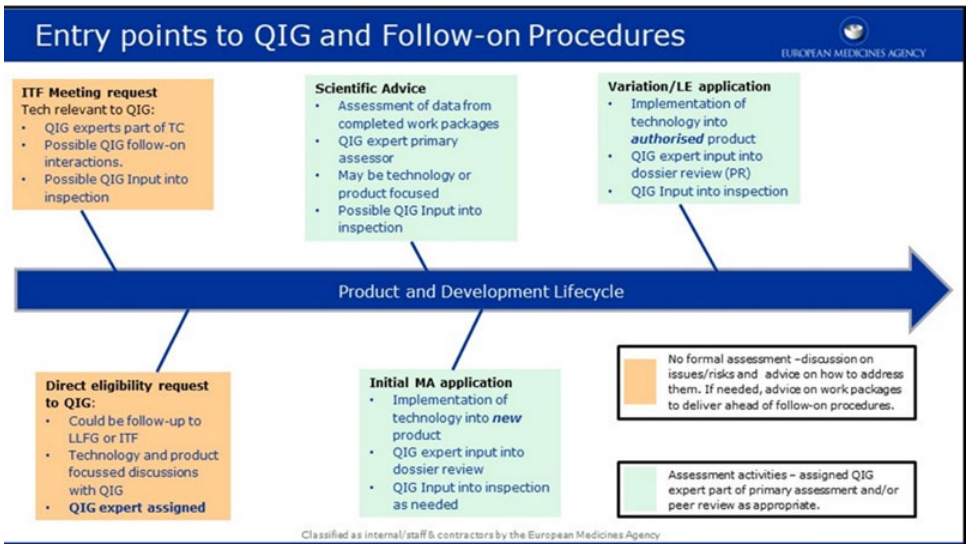
1. QIG structure and operation

The QIG gave an introductory presentation on the overall aims of the QIG and the plans for delivering these. QIG was established in 2022 to deliver on key goals of the EMA's Regulatory Science Strategy to 2025 such as enabling and leveraging research and innovation in regulatory science and catalysing the integration of innovative science and technology into medicines development.

The QIG is a multi-disciplinary group comprising GMP inspection and quality assessment expertise covering the spectrum of biological and chemical products. The interactions between the group and the EU working parties was also explained, as well as the intention to develop mutually beneficial links with academic experts in relevant fields. To meet the innovation goals for the network, the QIG is meant to be the point of entry to the EU's regulatory system for developers of CMC innovations in scope and will seek to establish a predictive EU regulatory framework and collaborate with other regional regulatory agencies to enable widespread implementation of these technologies via established multi-regional organisations.

The 2023 priorities of the QIG are CM, DM and automation/digitalisation of processes. The first two of these priorities were the focus of this initial LLFG while it is expected that automation/digitalisation will be the subject of a future LLFG meeting later in 2023.

The intention is that QIG will support developers of relevant technologies throughout the development lifecycle. This will be realised by providing a continuity of coherent advice at a level currently possible for the concerned technology, following up the development of the technology offering additional regulatory perspectives by e.g., stressing the challenges, actively exchanging information with other working groups and international partner agencies and thus initiating meaningful regulatory solutions. The ultimate goal is to help developers navigate the perceived and actual regulatory hurdles, thereby facilitating implementation of novel technologies. The QIG will interface with existing regulatory procedures (ITF, scientific advice, MAAs and post approval procedures) but will supplement this with (informal) discussions with developers of relevant technologies to help them plan their development programs. In addition, the QIG will use learnings from these interactions to establish regulatory principles and provide guidance to developers. A graphical representation of how QIG will interface with other EMA regulatory procedures is provided below for reference.



The QIG is committed to collaborate with other international regulatory authorities to ensure a predictable regulatory framework to enable implementation of innovative technologies which will ultimately benefit patients in the EU.

2. Continuous manufacturing

I. QIG presentation on current regulatory requirements

As a preamble to the first session on CM, the QIG presented the current regulatory framework for this technology. Special focus was given to the recently published ICH Q13 guideline, adopted by the CHMP in December 2022, for which a broad outline of the scope and the content was presented. Emphasis was given on the fact that the general principles of this guideline apply to both chemical and biological entities. In addition to ICH Q13[1], EU has developed and implemented other guidelines, Q&As and

[1] ICH guideline Q13 on continuous manufacturing of drug substances and drug products - Scientific guideline | European Medicines Agency (europa.eu)

compendial texts whose principles enable implementation of CM even though they are not specific to CM. Appropriate guidance on the requirements in terms of enhanced control strategies including design space, PAT tools, use of models, real-time release testing, or continuous process verification can be found in those EU guidance documents.

The limited experience with product applications using CM for biological products was noted. All the applications approved in EU through the centralized procedure, either new applications or variations to existing ones, pertain to the chemical field. This highlights the potential for progress in the implementation of CM. Although CM is not a new topic anymore, and ICH international guidance is now available, EU regulatory authorities are conscious of the fact that the technology is still evolving and there are outstanding challenges to be addressed to see the full potential of CM. Potential areas that may need further reflection include the implementation of full performance-based control strategies and the integrated (end-to-end) processes. These may warrant further follow-up discussion with stakeholders.

QIG expressed willingness to support the increased registration of CM processes for the benefit of patients. Thus, the aim of the CM discussions at the LLFG meeting was to understand the remaining perceived barriers raised by the participants.

Academia representatives enquired whether additional regulatory challenges regarding the combination of continuous manufacturing of drug substance and drug product not covered in ICH Q13 guideline were identified by the QIG. It was clarified that extensive discussions on this topic have taken place at the level of the ICH Q13 Expert Working Group and the guideline was developed based on the experience available at the time of drafting. The aim during the drafting process was to be as broad as possible to embrace new modalities/approaches not seen so far. While CM is still evolving, it is expected that not all the possible CM modalities have been seen in submitted applications. Therefore, decisions so far on continuous manufacturing have been taken based on the applications that have already been reviewed. The QIG reiterated that stakeholders can approach the group with their new developments (e.g., end-to-end CM) and ask any regulatory question they may have as part of the LLFG meeting, follow-up 1:1 meetings or CHMP scientific advice requests.

Industry supported the challenges identified in the QIG presentation regarding end-to-end manufacturing and how the GMP for active substances and finished products interact. They also expressed a concern on the EU Questions and answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters (EMA/CHMP/CVMP/QWP/354895/2017). Although these are not specific to CM, they are key components for CM and can present some challenges, particularly when considering how to describe model-based, parametric control strategies in an MAA .Industry also highlighted the lack of regulatory guidance on process models, creating certain uncertainties, particularly for the performance-based approaches.

II. CM of Biologicals: "time-to-results" analytics challenge, Merck

The second presentation of the CM session was delivered by industry speakers and focused on how biotechnological products could be continuously manufactured, with key aspect being that the process remains in a state of control, such that process input variables and process output variables including critical quality attributes (CQAs) are within specified control ranges.

One **challenge** pointed out was that currently there is a lack of on-line or at-line analytical tools for measurement of CQAs (e.g., HMW, LMWs, glycan, HCPs, rDNA, rPA, deamidation, oxidation, bioburden, endotoxins, etc.) with an appropriate "time-to-result" response. These are necessary to be implemented to control product diversion in a timely manner because of the high speed of the downstream product stream.

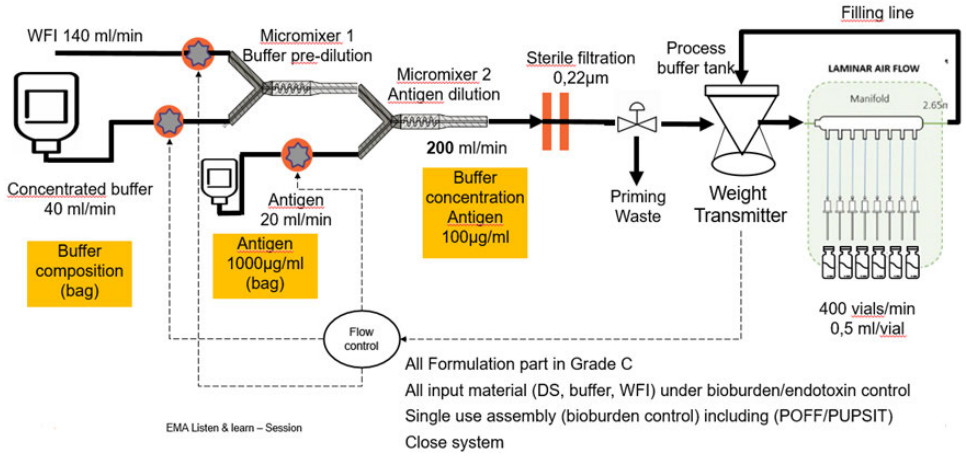
Another **challenge** described is that for upstream manufacturing, the impact of a process disturbance on CQAs may last for a variable period depending on the type, intensity and duration of the disturbance which could greatly exceed the simple diffusion effect characterized by the residence time distribution (RTD). To achieve a desired integration of the upstream and downstream processes, it would likely be essential that CQAs are monitored by a real-time measurement (e.g., utilizing process analytical technologies (PAT)) to ensure a proper period of product diversion to avoid the risk of mixing non-conforming with conforming materials. However, currently available PAT tools do not allow to directly monitor the CQAs of the product in continuous harvest. Multi-attribute mass spectrometry (MAM) is a potential PAT tool which is highly promising and that could address this limitation. However, there are still many challenges for its practical application because of an inadequate time-to-result response. At this time, industry has to segregate the upstream from the downstream for testing off-line the upstream CQAs prior to moving the harvest to continuous purification.

The presentation proposed some **solutions** that can compensate for the lack of CQA-related PAT such as:

- For the upstream process: real-time check of process parameters (e.g., temperature, pH, perfusion rate, capacitance) and rapid monitoring (e.g., less than 30 min time-to-result) of multiple performance attributes linking cell metabolism and product quality (e.g., cell density/viability/volume, pCO2, glucose, lactate, glutamine, glutamic acid, ammonia). Any result out of a control range would activate product diversion for a period of time based on excursion studies.
- For the downstream process: real-time check of process parameters (time, volume, flow, pH/conductivity/product concentration of sub-steps) and UV/pH/conductivity profiles. Any result out of a control range would activate product diversion for a period of time based on residence time distribution (RTD) studies.
- Additional process checks: at-line CQA monitoring (USP & DSP) should comply with their respective control ranges. Purified material is collected in multiple fractions, quality tested for most "sensitive" CQAs to slight variation of process parameters and released prior to further processing (e.g., pooling, pre-formulation, filtration) to generate a batch of multiple batches of drug substance.

III. Enabling implementation of continuous manufacturing through process models: a vaccine platform example, GSK

The presentation from GSK focused on a new continuous process applied to formulation and filling of a finished vaccine drug product, and the application of machine learning (ML) models to predict attributes from system inputs and which can be used for enhanced process control during manufacturing. A diagram of the process if provided below.



The case study gave an overview of the technology, including mixing elements, PAT sensors, connection with the filling line and digital models.

It was shown how PAT Sensors (conductivity, flow, weight and pressure) and PAT probes (UV and NIR) placed in the flow domain can produce a stream of process data that enables the process to be followed in real-time based on Chemometrics models coupled with machine learning models (ML). Together these elements can be used to build a system model ("Digital Twin") capable of simulating time profiles of product content. The case study illustrated how ML models to predict attributes (conductivity, pH, concentration, etc.) from system inputs can then be used as part of the product control strategy to deliver optimal product quality and minimise waste.

The discussion focused on considerations for building and justifying model-based controls including risk-based requirements for model verification and validation. There was a focus on scenarios where complex model-based control frameworks could still be seen as "low impact"[2] where the model performance is demonstrated as part of PPQ and the application of the model is not linked to simplified downstream controls.

A challenge identified is the need for a globally harmonised framework to enable companies to exploit the full potential of system models to link continuous biological manufacturing to real time release, including considerations on guidance for evidence in dossiers and for lifecycle management.

The GSK team highlighted that a regulatory framework that provides pathways to practical implementation is important, including appropriate evidence requirements in the Marketing Authorisation, opportunities to facilitate lifecycle management of models and the continuous manufacturing (CM) for biologicals of allowing alternative manufacturing processes within one marketing authorisation. It was also noted that manufacturing is a global activity, and hence the business case for implementation of such systems must consider global acceptance of the process and control strategy. It was hence noted that a framework built on ICH principles and implemented consistently across ICH regions is also essential.

[2] Q-IWG Points to consider for Q8\Q9\Q10 guidelines (europa.eu), Section 5.1

IV. Plenary discussion on Continuous Manufacturing

Stakeholders expressed their hesitation to apply models because of the fear that, at global level, this would result in additional regulatory burden for registration and lifecycle management.

The QIG acknowledged that there are different types of models and different application of models, requirements in each case may differ depending on their place on the control strategy. The classification of a model is a crucial issue when defining which data will be required in the dossier.

Taking as example the digital twin presented by GSK, this will bring other challenges like the need to cope with variability from the continuous processing, which is even more challenging for bioprocesses. This implies close monitoring of the process in order to divert non-conforming material if needed, in addition to end-product testing. With this model even though there is no reduced end-product testing, it will have an important role on the control strategy. Industry indicated that the model is used in addition to PAT tools to bring another level of control in case of failure and prevent that the product is lost (e.g., if the flow rate starts to decrease because one pump malfunctions, the other pumps will adapt to ensure the product is within specifications) and not run it in a fixed parametric manner within defined process ranges. The model will improve with time, as more data is generated, and there will be a strategy to validate and to improve the model.

On the contrary, the model presented by Merck would replace a PAT and the impact of the model will be higher. This presentation helped to understand the difficulty to predict the impact of disturbances for bioprocesses. Even when simulating worst case conditions, it is not possible to foresee all situations. A distinction was made between upstream processes and downstream processes. The latter remain more predictable than the former.

While industry recognized the need for a case-by-case evaluation, they expressed the willingness to have some guidance available for process models. EMA highlighted that a Q&A on models is in the 2023 BWP workplan to outline general principles based on the experience gained from QIG interactions with applicants. QIG expressed again that EU welcomes more dynamic processes, which offer better control and does not want to create additional regulatory burden. The QIG will have to explore how the EU regulatory framework can be applied to dynamic processes and control strategies. QIG invites stakeholders to approach the group to share the type of models they are developing and how they are proposing to use those (e.g., in addition to a traditional control strategy as presented during the meeting vs a model to replace actual testing) in order to inform discussions, support their product development and the development of guidance.

Expectations are thus for further regulatory guidance e.g., in terms of data needed in the dossier vs under PQS, and of lifecycle management. Both industry and regulators acknowledged the different levels of risk depending on the impact of models, and the need for commensurate data requirements. Developers pointed out that validation data might not be ready at the moment of marketing authorisation application (MAA) e.g., because a model may need significant production data before it is validated, and/or model will improve over time. The QIG noted that a continuous model verification could be envisaged, similar to the continuous process verification approach.

Industry also asked whether the EU regulatory framework is ready for ICH Q13. The QIG indicated that ICH Q13 is in line with EU expectations and several CM dossiers have been approved in Europe. Nonetheless, the QIG recognizes that alternative approaches not covered by ICH Q13 may be

developed in the future and that is why is inviting stakeholders to share them with the group, indicate their challenges so that the QIG can identify solutions and ensure there are no regulatory barriers.

With regards to the difficulties on PAT tools for biologics expressed in the Merck presentation, it was noted that some academics are working on the area and that can be followed-up. Merck indicated that the availability of technology will also depend on the use of surrogates (in terms of signal and attributes). Industry suggested to consider this when revising ICH Q6B and ICH Q5A. To move this forward in Europe, consideration can be given to have another LLFG meeting on alternative analytical biological methods offering adequate time to results.

3. Decentralized manufacturing

I. QIG presentation on current regulatory requirements

The QIG described the current developments in decentralized manufacturing of medicinal products and the different scale-out strategies that are now evolving.

Traditional centralized manufacturing approach is mainly developed with the intention to support mass production of a certain medicinal product following the scale-up strategy. In the end, a confined number of large-scale manufacturing sites, located in different global regions, are in place in order to facilitate global patient supply.

By comparison, a decentralized approach has the intention to allow a more agile manufacturing ability, by following the process scale-out strategy. This means in practice that several identical small-scale manufacturing sites are established, which would make it possible to easily increase or decrease the manufacturing volume for a medicinal product, depending on the demand. This includes new technologies like PODs (Portable on Demand) units. PODs may be moved to a different region where manufacturing is required (e.g., just filling or storage) and can be used autonomously or integrated into a facility. The POD can be connected remotely to a control site. By using identical replicated small-scale units or PODs the reproducibility of the process and product is expected to be enhanced.

As another example for decentralized manufacturing, modular manufacturing systems with a fixed central control site were described. The clonal manufacturing modules are plugged in and out to the central control site, depending on production needs and scale. Cloning of the modular manufacturing modules could help with reproducibility of the process and product.

Point-of-care manufacturing is another approach to DM which is intended for products that need to be manufactured (at least partly) close to the patients (e.g., as they require personalization or have a limited shelf-life). This could be at, or close to, a hospital or health care facility. Once the manufacturing process is qualified at a site, it will run autonomously. A risk to this approach is that the product manufactured at the different DM sites could potentially slightly differ. Implementation of a so-called central control site, that interacts with all the different DM sites could be a viable solution in order to have quality control over the process and product. The qualified person of the control site will have oversight over batch manufacturing and testing and will be responsible for batch release at all DM sites.

Some overarching challenges from a regulatory perspective, likely applicable for all DM approaches, were highlighted. These included challenges on executing site and product comparability studies for a high number of parallel manufacturing sites, or when introducing several sites in parallel. The need for

an efficient managing strategy on the supply chain organization, especially on raw and starting materials was another challenge. The requirement of a solid technical expertise to ensure integrity of data transferred between the central site and the DM sites and the required expertise and concept for big data processing and handling were also noted as challenges. Another challenge identified was the high number of manual interventions and the number of personnel interacting with the process and the product , and that the product quality and consistency strongly depends on the manual interventions during manufacturing. Therefore, new models and approaches to personnel training programs may be needed to provide assurance on consistent quality in all DM sites.

II. DM solution for autologous ATMPs, Tigen Pharma

The company presented the complexity of manufacturing ATMPs and how decentralised manufacturing has the potential to accelerate access to novel therapies by bringing manufacturing closer to the patient. However, this type of manufacturing comes with unique challenges.

An approach to DM for autologous ATMPs under development that consists of two main parts was presented:

1) a standardised, fully automated, and aseptically closed ATMP manufacturing & controls platform operated in GMP facilities in/close to hospitals

and

2) a digitally enabled remote-control system operated by a "Central Control Site". The Central Control Site (CCS) will be responsible for overseeing all aspects of the manufacturing process and controls through the remote-control system, including the addition of new Manufacturing Sites (MS) and the control of each manufactured batch. The CCS will own the Quality Management System (QMS) and ensure compliance with GMP and the marketing authorisation/clinical trial authorisation by the MS.

While decentralised manufacturing presents significant opportunities, several **challenges** were identified within the current regulatory framework , related to DM site registration, qualification, the comparability of the products and GMP inspections for the DM sites.

Some **solutions** for these challenges were presented by the stakeholders. The company proposes to implement a Master File System (MFS) to remove the need to describe all DM sites in the MA-Dossier, resulting in variations of the dossier whenever a site is added or removed. . This MFS will include information on the central control site and the manufacturing process, operations and controls, and lists all DM sites, and is maintained by the central site under the responsibility of the MAH. The MFS could leverage tools described in on ICH Q12 (Life-Cycle Management Plan (LCMP)) for new site addition and ICH Q12 (Post-Approval Change Management Protocol (PACMP)) for new additions and changes to process/product.

A structured proposal on how a new site could be implemented was made, followed by site selection (valid manufacturing license, product handling experience), site set up (qualification of equipment and utilities), personnel qualification (hands-on operator training, to be qualified for each handling step), process comparability (pre-defined number of technical runs using a standard, process-specific qualification kit) and product comparability (execute a pre-defined number of product runs with human starting material, process parameters stay within design space/pre-defined ranges). The process at the

new manufacturing site will then be set under ongoing process verification as monitored and assessed by the central control site.

Concerning the routine GMP-inspection schedule, the company proposes to conduct these on a risk-based inspection schedule, with the Central Control Site being inspected at the frequency currently used for traditional manufacturing facilities, and DM units inspected less frequently. The central control site will be responsible to ensure that a site inspection plan is in place and executed respectively, DM performance reporting system is in place and reported to authority annually, based on performance of sites, authorities could select sites to be inspected and renew GMP licenses accordingly.

The need for guidance on DM (e.g. Q&A document at the beginning while the technology matures) to clarify regulatory expectations was noted. Finally, early dialog with authorities and international alignment of authorities would support to clarify expectations.

III. DM individual manufacturing units, MSD

The industry described how DM is a shift from product-centric, to patient-centric manufacturing, where speed of product to patient is enhanced, volume fluctuations may be addressed more efficiently, and the supply chain is strengthened by multiple, highly similar manufacturing units in different geographical locations.

Prefabricated, standardized manufacturing cleanrooms such POD units, in conjunction with enterprise quality systems can enable DM by ensuring consistency (layout and flow, air handling and controls, equipment, SOPs, training). The standardization and consistency is expected to reduce risk compared to traditional site changes/additions, and incorporation of a risk-based approach to regulatory requirements (e.g., reduced PPQ and bridging, concurrent stability studies, and reduced reporting category) upon implementation can further aid the speed of product to patient.

Challenges with DM implementation were highlighted. One is related to the lack of guidance on how to show equivalency/consistency across a large number of DM sites. A second challenge is related to the current regulatory requirements on technology transfer and the requirements that need to be fulfilled before site implementation, are not suited to facilitate a fast implementation of several very identical sites. Other challenges highlighted were the diverse environmental/safety requirements need to be considered on different regions, and the differences in the regulatory terminology and approaches in different regions.

Some potential **solutions** were also outlined. Because POD DM can be used for multiple modalities and range from simple to very complex processes, risk assessments are a critical tool for risk-based approaches, aiding visualization and prompting mitigations and controls. In view of a reduced risk, cross-site validation should be possible based on the complete process performance qualification of the main site (PPQ) and that process qualification may be based on a single process performance qualification batch at the clonal site. It was proposed by the company to use the stability data of the main site to support the products shelf-life and collect the stability data of the product manufactured at the clonal site, in parallel.

Additionally, mature enterprise quality systems (e.g., SOPs, change management and deviation management) ensure oversight across the fleet of DM sites. The additive view across the fleet provides a significant repository of data, better visibility, and faster knowledge build. These tools, in conjunction with regulatory flexibility in a risk-based approach (e.g., new variation categories, harmonised

approaches to site registration and inspection, guidelines linking data requirements to risk) could facilitate the shift from product-centric, to patient-centric manufacturing.

IV. Plenary discussion on Decentralized Manufacturing

The presentations offered the chance to discuss different scenarios in which decentralized manufacturing can be used, i.e., from POD units that can be incorporated to manufacturing on different locations to Point of Care (POC) manufacturing. Some general challenges highlighted were the assurance of equivalency/comparability of process and products at different manufacturing sites and the assurance of GMP compliance of each site or the need for a MIA of each site under modalities that allow to be agile and flexible in the intention of the respective DM approach. In this regard, regulatory certainties and a harmonised approach and terminology between different regions were requested.

A need for specific guidance (e.g., Q&As) that provides tailored considerations for the different approaches and manufacturing processes with different complexity was highlighted. For instance, available comparability guidelines are focussed on two or a few sites. However, when there are many sites that guidance can be difficult to implement, as the requirements for alternative approaches to confirm product comparability with the same certainty as for traditional approaches are currently not entirely reflected. Industry also suggested current guidance could be considered prescriptive in terms of data requirements when PODs are using the same process, flow, SOPs etc. and are highly reproducible, with reduced risks compared to standard site transfer. The current guidance could negate the benefits of technology like PODs and serve as an impediment to their widespread adoption.

In general, it was agreed that automation and Pharma 4.0 implementation can greatly enable decentralized manufacturing with the intention to have a good manufacturing agility e.g., for adaption of the manufacturing volume to the demand or to support the supply of a crucial regional demand in a flexible and timely manner. The high standardization by automation and pharma 4.0 has been discussed to be indispensable for complex manufacturing processes and products such as ATMPs (especially in view of a donor variability). Industry proposed that it is possible to implement DM currently, without a fully connected, fully digitalized and automated system.

The QIG noted that the implementation of product specific release tests (e.g. potency assay) may not be amenable to automation, thus challenging the high degree of process standardization needed for DM for certain products. Industry mentioned that for these tests, a central testing site could be needed. The use of a product specific kit to be implemented for site qualification was proposed by industry as an alternative to traditional comparability studies. It was agreed that more details on the approach and data sufficient for site qualification, would be needed before a conclusion on the overall acceptability of such a strategy can be drawn.

The QIG expressed concerns on the generalized risk-based approach for inspections of new sites that was proposed. A more specific proposal for a concerned manufacturing process and medicinal product (to understand where is the medical need to manufacture under DM) would be needed, before such a general approach can be applied for DM. It was noted that the quality of GMP inspections is expected to be the same for centralized and decentralized manufacturing. On POD manufacturing sites, there were also concerns raised about the tracking of the address/location of the site. The overall conclusion was that further interaction was needed in order to understand what was feasible and determine some basic requirements.

5. General discussion and sum up

The final session of the meeting summarised the key take aways that stakeholders presented during the meeting as challenges and proposed solutions for continuous manufacturing and decentralized manufacturing. In addition to these points raised by external stakeholders, areas for follow-up concerning the two technologies were also noted and included in the summary below.

For ease of reference, these points are summarised in the tables below.

Continuous Manufacturing

Challenge 1

Lack of suitable PAT in-line/on-line analytical methods and inadequate time-to-results to monitor CQAs, in particular for the upstream processes (USP).

Proposed solution

In addition to the commitment to continue the development work on promising methods (e.g., Multi Attribute Methods, Multi Angle Light Scattering, Raman spectroscopy, etc.), a proposed way forward is to compensate the lack of CQA real-time results by real-time parametric control and by the use of relevant PAT-controlled surrogate attributes.

Challenge 2

Need for guidance on the development and use of models for process understanding and control.

Proposed solution

The need for product/process specific discussions, and development of general guidance based on learnings was emphasized. Industry would like model maintenance to be allowed within PQS depending on the application of the model. Suggestion was made to focus on the outcome (impact) of applying a certain model instead of the details of how the model is built and maintained.

Areas for follow-up

In terms of the analytical challenges, the QIG noted the proposed solutions and agreed to consider them through follow-up 1-to-1 meetings where additional details can be obtained. QIG acknowledged the need for revision of existing BIO guidelines (e.g., ICH Q6B and Q5) to ensure surrogate tests and alternative types of control, as enablers for CM, are covered. In the meantime, specific guidance (e.g., Q&A) will be considered to address these aspects. Engagement with experts from academia working on alternative analytical approaches and sensors was also recommended by QIG as a follow-up of this meeting. The topic could also be planned for discussion at a future dedicated LLFG.

As regards models, the QIG suggested case by case considerations are conducted and that company specific strategies are discussed in follow-up meetings. In parallel, dialogue is needed at the QIG level within the open forums or 1:1 meetings to identify principles that can be further developed. Based on these discussions, a Q&A document on models (particularly process models) will be considered for inclusion in the QWP/BWP/GMDP IWG workplans, as needed. International alignment

Continuous Manufacturing

on models should also be sought. The need to clarify applicability of NIRS Guideline addendum will be followed up within QWP NIRS drafting group.

Parametric control, with changes to process conditions within "design spaces is seen as "key enabler for CM control strategies. As such, the QIG wants to support registration of design spaces in dossiers. Concerning this matter, the QIG noted industry expectations for revision of EU guidance on NORs/PARs/DSp, currently seen as stricter and less flexible regarding description of parametric process controls than in ICH/other regions. In this context, QIG will open discussion with industry to clarify which specific aspects of the guidance raise issues.

Decentralised manufacturing

Challenge 1

Comparability (site, product) in view of a high number of clonal sites that are in place or installed within a short period.

Proposed Solution

The company proposed process implementation of a new site based on a highly standardized process (e.g., automatization, pharma 4.0, digital central control site) in combination with an internal standard product (kit), to confirm site and product comparability. An internal standard is considered to be a potential solution, as proposed by the company, when the product is based on highly variable starting material (e.g., autologous donor cells).

In view of a manufacturing process that is not based on variable donor starting material, the company indicated that implementation could be based on cloning of a fully established process (e.g., including PPQ and comparability of the initial site and one clonal manufacturing site). Prefabricated, standardized manufacturing cleanrooms are intended to be used, to duplicate the process. In addition to that, a risk-based approach was presented by the company, to be used to identify potential parameters that might impact CQA (and thus process and product comparability) due to location differences. Respective risk mitigation strategies are implemented based on the results of the RBA. For all sites that are already in place, identified CAPAs will be implemented across all sites. Process consistency may then be confirmed on a single process performance qualification lot, only.

Challenge 2

Quality control: To conduct release testing using complex biological assays (e.g., potency assay) which is often not suitable for automation because of i) the complexity and ii) product-specificity. At decentralized sites, such as hospitals there might be limitations due to personnel or resources for that.

Proposed Solution

Decentralised manufacturing

To centralize release testing for assays that are complex, that cannot be automated and are highly dependent on the experience of the personnel.

Challenge 3

Addition of new sites in a timely manner that reflects the agile intention of DM.

Proposed Solution

Upon site addition process and product comparability needs to be confirmed. The challenges in view of comparability are discussed under challenge 1 above. It was highlighted by the company that the regulation concerning the implementation of a new site, like the variation regulation, may need to be adapted to cover new DM-specific approaches (e.g., site implementation via an approved internal standard) that might be developed. It should also be justifiable to conduct stability studies in parallel to implementation; which can save significant amounts of time compared to running the study, collecting the data, and submitting it before implementation. The QIG took note of this suggestion, and highlighted, that the respective pharma legislation is currently under review and thus not in the focus of the current LLFG meeting.

Challenge 4

Inspections of the parental site and the new clonal DM sites. Currently, every newly introduced manufacturing site needs to be inspected before implementation. Moreover, the active sites undergo routine inspection.

Proposed Solution

The company proposes to conduct these based on a risk-based inspection schedule. In case a central control site or a central hub in place, these could be inspected at the frequency currently used for traditional/centralized manufacturing facilities, and DM units inspected less frequently. A reporting system might be in place that annually reports pre-defined data to the authorities that can be used to decided which DM sites will be inspected in addition to the central site.

The concerned manufacturing process and product could be based on a Master File System (MFS). The MFS could be based on ICH Q12 (Life-Cycle Management Plan (LCMP)) for new site addition and ICH Q12 (Post-Approval Change Management Protocol (PACMP)) for changes on process/product.

Areas for follow-up

The proposed solutions for the challenges in product and process comparability for new DM sites are currently presented on a general strategical level. From a regulatory perspective, their feasibility would need to be further evaluated based on respective data. QIG suggests to have both companies for a follow-up meeting to evaluate the respective data package for the individual case. Ideally, this will facilitate to develop some overarching strategies that might in mid-term be used to adapt the current comparability guideline (ICH Q5E) or to trigger the draft of a Q&A document on comparability considerations for DM. In the follow-up meeting it may also be figured out whether the company may go for a written EMA Scientific Advice (including QIG members in the Rapp team) to

receive advice on the proposed strategy based on a in depth review of the data. The challenges on Quality control are considered to be associated with the comparability question.

The adaption on the variation regulation is currently included in the review of the pharma legislation and will not be further discussed during the LLFG follow-up.

The proposed solutions for registration, maintenance and on an GMP inspection strategy for several DM sites in parallel needs to be further evaluated, and the proposed solutions by stakeholders will be considered. This could be part of the proposed closed follow-up meetings with the companies to further support their proposals based on data.

6. Next Steps

The LLFG meeting has been a fruitful interaction to some of the challenges that lie ahead for the implementation of CM and DM technologies. The QIG has taken note of the issues raised by stakeholders and will consider what measures are necessary to be implemented in collaboration with the EU network. Alignment with international partners in terms of solutions put forward will also be a key element for the consideration of the QIG.

In terms of other innovative manufacturing approaches, the QIG will organise further LLFG meetings in the future with relevant stakeholders. The QIG is planning to have a further LLFG meeting in 2023 to focus on another priority topic linked to automation and digitalisation, and further details will be communicated to stakeholders in due course.

The QIG is also open for 1-to-1 meetings with individual organisation from academia or industry that would like to confidentially discuss details on their innovative technologies as well as the challenges and potential pathways for assessment of such technologies as scientific advice, marketing authorisation applications and related post-authorisation lifecycle changes. For details on how to get in touch with the QIG, please consult the following webpage.

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Quality Innovation Group (QIG): Listen and Learn Focus Group (LLFG) meeting report