EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Quality Innovation Group (QIG)

Listen and Learn Focus Group (LLFG) on innovative technologies to advance sustainability goals in pharmaceutical manufacturing – meeting report

4 – 5 March 2026

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Introduction

The Quality Innovation Group (QIG) is a multi-disciplinary group that brings together expertise in both quality assessment and good manufacturing practice (GMP) inspections, covering both chemical and biological medicinal products.

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

Expectations around sustainability and responsible manufacturing practices have strengthened across Europe and internationally, including the health sector. In the pharmaceutical domain, this translates into increased attention to how medicinal products are developed and manufactured, with a view to reducing the environmental footprint of operations and complying with the principles of social responsibility, while maintaining the highest objectives of quality, safety, efficacy and uninterrupted supply.

Sustainability in pharmaceutical manufacturing should be approached as a lifecycle-oriented objective, spanning development and commercial manufacturing activities. Starting from sustainable product design using eco-friendly materials and green chemistry, through continuous manufacturing and process optimisation to minimising waste and emissions, to sustainable packaging, distribution, and end-of-life management — each stage offers opportunities to reduce environmental footprint. Addressing these elements in a structured and transparent manner can support footprint reductions and environmental sustainability, while remaining consistent with established quality systems and GMP principles. The link between innovation and sustainability in pharmaceutical manufacturing has highlighted the importance of continued collaboration between industry and EMA. Several meetings between EMA working parties and industry have explored opportunities for collaboration on specific topics, including how to facilitate the implementation of more sustainable pharmaceutical manufacturing approaches and support changes that contribute to more sustainable supply chains [1].

In this context, advanced manufacturing can represent an important enabler of sustainability objectives. Approaches such as continuous manufacturing, digitalisation, advanced automation, or enhanced process monitoring and control strategies may improve efficiency and reduce variability, thereby supporting better use of resources and reductions in waste and emissions. Importantly, these approaches can also strengthen process understanding and operational robustness, aligning sustainability efforts with quality-by-design concepts and regulatory expectations.

However, introducing sustainability-oriented changes—particularly when supported by novel technologies—requires careful alignment with pharmaceutical quality requirements and demonstration of process control. Developers are expected to provide evidence that proposed changes are scientifically justified, appropriately validated and supported by an effective, risk-based control strategy, ensuring that critical quality attributes, product consistency and supply reliability are maintained throughout the lifecycle.

To support the adoption of sustainability-oriented innovation, timely engagement between developers, regulators and other relevant stakeholders is important to identify regulatory pathways for

implementation, clarify expectations and to anticipate practical considerations during assessment and GMP oversight.

In response, the QIG organised a listen and learn focus group (LLFG) meeting to discuss stakeholders' innovative approaches to integrating sustainability through advanced manufacturing and quality control. Stakeholders were invited to submit abstracts from real or mock case studies, illustrating the proposed advanced manufacturing technologies for integrating sustainability in manufacturing operation and reducing the environmental impact of pharmaceutical manufacturing.

These case studies were intended to illustrate the scientific and/or regulatory challenges encountered during the pharmaceutical development, manufacturing and quality control. They also presented proposed solutions, which were discussed with participants to identify any necessary follow-up action to support the implementation of the proposed technologies

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

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

The event was attended by 114 participants from industry, academia and regulatory authorities, including representatives from the European Commission, EDQM, US FDA, PMDA and Swissmedic.

The meeting comprised the following sessions:

Day 1, Wednesday 4th March 2026

1. Current scientific understanding and regulatory perspective on sustainability

2. Session 1

    2.1. A digital approach to sustainable pharmaceutical process design and product distribution

    2.2. Advancing Biobased Plastic in Pharmaceutical Packaging

    2.3. Innovative approach to enable transition to sustainable blister packaging in the pharmaceutical industry

    2.4. Adaptive Airflow HVAC Technology

    2.5. Environmental Sustainability of pharmaceutical products: trade-offs, dilemma's, barriers and solutions

    2.6. Panel Discussion

Day 2, Thursday 5th March 2026

3. European Commission: Driving Green Pharmaceuticals Innovation in Europe: Policy Context and Horizon Europe Initiatives.

4. Session 2.

    4.1. Solvent Recovery and Nitrosamine Risk Mitigation: Advancing Sustainability in Pharmaceutical Manufacturing

    4.2. Model-based Process Improvement and Control of Solvent Switches

    4.3. Mechanochemistry: a transformative opportunity for sustainable pharmaceutical manufacturing

4.4. Implementing Recombinant Endotoxin Testing

4.5. Panel Discussion

5. Sum up, next steps and closure of meeting

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

1. Current scientific understanding and regulatory perspective on sustainability

The session opened with a scene setting presentation by Veronika Jekerle (Head of Pharmaceutical Quality Office at the European Medicines Agency) and Ciara Turley (GMP inspector at HPRA and member of the QIG), outlining why sustainability has become a strategic priority for pharmaceutical development and manufacturing within the European regulatory landscape.

Drawing on recent global risk assessments, the speakers highlighted those environmental risks — particularly climate change, biodiversity loss, and systemic environmental degradation— representing the most significant long-term threats to human health and economic activity. Pharmaceutical manufacturing contributes to these risks through greenhouse gas emissions, waste generation, resource extraction, and the release of residues into ecosystems. At the same time, regulators are increasingly observing concrete sustainability driven innovations entering scientific advice procedures, marketing authorisations, and lifecycle variations.

The presentation framed sustainability as an increasingly explicit objective of medicines development, alongside quality, safety, efficacy, and supply. Within the EU context, this objective is embedded in broader policy frameworks such as the European Green Deal and is reflected in the EU regulatory strategy to 2028, where innovation and sustainability are explicitly linked priorities. The speakers emphasised that innovation, particularly advanced manufacturing and control technologies, is viewed as a key enabler to implement sustainable developments for medicines.

The example of fluorinated gases was shared to demonstrate how horizon scanning, impact analysis, stakeholder engagement, and scientific advice were translated into regulatory guidance, international alignment, and ultimately successful implementation via approved lifecycle variations. This example serves as a potential model for how sustainability driven innovation can be supported within the EU regulatory framework.

The role of the QIG is considered central to this effort. QIG acts as an interface between regulators, industry, and academia, offering early dialogue, scientific and regulatory support, and a platform for knowledge generation. Through its "listen and learn" focus groups (LLFGs) and 'one to one' engagements, QIG has explored advanced manufacturing technologies, including continuous and decentralised manufacturing, digitalisation, modelling, automation, and novel control strategies, that serve as direct enablers of sustainability.

The speakers stressed, however, that key challenges remain, for example how to holistically quantify environmental impact and trade-offs across the product lifecycle, including the footprint of enabling technologies themselves.

The speakers closed with a reminder on the objective of QIG's LLFG meeting, to connect stakeholders from Industry, Academia, Regulators and the European Commission, to share case studies, identify bottlenecks and reflect on potential solutions.

Through shared case studies, discussions and online polls, participants will determine enabling technologies that are sufficiently mature and with a potential to deliver measurable sustainability gains across pharmaceutical development, manufacturing, and supply chains. The sessions will also highlight priority areas where regulatory guidance, knowledge generation, and global alignment can most effectively support implementation.

2. Session 1

2.1. 'A digital approach to sustainable pharmaceutical process design and product distribution', Imperial College.

Summary as provided by the presenters:

Imperial proposed digitalisation enhanced with Artificial Intelligence (AI) as a means of streamlining, accelerating and quantifying how innovation can scale effectively. This in turn, can contribute to an improved environmental footprint. The presentation discussed how computer-modelling tools can enable fact-based decision making, while (1) providing early insights on process feasibility and performance, (2) offering the ability to assess different manufacturing scenarios simultaneously and (3) integrating formal uncertainty and sensitivity analyses to quantify and hedge against the impact of fragmented data. The team from Imperial showcased how digital tools can enable a transition to sustainable operation, by quantifying the cost and footprint of process alternatives in biopharmaceutical manufacturing, including quantification of prediction uncertainty. This was demonstrated through two use cases.

- *Use Case 1: Viral vector manufacturing and distribution.*

  A sustainable capacity planning framework for lentiviral vector manufacturing was introduced. The framework is based on the integration of technoeconomic analysis and lifecycle assessment (LCA) models, connecting those to formal optimisation models describing the supply chain. This integrated, digital approach is used to compare the economic and environmental profile of multi-use (stainless steel) and single-use (plastic) equipment, highlighting trade-offs between setup time, flexibility, cleaning requirements, and plastics disposal. Rigorous optimisation is deployed to quantify when a switch in capacity or equipment type becomes economically and environmentally optimal. Extending to supply chains, Imperial evaluated responsiveness under uncertain, unforeseen demands, showing how scalable designs can enlarge the feasible region encapsulating good candidate manufacturing setups, while improving supply resilience. The presented approach and methodology enable transparent trade-off assessments among sustainability, cost, and scalability, providing practical guidance to manufacturers and regulators on approval decisions and transition pathways to greener processes, while critically ensuring continuous drug supply.

  Relevant references:

  - Sarkis M, Sachio S, Papathanasiou M. A Process Systems Engineering approach towards responsive and sustainable (bio-)pharmaceutical supply chains. 2025;201:109197. doi: 10.1016/j.compchemeng.2025.109197

- Sarkis M, Shah N, Papathanasiou M. Resilient pharmaceutical supply chains: Assessment of stochastic optimization strategies for process uncertainty integration in network design problems. 2025;195:109013.
  doi: 10.1016/j.compchemeng.2025.109013
- Sarkis M, Shah N, Papathanasiou M. Sarkis M, Shah N, Papathanasiou M. Supply chain flexibility to unforeseen demand under quantified process uncertainty: a pharmaceutical case study. 2025; 7(4):70049.
  doi: 10.1002/amp2.70049
- Sarkis M, Shah N, Papathanasiou M. Characterization of key manufacturing uncertainties in next generation therapeutics and vaccines across scales. 2023;5(3):10158.
  doi: 10.1002/amp2.10158

➢ *Use Case 2: Monoclonal antibody (mAb) manufacturing.*

A systematic framework that focuses on process design, emphasising the impact of upstream variability on costs, environmental footprint, and the overall drug manufacturability was introduced. Imperial discussed the need for LCA-based sustainability quantification and highlighted how impurities in bioprocesses can influence equipment choices, process uncertainty, and purification strategies. The framework integrates experimental upstream measurements with technoeconomic and LCA models to assess robustness–footprint trade-offs across upstream and downstream operations. By mapping species concentrations and purity targets onto candidate designs, the framework quantifies how upstream variability propagates into costs and environmental impacts. This comprehensive digital approach that couples impurity tracking with modelling tools to evaluate trade-offs among cost, footprint, and quality, can enable more sustainable and scientifically justified process decisions.

Relevant references:

- Sarkis M, Monteiro M, Bernardi A, Chiplunkar R, Kontoravdi C, Papathanasiou M. Sustainable by design: A first attempt on bioprocessing. 2026; 205(1):109454.
  doi: 10.1016/j.compchemeng.2025.109454
- Sarkis M, Fyfe A T, Kontoravdi C, Papathanasiou M. Towards a Net Zero, socially sustainable and eco-efficient biopharma industry: how far are we? 2024; 44:101027.
  doi: 10.1016/j.coche.2024.101027

The presentation demonstrated that digital frameworks, integrating mechanistic insights with technoeconomic–LCA models, can enable rigorous assessment of manufacturing robustness, quality-driven performance, and sustainability trade-offs across therapeutic platforms. These evidence-based tools can support regulatory evaluation by providing mechanistic insight, transparent, quantitative comparators for innovative, environmentally optimised, quality preserving bioprocesses, while offering resilience guarantees when transitioning to greener alternatives.

Concluding remarks discussed challenges related to data sparsity and scarcity, presently addressed via rigorous uncertainty quantification methods as demonstrated in the use cases. The adoption of such tools was further discussed, highlighting the need for a harmonised approach and metrics for sustainability.

Questions and Answers:

During the Q&A session, participants discussed how different manufacturing approaches/processes can be compared in terms of their sustainability benefit and what constitutes a robust approach to quantify sustainability benefits.

The speaker highlighted the need for transparency of the data (e.g. where it is coming from, what the missing points are) to quantify the benefit. In manufacturing, data is often proprietary to the sponsor and held in house and often manufacturers may not even have information from their own suppliers to do the analysis. In this context, uncertainty quantification is important and the speaker further advocated for a gold standard for the quantification based on data that is non-confidential. It was noted that the data packages submitted by applicants to regulators should provide a transparent transcription of the approach used, including its scope, the unit operations considered, etc. A question was raised if the pharmaceutical industry can learn from sustainability advances from other sectors or if a cross-sectorial standard exists that could also be applied to pharmaceuticals. It was clarified that, although the research is conducted for the pharmaceutical sector, academic exchange occurs across sectors. In this regard, EFPIA colleagues referenced work to derive a standard on carbon footprint assessment [2] and one of the participants quoted the PAS 2090:2025, Pharmaceutical products – Product category rules for environmental life cycle assessments [3].

In conclusion, participants agreed that digitalisation and automation can be a key enabler to sustainability efforts in pharmaceutical manufacturing. However, users implementing digital approaches need to consider the quality and limitations of their datasets and models. Participants also emphasized the need for standards to enable consistent and credible quantification of sustainability benefits.

2.2. 'Advancing Biobased Plastic in Pharmaceutical Packaging', Sanofi.

Summary as provided by the presenters

This presentation discussed regulatory aspects related to transitioning from fossil-based to biobased feedstocks in pharmaceutical packaging materials. It was explained that fossil-based plastics utilise multiple feedstock sources, and regardless of origin, the production process results in chemically identical polymers; the same principle applies to biobased feedstocks: when processed through standard plastic production pathways using the same monomers, they yield polymers chemically identical to their fossil-based counterparts.

Comparability of bio-based polyethylene (PE) versus fossil-based PE was presented. It was discussed that the quality of the packaging components made of biomaterial origins should not impair the CQAs of the finished product throughout its shelf life, for example by introducing a risk of new extractables and leachables. Other attributes such as workability of material, which is pertinent to for example blow fill seal containers, need to be assessed, hence mechanical comparability needs to be understood but it is expected to be identical.

The presentation emphasized that biobased materials represent an essential component of holistic sustainability strategies, supporting EU circular economy objectives and corporate decarbonization commitments. Sanofi indicated that as a first step they are considering proposing a blend between the fossil and the biobased material and as knowledge evolves transform to 100% biobased. Additionally, Sanofi outlined a phased implementation approach beginning with biobased drop-in plastic materials[1] (with focus on materials from second-generation renewable sources) to build experience with biobased

[1] **Biobased drop-in plastic material:** A plastic material manufactured from chemically identical monomers derived wholly or partially from certified second-generation biological resources, including organic waste, agricultural or forestry residues, by-products, and intermediate crops. This definition applies irrespective of the biodegradability of the material.

feedstocks before advancing to novel biobased solutions. In the context of this presentation, Biobased drop-in plastic material is defined as a plastic material manufactured from chemically identical monomers derived wholly or partially from certified second-generation biological resources, including organic waste, agricultural or forestry residues, by-products, and intermediate crops. This definition applies irrespective of the biodegradability of the material.

Key collaboration opportunities identified included navigating regulatory expectations for different use cases (new packaging in initial marketing authorisation applications versus post-approval changes), considering dosage form and route of administration implications, and exploring expectations for novel biobased material introduction.

Questions and Answers

During the Q&A the EMA acknowledged that the current EMA Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03) is silent with regards to the origin of the packaging materials. Similarly, the source of the monomers is not mentioned in the respective Ph. Eur. Monographs on plastic materials for containers for pharmaceutical use.

The source of the polymer is generally not part of the information included in the marketing authorisation, hence confirming that no variation would be required when transitioning from fossil-based to biobased plastic materials if the resulting polymer is physically and chemically identical and meets all guideline requirements, including general information, specifications, extraction studies, migration studies, and toxicological documentation and if there is no change in the manufacturing process of the medicinal product). This is also in line with the intent of the revised EU variation classification guideline [4], which aimed at simplifying and reducing the number of variations needed to be submitted.

Equivalence of biobased versus fossil-based plastic materials need to be supported by risk assessment and data, as applicable, to evaluate whether there are implications that go beyond the composition of the material e.g. physical characteristics (e.g. porosity, density) of the polymer, and characteristics of the medicinal product such as pharmaceutical form, type of container closure system, manufacturing process (including that of the container), quality control testing and stability that could have an impact on the medicinal product and its manufacture.

Additionally, it was highlighted that manufacturers remain fully responsible for ensuring that the shift to biobased plastic materials introduces no additional risks. If the change is considered "blind" (not subject to variation), risk control measures and supporting data remain internal to the manufacturer's quality management system.

The use of Article 5 of Commission Regulation (EC) No 1234/2008 for this was discouraged.

Instead, manufacturers are encouraged to contact EMA directly to align on expectations and solutions for specific cases and to request CHMP scientific advice [5] as needed.

Sanofi suggested including clarifying questions to the public EMA Quality of Medicines Q&A page as the preferred communication pathway for providing broader industry guidance. In Sanofi’s opinion, this approach would enable a fast implementation while ensuring the widest reach across stakeholders.

There was consensus that when sustainable biobased plastic packaging aligns with pharmaceutical regulations, namely when material equivalence is demonstrated and quality standards of the medicinal product are maintained, without compromising patient safety or product quality, it can be seen as supporting sustainability goals. This conclusion was formulated based on the information presented

during the meeting and it should not be interpreted as a comprehensive or final endorsement, nor as a carte blanche decision, should additional information come to light.

2.3. 'Innovative approach to enable transition to sustainable blister packaging in the pharmaceutical industry', PMF – AstraZeneca (AZ).

Summary as provided by the presenters

Blister packs are the preferred packaging choice for oral solid dose medicines across Europe and many other parts of the world. These packs are predominantly composed of combinations of polyvinyl chloride (PVC) and aluminium, materials that have been widely accepted due to their excellent attributes, particularly their ability to protect products from physical damage, manufacturability, and barrier performance.

PVC has, however, become a plastic material of environmental concern. Its lifecycle, from production and use to disposal, releases potentially harmful chemicals and PVC is challenging to recycle. Given the scope of the change of this packaging material across pharmaceutical industry – impacting thousands of medicinal products and multiple companies – pre agreement of a defined approach and the regulatory tools and process to enable the shift away from PVC is seen as high value.

A cross-industry collaborative team of companies was established by the Pharmaceutical Manufacturing Forum (PMF) to identify the technical and regulatory challenges, and opportunities for accelerating the transition to alternate blister packaging materials. The PMF team has developed a collaboration strategy, working with suppliers of packaging materials based on understanding of the barrier properties and manufacturing requirements for alternative blister packaging materials.

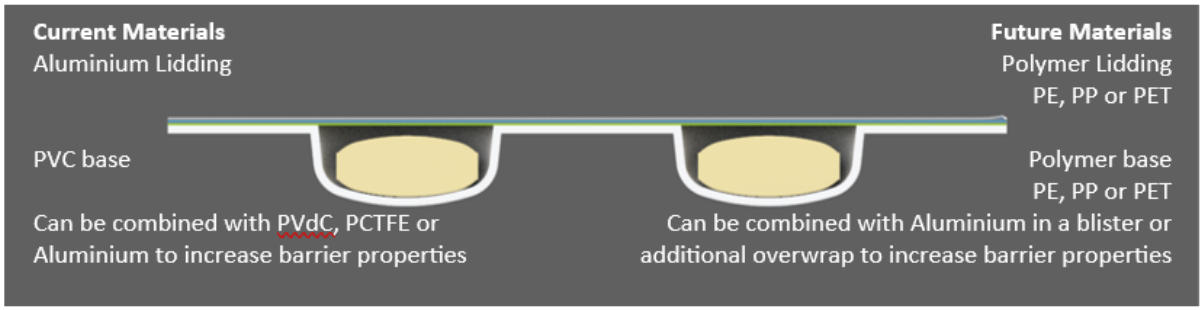

Figure 1. Illustration of current and future materials as presented by AZ.

Based on the collective assessment of a panel of experts from across industry, AZ has sought EMA scientific advice on establishing platform risk assessment approaches to establish what data is appropriate to support the change. Given this change may impact thousands of products, flexibilities might need to be explored and agreement with EMA is an essential step to enable the change. Technical points to address include:

- Where, through stability risk assessment, resistance to moisture permeation is identified as the critical quality attribute (CQA) for protection of the drug product, moisture permeation can be used as the primary criterion to assess packaging changes.
- That platform and prior knowledge of the new materials' barrier properties can be the basis for risk assessment and determination of data requirements.
- That Application of Moisture Vapor Transmission Rates (MVTR) can be used to classify the relative resistance of blister packaging.

- That where equal or better moisture protection can be demonstrated for the material, product specific stability studies can be deferred.

The approach described hinges on the comparison MVTR between packaging materials and generation of prior knowledge using moisture sorption isotherm modelling for drug product packed in different blister materials.

Whilst EU guidance is clear on data requirements and submission pathways for changes to packaging materials, industry has recognized that the global change program to replace PVC can potentially be enabled by a more detailed framework based on agreed scientific principles.

Although this change is seen as a non-complex type of variation, global implementation will be complex given the number of submissions, different regulatory requirements and varying timelines. The application of reliance could be an enabler for implementation worldwide. EMA plays an important role in the reliance process whereby non-EU countries look towards the EMA for guidance on regulatory assessments. The PMF would like to continue to collaborate with the EMA on the application and use of reliance to support access to medicines worldwide.

This approach could potentially be a blueprint for enabling other changes to packaging materials to enable sustainability and circularity. The PMF would like to discuss applicability of similar approaches to other scenarios, for example the replacement of PFAS layers in other primary packaging or the introduction of recycled materials into new primary packaging.

Questions and Answers

While it was acknowledged that the magnitude of the change (impacting thousands of products and multiple companies worldwide) is challenging from a regulatory perspective, the QIG LLFG discussion focused on the scientific aspects. The use of prior knowledge and modelling to understand stability risk (e.g. forced degradation studies, accelerated predictive stability protocols and modelling e.g. APS) supported by real time stability data (ICH conditions, commercial scale) is welcome. The discussion clarified that the same model platform is envisaged for all products, but a specific model is intended to be built, validated and later verified for each product. As indicated in the initial EMA scientific advice, more details on the proposed modelling and statistical packages as well as how they are validated, and the proposal for on-going verification of the models are essential to be presented and justified in the follow-up scientific advice. Although stability modelling is not in the scope of the Preliminary QIG Considerations regarding Pharmaceutical Process Models [6], principles developed in this guidance can be considered in this regard. It was reiterated that modelling should not replace ICH stability studies. Such studies should continue to be conducted in accordance with ICH guidelines to support the ongoing verification of the models, even if they are not included in the regulatory submission. As with other post approval stability studies, in the unlikely event that an out of specification result is obtained, the MAH should report it to the relevant competent authority.

In addition, as part of the discussion it was clarified that changes to the packaging process conditions (e.g. due to need of different sealing temperatures) are likely and may need to be considered too (e.g. regarding the risk of nitrosamine formation, or impact on product stability).

The presenters agreed to consider the feedback provided and address the points in the planned follow up scientific advice request.

2.4. 'Adaptive Airflow HVAC Technology', GSK.

Summary as provided by the presenters

Up to 60% of the energy used in pharmaceutical production facilities may be consumed by Heating, Ventilation and Air-Conditioning (HVAC) systems. HVAC systems are typically designed for worst-case conditions, but adaptive systems, where the rate of airflow is a controlled variable, can control airflow for both routine and worst cases situations. Via adaptive airflow, the HVAC can be controlled as a real-time function of measured particle levels and other parameters (including pressure, temperature, and humidity).

GSK proposes to implement adaptive airflow technologies to significantly reduce energy use in pharmaceutical manufacturing facilities and has initiated use of this technology in pilot facilities. Use of adaptive systems has greatest impact in areas constantly operating at high airflow rates, and where particulate burden can vary significantly (e.g. based on operational patterns). By targeting Grade C and D cleanrooms, the most common areas in manufacturing facilities, at least 30% energy saving is likely possible for a sterile manufacturing facility.

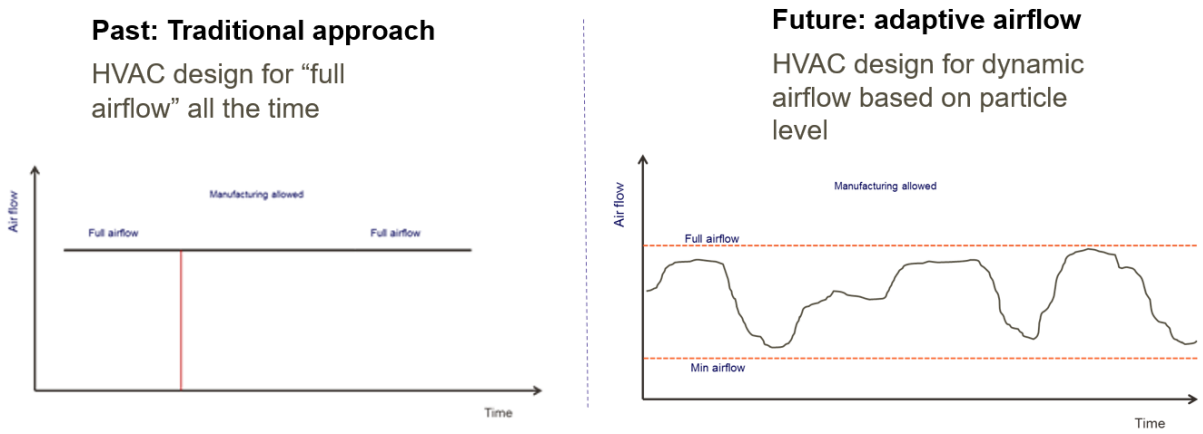

Figure 2. Illustration of traditional full 'airflow' versus 'adaptive airflow' as presented by GSK.

The approach to qualification of an adaptive HVAC system was outlined, using minimal airflow as worse case. In addition, GSK is investigating deterministic, risk-based adaptive airflow controls. This may include a rule-based supervisor or Model Predictive Control scheduler making operating decisions, with controls to return the system to fixed, validated settings if sensors drift, or environmental trends deteriorate. A later, optional step could introduce a model-assisted set-point with a human-in-the-loop and even digital twin control models for optimising airflow control.

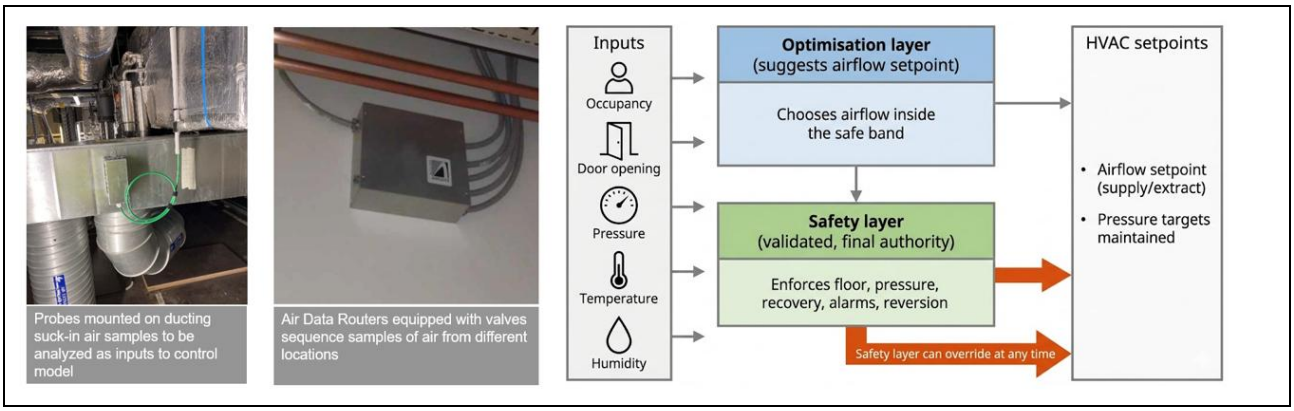

Figure 3. Aircuity Physical Installation as presented by GSK.

Questions and Answers:

The discussion focused on how the adaptive airflow controls would be qualified and verified in real world scenarios, with a focus on sterile manufacturing facilities. Discussions included the impact of an adaptive system on an environmental monitoring programme, appropriate monitoring systems (e.g. setting of alarm limits) and use of both adaptive technology and traditional HVAC in a facility and integration into a single building management system.

Whilst the proposal for implementation is in Grade C and D facilities, the meeting discussed whether a risk-based approach could also enable an appropriate control verification and monitoring program for use in higher risk Grade A and B cleanrooms, and for deployment of the more complex digital twin control principle (e.g. to determine sampling locations). It was discussed that the number of air changes would be reduced in adaptive technology and that this posed a challenge for meeting recommended minimum number of air changes for higher grade cleanrooms.

As for other model-use scenarios, a key factor impacting the degree of verification/validation would be the extent to which the adaptive control system operates within fixed or flexible parametric boundaries.

The discussion also focused on the alignment with the requirements of GMP Annex 1 Contamination Control Strategy (CCS) principles, and on the need for presenting the control strategy to GMP inspectors underlying the use and qualification of the system with risk assessment.

2.5. 'Environmental Sustainability of pharmaceutical products: trade-offs, dilemma's, barriers and solutions', RIVM.

Summary as provided by the presenters

RIVM presented three international projects, in which they are actively engaged, i.e. IMI-PREMIER, EU Horizon TransPharm, and IHI-PHARMECO.

The IMI-PREMIER (Prioritisation and Risk Evaluation of Medicines in the EnviRonment) project is a public-private partnership running from 2020 to 2026, focusing on the development of greener active pharmaceutical ingredients. Within this project, GREENER criteria have been developed, starting with Good Practice for patients, progressing to issues related to (eco)toxicity and environmental fate, and concluding with Risk and hazard mitigation. The aim of the GREENER concept is to foster dialogue between environmental specialists and pharmaceutical discovery and development experts, and to explore the feasibility of applying these criteria in drug R&D. Within the project the significant

interactions between drug properties and environmental characteristics were also demonstrated. To further support the development of greener active pharmaceutical ingredients, harmonized criteria and thresholds are needed for the R&D phase, along with tools and assays that can be applied early in the process (high-throughput, requiring minimal material). Further information can be found at https://imi-premier.eu.

The EU Horizon TransPharm Project runs from 2022 to 2026 and focuses on developing greener active pharmaceutical ingredients, solvents, and more environmentally sustainable manufacturing processes. One of its goals is the development of environmental sustainability assessment methods, which are essential for identifying and evaluating trade-offs across multiple, potentially competing factors throughout the medicinal product lifecycle. Since not all trade-offs are obvious or well understood, a systematic environmental sustainability assessment framework is needed to identify and evaluate them. However, progress is hindered by a lack of data, clear definitions, and harmonized methods.

In addition, within the project barriers, solutions, and incentives throughout the entire pharmaceutical lifecycle, from development to waste were revealed. The identification of these barriers was achieved through workshops, interviews with actors across the pharmaceutical lifecycle, a scoping literature review, four focus group meetings with stakeholders, and additional discussions with experts. For regulatory issues, EMA was consulted. This resulted in a comprehensive overview of barriers and their corresponding solutions or incentives; some are overarching, others are regulatory, and some are specific to particular phases or actors within the lifecycle.

Examples of overarching barriers include concerns that sustainability might take precedence over efficacy or safety, as well as the lack of definitions and harmonized assessment methods, criteria, indicators, and thresholds, even within jurisdictions. There are numerous regulatory barriers, but many appear to be perceived rather than real. Perceived barriers can often be addressed through improved guidance or education, whereas genuine regulatory barriers would require legislative changes, which are much more challenging. Further information can be found at https://transforming-pharma.eu/.

The IHI-PHARMECO Project, which will run from 2024 to 2030, will build on the results of TransPharm through a 'regulatory preparedness' work package. This project aims to develop more sustainable pharmaceuticals. Stakeholders, including industry representatives, regulators, and experts from public institutions—are invited to participate in workshops and engage in discussions. Further information is available at https://pharmeco.eu/.

As a take-home message, RIVM presented the vision articulated by participants of an international workshop organized by RIVM in 2025: "We need a scientifically sound Environmental Sustainability Assessment (ESA) system for pharmaceuticals, with consensus from all stakeholders, that is tiered, robust, harmonized, and adaptable to different contexts."

Questions and Answers

The need for a better standardized evaluation system for environmental sustainability was also emphasized during the discussion following this presentation. A systematic and harmonized evaluation system would enable the comparison of products' environmental sustainability impacts and clarify data needs. However, a paradox exists: while a standardized system is necessary to clarify these needs, developing the system itself demands substantial data and collaboration. Consequently, stakeholder cooperation is considered essential to overcome this initial barrier.

Communication among the various stakeholders is also considered essential for making effective use of both the existing resources within companies and the existing regulatory guidelines. In this regard, it

was noted that one of the perceived barriers from some stakeholders is that a full update of the regulatory file is needed to meet standards when small changes are introduced to improve sustainability. To address this, the presenters suggested that EMA develop further specific guidance on sustainability issues. In response, QIG pointed out existing EU guidance, such as the guidance on regulatory expectations for post-authorization changes [4] and the possibility to request CHMP scientific advice [5] that already cover relevant aspects. The presenters therefore suggested strengthening the communication on existing guidance e.g. by developing a simple Q&A on sustainability issues that refers to relevant existing guidance.

Conversely, EFPIA representatives argued that the challenges outlined do not accurately mirror the current state of the industry. They emphasized that many companies have already integrated eco-design toolkits and sustainability assessments into their R&D and commercial manufacturing processes. For these organizations, the primary barrier is not a lack of desire or understanding of impact, but rather the operational difficulty of enabling change. The presenters countered this view by noting that their research partners and industry environmental experts often struggle to find R&D personnel willing to engage with environmental aspects, even within large companies, highlighting the existence of silos within companies.

It was acknowledged that the presentation listed potential solutions to be addressed by industry, changes in legislation, etc. With regards to QIG, in addition to the suggestion of the development of a sustainability Q&A, the presenters proposed to ensure a harmonized approach for assessment and transferability of data, and to define key concepts to stimulate circularity (e.g. what is green, what is environmentally sustainable, what are environmentally sustainable active substances and pharmaceutical processes). In addition, industry was invited to avoid silos by strengthening communication between the teams in charge of the environmental sustainability plans and the regulatory teams. Although all participants agreed that such a sustainability exercise is beneficial during development phases and to accompany e.g. manufacturing changes, there is the clear view that making a sustainability assessment mandatory during Marketing Authorisation Application, as a fourth authorisation pilar in addition to safety, quality and efficacy might not be beneficial.

2.6. Panel discussion (day 1)

The first day of the meeting emphasised the increasing significance of sustainability as a strategic factor in the development and manufacture of pharmaceutical products. Through a combination of presentations and panel discussions, participants explored practical ways to minimise the environmental impact of pharmaceutical products and manufacturing processes while ensuring that product quality, patient safety and supply security are maintained.

Topics discussed included harmonised sustainability assessment methodologies, improved data transparency, and the role of digitalisation and advanced manufacturing technologies in supporting sustainable innovation. Case studies were used to illustrate the opportunities and challenges of adopting sustainable packaging materials, such as biobased plastics, and reducing energy consumption in GMP manufacturing environments through advanced HVAC systems and digital technologies.

The meeting also emphasised the importance of robust lifecycle assessment approaches, evidence-based decision-making and ongoing regulatory engagement in supporting sustainability-driven improvements. Collaboration between regulators, industry, academia and policymakers was identified as essential for future progress and emerged as a consistent theme throughout the day.

The panel discussion focused on the regulatory and practical challenges of integrating sustainability into the development and manufacturing of pharmaceutical products. Participants broadly agreed that, while maintaining product quality, patient safety, supply security, availability and patient access, sustainability should become an increasingly important consideration throughout the product lifecycle.

There was a recurring emphasis on the importance of addressing sustainability early in product and process development ('sustainability by design'), as opportunities for improvement may become more limited once manufacturing processes and control strategies have been finalised. Participants also noted that early-stage developers often face competing priorities relating to development timelines, resources and competitiveness.

The discussion emphasised the necessity of harmonised sustainability assessment methodologies and lifecycle assessment approaches, as well as the need for greater alignment of sustainability-related initiatives across jurisdictions. The fragmentation of methodologies, data requirements and assessment approaches was identified as a significant challenge. Participants further emphasised the importance of improving data availability, transparency, and governance, while recognising the complexities associated with data ownership, confidentiality, and sharing data across the pharmaceutical value chain.

Several regulatory aspects were discussed. Participants noted that sustainability is not currently part of the formal benefit-risk assessment of medicinal products, and that introducing sustainability as an additional assessment pillar, alongside quality, safety, and efficacy, is not currently feasible. It was recognised that sustainability-related changes in medicinal products, such as changes to packaging or manufacturing, are often not included in the regulatory submissions. Considerations were given to including sustainability impact as a factor in funding of projects but that this should not restrict development or access to vital medicines, especially for those serving smaller patient populations.

The panel also discussed the challenges of implementing sustainability-driven improvements after approval, particularly where comparability requirements and post-approval change procedures create practical barriers. Opportunities to support innovation through greater regulatory flexibility, improved scientific advice and modelling approaches, and exploratory concepts such as regulatory sandboxes were also highlighted. It was also noted that some perceived regulatory barriers may be due to uncertainty or misconceptions rather than explicit restrictions.

Digitalisation, modelling, AI, advanced manufacturing technologies and flexible manufacturing approaches were recognised as important enablers of both sustainability and operational resilience. Use of these enablers to extend shelf-life of medicines has potential to reduce waste. Participants also acknowledged that global supply chains present additional challenges, particularly where environmental expectations and standards differ across regions.

The QIG is positioned to help provide guidance regarding regulatory requirements that must be considered to implement manufacturing changes to support sustainability.

Overall, the discussion emphasised the need for harmonised standards, robust and transparent data infrastructures, regulatory dialogue and ongoing collaboration between regulators, industry, academia and policymakers to facilitate the implementation of sustainability-driven innovation in the pharmaceutical sector. Industry noted the recent publication of new standards such as PAS 2090 Product category rules for environmental lifecycle assessments as examples of how lifecycle assessments should be undertaken [3].

3. European Commission: Driving Green Pharmaceuticals Innovation in Europe: Policy Context and Horizon Europe Initiatives.

The presentation delivered by Martin Uriarte, Policy Officer at the European Commission, DG Research and Innovation, focused on sustainable competitiveness in the European pharmaceutical sector and the initiatives under Horizon Europe aimed at promoting eco-friendly pharmaceutical innovations. The European Medicines Agency and the Quality Innovation Group were thanked for fostering discussion and creating forums for collaboration and regulatory development.

The concept of sustainable competitiveness, a central theme in the European Commission's agenda, was highlighted. This involves thriving in the global market while ensuring lasting prosperity and sustainability. The pharma sector is a crucial industry contributing to public health, societal productivity, and economic prosperity, with significant investments in research and development and employment across Europe. However, the sector also contributes to pollution, with pharmaceuticals driving a large amount of healthcare's carbon footprint according to existing estimates, presenting challenges but also opportunities for the pharma sector to maintain its lead in cutting edge innovations and facilitating a transition towards an environmentally sustainable sector.

Under Horizon Europe, the European Commission promotes eco-friendly pharmaceutical innovations, collaborating with industry and other stakeholders. Initiatives such as the PHARMECO IHI project and the green pharmaceuticals Horizon Europe projects aim to develop sustainable pharmaceutical manufacturing technologies. Projects like SUSPHARMA, TRANSPHARM, IMPACTIVE, ENVIROMED, and ETERNAL focus on creating greener drugs, optimising synthesis, reducing solvent usage, studying environmental impacts, and incorporating sustainability throughout pharmaceutical processes. Despite promising less polluting processes and technologies, challenges remain, including economic viability, access to data for lifecycle assessments, and adapted regulatory pathways.

An upcoming policy brief by the green pharmaceutical projects cluster will provide recommendations for developing and adopting green pharmaceuticals. The European Medicines Agency and relevant stakeholders are invited to consider the outcomes of the EU funded projects in this area and the conclusions presented in the brief when designing sustainable pharma regulations and strategies.

All the steps discussed aim to build a sustainable, competitive European pharma sector, and the presenter expressed anticipation and confidence that the discussions and insights gained will further advance the sector towards sustainability.

4. Session 2

4.1. 'Solvent Recovery and Nitrosamine Risk Mitigation: Advancing Sustainability in Pharmaceutical Manufacturing', EFPIA.

Summary as provided by the presenters

This presentation outlines the scientific, regulatory, and sustainability rationale for solvent recovery in pharmaceutical manufacturing, with a particular focus on nitrosamine risk control and acetonitrile regeneration for oligonucleotide production. It begins by defining key terminology, i.e., direct reuse, reuse after minor processing, recycled solvent, and recovered solvent, to ensure common understanding of recovery pathways. The environmental motivation is emphasized: solvent use accounts for 40–50% of an API's carbon footprint, largely driven by solvent production and waste

disposal. Recovering or recycling solvents markedly reduces CO_2 emissions compared with incineration or production of virgin materials.

The presentation reviews available recovery technologies, noting that distillation, especially rectification, remains the dominant industrial method, often supported by membrane or adsorption techniques. Regulatory frameworks generally support solvent recovery. However, use of recycled/recovered solvent has been identified as root cause for nitrosamine contamination in medicinal products.

The scientific section of the presentation proposes a possible justification and aims to demonstrate that nitrosamine risk can be predicted, and that many recovery processes can be expected to effectively remove potential nitrosamine contaminations. The technical foundation are predictive thermodynamic models such as COSMOtherm, which estimate Vapor Liquid Equilibria for non-ideal systems such as solvent-nitrosamine pairs, and average relative volatilities (ARVs), which can serve as a quantitative predictor of separation efficiency. Notably, ARVs above 3 minimize the possibility of azeotrope formation and ensure high nitrosamine purge factors. Monte Carlo simulations show that for ARV ≥ 3, more than 94% of modelled distillations achieve purge factors ≥ 10^6, and all achieve at least 10^3, even under conservative assumptions.

A case study examines acetonitrile, the principal solvent in solid-phase oligonucleotide synthesis (SPOS). Given the escalating global demand for oligonucleotide therapeutics and the substantial acetonitrile volumes required (2.7 L per gram product), sustainable recovery is increasingly important. Process-related impurities in SPOS are well understood and efficiently purged, making controlled recycling feasible. Literature examples demonstrate that distillation-based acetonitrile regeneration can achieve >85% recovery. Applying our predictive model, this process is expected to remove nitrosamines such as NDMA, NDEA, and NMOR by at least six orders of magnitude. Experimental validation shows a >200,000-fold depletion in these nitrosamines, limited only by analytical sensitivity. Quality requirements for repurified acetonitrile used in SPOS include specifications for purity, water content, UV absorbance, acid/base impurities, and residue on evaporation. Risk assessments indicate that specific nitrosamine controls are not required, based on the inherently low nitrosamine risk of the SPOS process and because of the high purge capability of the recovery process, which would lead to negligible patient exposure even under worst case conditions.

The conclusions underscore that solvent recovery substantially reduces environmental impact, that many widely used solvents exhibit ARVs > 3 for worst-case nitrosamines indicating excellent separability, and that science based, process specific assessments enable safe, sustainable recovery. Robust oversight and quality controls remain essential, but blanket classification of recovered solvents as high-risk for nitrosamines is not scientifically justified.

Questions and Answers:

A key point emphasised by regulators was that current guidance does not prohibit the use of recovered solvents but requires a robust, science-based justification [7]. Several participants noted that industry presentations provided reasonable approaches for such justification, particularly through risk assessment and process understanding.

However, from a technical perspective, there was an in-depth debate on the applicability of modelling approaches to predict nitrosamine behaviour during solvent recovery. Concerns were raised about the use of thermodynamic models (e.g., Raoult's law vs. Henry's law), especially at low concentrations and for non-ideal systems. It was highlighted that certain solvent–nitrosamine combinations (e.g., DMF and NDMA) cannot be effectively separated due to similar physicochemical properties. Several participants

emphasised that the proposed models depend heavily on input data quality and underlying assumptions. It was therefore recommended to complement modelling with experimental verification. This was seen as essential to ensure scientific robustness and regulatory acceptability.

Participants also stressed that solvent recovery risks are not solely driven by thermodynamics. Practical factors such as third-party recycling processes, mixing of solvent streams, and the presence of water or other components can significantly impact impurity carryover. For example, water content in recycled solvents may facilitate the transfer of nitrosamines, underscoring the importance of solvent purity and process controls.

Another key challenge identified was the lack of clear guidance on acceptable nitrosamine limits in recovered solvents. According to some stakeholders, acceptability depends on multiple factors, including maximum daily dose (MDD), compound-specific limits, and solvent specifications, making universal thresholds difficult to define.

The discussion also included a case study on oligonucleotide manufacturing, where large volumes of acetonitrile are used. This area was highlighted as a potential candidate for platform approaches, given the standardised nature of synthesis processes across products. Industry representatives suggested that modelling combined with prior knowledge could help "de-risk" nitrosamine concerns at a platform level, while product-specific assessments would still be required.

Furthermore, there was a strong call for clearer regulatory guidance and enhanced collaboration between industry and authorities. Industry stakeholders expressed uncertainty regarding what constitutes sufficient justification for the use of recovered solvents, despite the flexibility provided in current guidelines. Regulators outlined existing pathways for engagement and encouraged joint industry initiatives to develop harmonised approaches.

4.2. 'Model-based Process Improvement and Control of Solvent Switches', Johnson & Johnson.

Summary as provided by the presenters

The pharmaceutical industry is facing a growing imperative to improve sustainability, operational efficiency, and supply resilience while maintaining the highest standards of product quality and patient safety. In small molecule drug substance manufacturing, solvent swaps represent a critical opportunity in this context. These unit operations are ubiquitous, resource intensive, and highly influential on cycle time, energy consumption, and waste generation. Model based optimization and control offer a scientifically sound and industrially proven pathway to address these challenges.

Models for solvent swaps are built on mature mechanistic foundations, combining thermodynamics, mass and heat balances, equipment characteristics, and defined operational constraints. They enable systematic optimization of solvent exchange trajectories, either as one-time offline improvements or as adaptive strategies through model predictive control. Importantly, these approaches do not inherently alter product quality targets or intended end state specifications; rather, they optimize how the process transitions between defined and accepted start and end points. Regarding the magnitude of solvent reduction, it was indicated a reduction of 30% of the solvent that was switched to, in addition to the reduced energy consumption for heating.

Presenters considered that despite demonstrated technical maturity and clear sustainability benefits, broader deployment is currently constrained by filing related challenges. A key issue is the lack of harmonisation in how solvent swaps are described in regulatory dossiers. In some cases, unit

operations are defined at a high level, specifying objectives and boundaries while allowing flexibility in execution. In others, they are described in highly prescriptive terms, detailing fixed solvent quantities and operating conditions. These divergent approaches can result in fundamentally different levels of post approval flexibility for processes that are scientifically and operationally equivalent.

The level of details in the regulatory dossier becomes particularly critical when adaptive control strategies are envisaged. Model predictive control systems are designed to respond to normal batch-to- batch variability, equipment differences, and changing economic or sustainability drivers. As a result, operational parameters such as solvent usage, temperature, or pressure may vary dynamically within predefined and justified limits. Traditional expectations around fixed setpoints and targets are therefore not always compatible with such approaches, even when product quality and process performance remain fully controlled.

The strong need to evolve toward more consistent, principle and scientifically based regulatory descriptions of unit operations to support quality innovation, was expressed by the presenters. Such descriptions should clearly define acceptable boundaries, control strategies, and assurance of quality, while avoiding unnecessary prescriptiveness that limits future optimization without adding patient or product benefit.

Questions and Answers:

The added value of model predictive control over fixed model-based approaches was highlighted in its ability to respond to batch-to-batch variability and unforeseen process variations. It enables dynamic adjustment of process conditions and optimisation objectives (e.g. prioritising sustainability or throughput), increasing operational flexibility. However, limitations remain. Current models struggle to capture complex physical phenomena such as phase separation or crystallisation events, requiring experimental definition of safe operating spaces.

The QIG indicated that performance-based approaches built upon enhanced process understanding are greatly encouraged. The existing regulatory guidance, e.g. ICH Q11 [8], already allows that process descriptions include process parameter ranges or design space when supported by an enhanced development and knowledge. Representatives from industry recognised that more detailed guidance on process descriptions was not desirable.

Equally important is clarity on when and how models should be referenced in regulatory submissions, particularly when they are used to support execution rather than to redefine the registered process.

In this regard, the QIG reminded participants about the published "Preliminary considerations regarding pharmaceutical process models" [5] which provides guidance on when and how to present model information based on the model context of use and the model risk.

Continued dialogue between industry, regulators, and scientific consortia is essential to establish shared expectations for model based and adaptive manufacturing. Aligning on these principles will enable responsible innovation, support sustainability goals, and ensure that advanced digital technologies can be deployed in a manner that is both compliant and futureproof.

4.3. 'Mechanochemistry: a transformative opportunity for sustainable pharmaceutical manufacturing', IMPACTIVE.

Summary as provided by the presenters

Mechanochemistry is a chemical approach in which reactions are driven by mechanical forces such as grinding, compression, or shear instead of traditional solvent-based methods. It enables the synthesis of molecules with little or no solvent, leading to reduced waste, lower energy consumption, and improved environmental sustainability.

Major European initiatives in mechanochemistry for sustainable API manufacturing include the COST Action CA18112 ("Mechanochemistry for Sustainable Industry", 2019–2023) and the Horizon Europe project IMPACTIVE (2022–2026).

These initiatives have collectively advanced the adoption of mechanochemistry by fostering collaboration between academia and industry, bridging the gap between research and industrial application, and supporting the integration of these technologies from early development to scale-up. Building on this foundation, IMPACTIVE focuses on addressing remaining scientific challenges and accelerating the transition of mechanochemical processes toward industrial implementation and commercial readiness, thereby strengthening Europe's position in sustainable and resilient pharmaceutical manufacturing.

Therefore, the presentation outlined the transformative potential of mechanochemistry as a sustainable, efficient pathway for future pharmaceutical manufacturing. It began by highlighting the pressing environmental challenges facing the pharmaceutical sector, which generates disproportionately high CO_2 emissions, large volumes of solvent-based waste, and suffers from vulnerable, increasingly complex global supply chains. Traditional solution-based synthesis relies heavily on organic solvents—responsible for up to 90% of reaction mass, 75% of energy consumption, and 50% of global warming potential—making greener alternatives essential.

This approach significantly reduces waste, eliminates the hazards of solvent handling, shortens reaction times, and allows access to new reactivities not achievable in solution.

These advantages were concretely illustrated through the mechanochemical preparation of active pharmaceutical ingredients (APIs) (including a co-crystal), at different scales in batch and/or in continuous, and the results were systematically and quantitatively benchmarked against the solution-based counterparts. Four case studies were presented and discussed, with a special emphasis on mechanochemical productivity, scalability, sustainability of the mechanochemical processes, including the investigation of the impurities.

Among the examples, the mechanochemical synthesis of nitrofurantoin, a WHO-listed essential antibacterial agent was presented. Its preparation by Twin Screw Extrusion (TSE), which represents the seminal approach for the continuous flow mechanochemical manufacturing of API, showed dramatic gains with 85% reduction in CO_2 emissions and ecotoxicity, 12% lower costs, no solvents, no workup, and higher productivity. Unprecedented life cycle assessments (LCAs) across multiple impact categories showed that mechanochemistry drastically reduced footprint for this target.

In the case of Osimertinib Mesylate (Tagrisso), an anticancer drug, the total mechanochemical synthesis, proved to be shorter than the patented route in solution, delivering the same crystalline form as the approved drug.

The presentation also introduced frontier developments such as an autonomous, self-driving mechanochemical platform for reactive extrusion. Using machine learning and Bayesian optimization in a closed loop, this system autonomously designs, runs, and refines experiments, enabling faster, more accurate optimization with minimal resources. This innovation aligns mechanochemistry with Industry 4.0 digital manufacturing strategies.

The presentation also identified strategic enablers for widespread adoption of mechanochemical processing, as an impactful pathway for sustainable API manufacturing. Mechanochemistry naturally aligns with Safe and Sustainable by Design (SSbD) principles and responsible chemistry frameworks, with a great potential of both environmental and economic benefits.

Relevant references:

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Questions and Answers:

The discussion focused on key scientific and regulatory aspects of mechanochemistry, particularly its applicability in pharmaceutical manufacturing. It was highlighted that mechanochemical processes can be described using predictive kinetic models, although reaction kinetics may vary depending on scale, indicating a need for further framework development. Reproducibility across different equipment and scales was confirmed, with observations that scale-up can even improve productivity and reduce reaction times.

Concerns regarding impurity formation and degradation pathways were addressed, with the clarification that mechanochemistry does not inherently lead to increased degradation, as processes are carefully designed to avoid such outcomes. It was emphasised that process design and control of parameters are critical to maintaining product quality and avoiding the need for additional purification steps.

From a quality perspective, key attributes such as crystallinity and polymorphism were discussed, with initial findings showing comparable or improved properties relative to conventional processes. Nitrosamine formation was considered not to be specific to mechanochemistry but rather dependent on broader chemical and process conditions.

The discussion also addressed challenges related to complex multi-step syntheses and highlighted that mechanochemistry can reduce the number of synthesis steps while maintaining product quality. Finally, the need for further development of GMP frameworks adapted to mechanochemical processes was identified, alongside continued collaboration between industry and regulators to support implementation.

4.4. 'Implementing Recombinant Endotoxin Testing', EFPIA.

Summary as provided by the presenters

The current Bacterial Endotoxins Test (BET) relies predominantly on Limulus amoebocyte lysate (LAL), an extract from the Atlantic horseshoe crab. This poses a sustainability and supply risk: horseshoe crabs are ecologically critical as a food source for migratory birds, and their exploitation threatens coastal biodiversity. LAL supply is inherently volatile because it depends on harvesting and bleeding a threatened species, creating potential reagent shortages that jeopardize timely testing and release for parenteral products. Additionally, natural LAL contains Factor G, which can cause β-glucan–triggered false positives and assay variability, adding quality and operational burden.

Sustainable alternatives to traditional BET are now available, offering improved consistency and reduced environmental impact. Recombinant bacterial endotoxin tests (rBET) include recombinant Factor C (rFC) and recombinant Cascade Reaction (rCR) methods, which use defined recombinant proteins to detect endotoxin. While rFC relies on direct Factor C activation, the rCR mimics the enzymatic cascade in a fully recombinant format. By eliminating Factor G, these methods reduce the risk of false positives while maintaining high sensitivity and reliability.

In-house and published data indicate that rBET achieves comparable or superior recovery and precision across different water sources and diverse pharmaceutical matrices, with recoveries consistently within the compendial acceptance range of 50–200%. Multiple suppliers and formats (e.g., plates and microfluidics) have been validated for both rFC and rCR. Furthermore, rBET has been registered in regulatory submissions, and the number of approved products utilising recombinant methods continues to increase globally.

Despite strong scientific and technical justification, a wholesale transition from BET to rBET across all parenteral drug products remains complex. BET encompasses six methods described in pharmacopoeias (further referred to as compendial methods) and is deeply embedded in pharmaceutical quality systems (PQS) and regulatory dossiers, with methods often tailored to address product-specific matrix effects. Recombinant methods are currently less diversified (primarily limited to rFC and rCR quantitative formats) and require either matrix-specific verification or full validation depending on regulatory acceptance and recognition by pharmacopoeias to become official. For approved products, regulators may request comparative (head-to-head) studies, and implementation can necessitate post-approval variations across multiple markets, potentially extending timelines by several years.

Water testing is a practical first step given its low matrix complexity and typical exclusion from regulatory dossiers. However, broader adoption across parenteral products will require collaborative efforts between the industry and regulators, as well as aligned regulatory pathways and globally harmonised pharmacopeial status.

Questions and Answers:

The discussion focused on key regulatory and technical aspects that can facilitate the transition to recombinant endotoxin testing methods. Under the 2025 EU Variations Guideline, the replacement of BET with rFC or rCR is currently classified as a Type II variation (change to biological/immunological analytical procedures). However, the industry considers this transition to constitute a minor technical change when the recombinant method has been demonstrated to be fit for purpose and therefore proposes a risk-based reclassification to Type IA (or, at most, Type IB). This position is supported by extensive in-house platform knowledge, supplier validation, and product-specific verification, as well as the absence of additional risk to patients when acceptance criteria and endotoxin limits remain unchanged. EMA/BWP has acknowledged that, for rFC, given its compendial status, a Type II classification may be overly stringent and has agreed that a Type IB classification is more appropriate. An EMA Biologics Q&A is currently under development to reflect this position. For rCR, as the method is not yet pharmacopoeial and typically requires full validation prior to approval, a Type II variation classification is expected to remain applicable until compendial status is achieved, unless an alternative regulatory mechanism (e.g., a PACMP) is applied. Furthermore, the relatively limited number of approved applications using rCR to date contributes to a more cautious regulatory approach at this point in time.

The initial introduction of rFC in Ph. Eur. 2.6.32 and its transition to the harmonised chapter 2.6.14 (effective 1 January 2027), together with recent updates to water monographs, represent key milestones facilitating its broader adoption. This progression also establishes a regulatory precedent for the integration of recombinant methods into pharmacopoeial frameworks. In this context, the inclusion of rCR (as a kinetic chromogenic method, i.e. Method H) in Ph. Eur. general chapter 2.6.14 would recognise its scientific equivalence, remove the current non-compendial barrier, and enable more efficient post-approval changes. To support EDQM in progressing rCR towards compendial status, robust evidence demonstrating broad applicability across diverse product types and matrices is needed. Ongoing industry-generated data, together with current and pending regulatory approvals, can contribute significantly to building this evidence base. Accordingly, the industry is encouraged to notify EDQM of regulatory approvals involving the replacement of existing endotoxin methods with rCR, including details on product type, matrix, and scope of the approved change. Systematic sharing of such information would help demonstrate broader use in practice and significantly accelerate the implementation of rCR as a compendial method.

According to the Ph. Eur., alternative methods may be used with the acceptance of regulatory authorities, provided that they enable an unequivocal decision on compliance with Ph. Eur. methods. In practice, this is often achieved by direct analytical comparison. The industry members emphasised that all bacterial endotoxin methods (i.e., BET and rBET) are matrix-dependent and subject to interference/adjustments, and the method-specific LoDs may differ, making direct comparisons (especially near/below LoD) of limited value. As such, the industry proposes to focus on method suitability, including control of matrix effects and reliable endotoxin detection in the specific product context, in line with ICH Q2 principles. For rFC, such extensive equivalence demonstrations are no longer typically required, as its inclusion in Ph. Eur. 2.6.14 provides a recognised pharmacopoeial framework. For rCR, regulators acknowledge the scientific rationale for waiving request for direct analytical comparison. However, given its current non-compendial status and limited regulatory experience, emphasis should be placed on building confidence through data generation and regulatory submissions. Continued accumulation of approvals and real-world use is essential to establish regulatory familiarity and acceptance. Once sufficient experience has been gained, it may become

possible to consider reduced reliance on formal equivalence testing through appropriate regulatory forums.

For rCR, the establishment of platform analytical procedures (as described in ICH Q2) offers a key opportunity to streamline lifecycle management and enable more efficient implementation across product portfolios. Companies acknowledge this potential and are actively considering platform approaches. For example, one company is planning an ICMRA pilot exploring portfolio-wide adoption of recombinant methods (e.g., via a multi-use, multi-product PACMP spanning synthetic peptides, small molecules, vaccines, antibody-drug conjugates and monoclonal antibodies), with the aim of generating a comprehensive, cross-product evidence package to support platform applicability and facilitate regulatory acceptance. Industry members are encouraged to engage early with the QIG (e.g., via a 1:1 meeting) to discuss the proposed platform strategies, including the scope and supporting data package.

4.5. Panel discussion (day 2)

The panel discussion focused on identifying how regulators, and in particular the QIG, can better support the implementation of sustainability in pharmaceutical development and manufacturing. A central theme emerging from the discussion was the need for a clearer and more practical roadmap to help companies navigate existing regulatory frameworks when implementing sustainability-related changes. Participants emphasised that while regulatory pathways exist, uncertainty regarding expectations—particularly around data requirements and the level of evidence needed—remains a significant barrier to progress.

Industry representatives highlighted that this uncertainty could delay or even prevent the adoption of innovative and more sustainable approaches, especially when companies are unsure whether new methodologies such as modelling or platform approaches will be accepted without additional verification using traditional methods. In this context, the QIG was recognised as a highly valuable forum due to its unique position in bringing together expertise from both assessment and inspection domains. Continued engagement through QIG meetings, as well as increased opportunities for targeted interactions and case-specific discussions, were strongly encouraged to build confidence and provide clarity.

The discussion further highlighted the importance of moving towards more consistent interpretation and application of regulatory principles. There was a clear call for increased transparency regarding expectations, as well as for the development of more structured outputs such as guidance documents or Q&A frameworks. At the same time, it was acknowledged that such guidance cannot be developed in isolation and requires a collaborative effort between regulators and stakeholders, supported by real-case studies and experience.

Harmonisation across jurisdictions was identified as another potential critical factor that could influence the implementation of sustainability initiatives. Given the global nature of pharmaceutical supply chains, companies need solutions that can be applied internationally.

In this regard, participants noted that, in practice, there is rarely a purely regional (e.g. European-only) regulatory context, as many jurisdictions follow key elements of the European model, particularly for post-approval changes and regulatory pathways. In addition, the EMA's role in international collaboration and reliance mechanisms was highlighted as an important driver for global alignment, with engagement of other major agencies supporting broader acceptance of regulatory approaches developed in Europe.

This provides an opportunity to drive broader alignment, even in regions where sustainability may not yet be a primary focus. However, achieving meaningful harmonisation will also require agreement on fundamental aspects such as the definition and assessment of environmental sustainability, which should extend beyond carbon footprint considerations to a more comprehensive evaluation of environmental impact.

A strong consensus emerged that sustainability should be considered in conjunction with innovation and supply chain resilience. Rather than being competing objectives, these elements were described as mutually reinforcing. Sustainable manufacturing approaches can contribute to more robust and adaptable supply chains, while innovation provides the tools needed to achieve sustainability goals. Participants highlighted the importance of taking a lifecycle perspective, with increasing interest in developing systems that are not only environmentally sustainable but also resilient to disruptions and capable of adapting over time.

Digitalisation and modelling were discussed as key enablers of sustainable development, offering the potential to reduce experimental burden and improve efficiency. However, regulatory uncertainty regarding the acceptance of such approaches was again identified as a major bottleneck. Companies expressed concern that in silico models may still need to be confirmed by traditional experimental data, which undermines the efficiency gains they are intended to provide. Regulators acknowledged these challenges and emphasised that modelling approaches are increasingly being considered, with scientific advice procedures and ongoing discussions within the EMA working parties serving as important mechanisms to build consensus and experience.

The discussion also touched on the sustainability of digital technologies themselves, particularly the energy consumption associated with artificial intelligence. While concerns were raised, it was suggested that the overall impact needs to be assessed in context, as digital tools may ultimately reduce resource use by decreasing the need for physical experiments and improving process efficiency. At present, there is a lack of quantitative data to fully assess this balance, indicating a need for further analysis at a sector level, as also mentioned in day 1.

Another important topic was the implementation of new, more sustainable manufacturing processes for existing products. While regulatory frameworks for post-approval changes are well established in EU, they require comprehensive evidence demonstrating comparability between the existing and the new process. This includes detailed data on process performance, impurity profiles, and product quality. The need for such rigorous evaluation reflects the fundamental requirement to ensure that quality, safety, and efficacy are maintained. However, it also contributes to the complexity and resource intensity of implementing change, highlighting the importance of regulatory support in facilitating these transitions.

Collaboration and data sharing were repeatedly emphasised as essential for progress. Regulators encouraged companies to work together, for example through consortia, to develop joint proposals supported by robust data. Such collaborative approaches can accelerate the development of guidance and enable solutions to be applied more broadly. In addition, sharing of learnings and best practices across the sector was seen as critical to building confidence and reducing duplication of effort.

Attention was also drawn to the generics sector, which represents a large proportion of production volume. It was noted that even small improvements in manufacturing practices within this segment could result in significant overall environmental benefits. At the same time, broader environmental considerations, such as pollution related to pharmaceutical manufacturing and antimicrobial resistance, were identified as important areas for future discussion.

Looking ahead, participants agreed that there is unlikely to be a single regulatory change that will enable sustainability to be fully integrated into pharmaceutical development. Instead, progress will depend on a series of incremental improvements, supported by a mindset that enables change and continuous optimisation. Facilitating more flexible and efficient implementation of manufacturing changes will be key to allowing companies to iteratively move towards more sustainable processes.

Finally, the question of whether sustainability should be considered as a potential additional pillar for medicinal products assessment (alongside quality, safety and efficacy) was raised during the discussion. While most participants considered that at the present time sustainability should not be part of the benefit/risk balance assessment, there should be ongoing reflections within the regulatory and stakeholder community on how sustainability considerations could be further integrated into regulatory decision-making frameworks.

In conclusion, the discussion highlighted that sustainability in pharmaceutical manufacturing is a complex and cross-cutting challenge that requires coordinated action across stakeholders. Regulatory uncertainty remains a central barrier but can be addressed through increased transparency, engagement and collaboration. It was highlighted from participants that the QIG may act as a critical platform for enabling this dialogue and supporting the development of practical solutions. A key takeaway was that proactive engagement between industry and regulators, combined with collective efforts and data sharing, will be essential to drive sustainable innovation forward within the existing regulatory framework.

5. Conclusions and next steps

This two-day LLFG meeting confirmed that sustainability is becoming an increasingly important consideration across pharmaceutical development and manufacturing, while reaffirming that any change must remain firmly grounded in the established principles of quality, safety, efficacy and supply continuity. Across the meeting, participants discussed a broad range of scientific approaches intended to measure and reduce environmental and ecosystem impact, improve resource efficiency and strengthen resilience, and there was broad recognition that these objectives may be advanced using innovative technologies when supported by an appropriate scientific rationale and proportionate evidence.

Sustainability considerations can be implemented across the pharmaceutical lifecycle, starting from product design approaches such as the use of ecofriendly materials and green chemistry, through continuous process optimisation aimed at minimising waste and emissions, and extending to packaging, quality control testing, supply chain and end-of-life management. Each stage was discussed as offering opportunities to reduce environmental footprint. The case studies presented during the LLFG illustrated that sustainability-related innovation is already being explored across different parts of the product lifecycle; however, they also underscored that broader implementation depends on a clear definition of sustainability and common approaches to measure context of use, an adequate understanding of product and process risks.

Several scientific and regulatory challenges were identified. These included:

- the absence of harmonised methodologies and accepted metrics for assessing environmental benefit,
- undefined scope of impact (carbon versus broader environmental impact) and the need to better understand lifecycle trade-offs

- limited data availability and transparency across supply chains,
- uncertainty regarding expectations for the use of modelling, platform approaches and other innovative tools in regulatory submissions. In several examples, the principal challenge appeared to be less the scientific potential of the approach itself than the difficulty of establishing sufficiently predictable and practical implementation pathways for change within existing regulatory frameworks and in a global setting.

A consistent message throughout the discussions was that sustainability should be supported through the evolution and application of existing scientific and regulatory tools, rather than through the introduction of a separate formal pillar for medicinal product assessment. In this context, the final discussion indicated limited support for treating sustainability as an additional standalone criterion in medicines evaluation.

The LLFG covered multiple enabling technologies and approaches with potential relevance for more sustainable pharmaceutical manufacturing, including digitalisation and modelling, advanced process control, solvent recovery, alternative synthetic routes, packaging innovation, adaptive facility controls and more sustainable quality control methods. Within this broader context, advanced manufacturing approaches were discussed as potentially contributing to sustainability objectives. Innovative approaches such as digital production, advanced automation, additive manufacturing, green biotechnologies and intelligent monitoring systems were noted as having the potential to enable more efficient resource management, reduce energy consumption and support greater circularity of materials. Participants also noted that such approaches may contribute to more resilient, transparent and secure processes, with potential benefits for traceability and quality assurance.

The adoption of advanced manufacturing technologies was also recognised as an increasingly relevant field of academic research, and participants noted that synergies between industry and academia can support the development of practical and scalable solutions. At the same time, the discussions emphasised that sustainable innovation needs to be developed in parallel with regulatory expectations, ensuring that new methods continue to comply with established quality and safety standards.

The meeting underlined the importance of early scientific exchange between developers and regulators and international collaboration to support mutual understanding of challenges to help identify appropriate pathways for the integration of sustainability enabling technologies within pharmaceutical production, while maintaining core public health objectives. Therefore, proactive engagement between manufacturers, academia and regulators facilitates early identification of potential bottlenecks, clarifies expectations and can inform the development of guidance to increase predictability for developers.

Participants noted that collaborative approaches, including the use of shared prior knowledge and discussion of common scientific principles, may help reduce duplication, support convergence and increase confidence in sustainability enabling innovations. In this regard, the role of the QIG as a forum for early scientific exchange between regulators, industry and academia was recognised as particularly valuable for clarifying challenges, identifying areas where further reflection may be helpful, and supporting a more consistent understanding of existing regulatory expectations.

Overall, the LLFG confirmed both the growing momentum in this field and the complexity of integrating sustainability considerations into pharmaceutical development and manufacture in a meaningful and proportionate way. The discussions suggested that progress is most likely to come through incremental, science-based advances supported by transparent evidence, continued engagement and practical learning from experience, rather than through a single overarching regulatory change.

The meeting therefore provided a useful basis for continued reflection on how sustainability enabling innovation can be supported within the current framework, while maintaining the core public health objectives of medicines regulation.

In conclusion, QIG proposes the following next steps:

- Stakeholders, including scientists, companies, consortia and technology developers, are encouraged engage with QIG through confidential one-to-one meetings to discuss innovative manufacturing approaches that support sustainability objectives. These interactions provide an opportunity for stakeholders to explore potential pathways for the development and implementation of their innovations, while enabling QIG to gain insight into emerging scientific and technological advances and provide tailored regulatory support to facilitate innovation and regulatory preparedness.
- QIG and other EMA groups to communicate key learnings and develop regulatory guidance in areas where science is sufficiently mature (e.g. some of the topics presented in this LLFG) to increase regulatory predictability for stakeholders pursuing sustainability-related innovations.
- QIG to discuss and share learnings from this LLFG with the EU Regulatory Network (e.g. QWP, BWP, IWG) to support broader awareness and continued regulatory dialogue on sustainability-related topics.
- QIG will continue cooperation with international partners to support sustainability initiatives and promote greater convergence in regulatory expectations for pharmaceutical development and manufacturing.
- QIG, considering the importance of the topic, will monitor developments in this area and re-assess the need for follow-up stakeholder engagement in sustainability-related topics, taking into account scientific advances, stakeholder needs and emerging regulatory challenges.

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