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Short communication

# Second regulatory workshop on utilising *in silico* models to expedite vaccine development, testing, and lifecycle management - an expert meeting report

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ABSTRACT

The Inno4Vac consortium, funded under the Innovative Medicines Initiative 2 Joint Undertaking, was launched in September 2021. Among its four key objectives is the development of an open-source, *in silico* simulation platform designed to support the design, scale-up, operation, and technology transfer of vaccine manufacturing processes, including stability testing. A workshop was held on May 27, 2025, in Brussels, Belgium, which provided an opportunity for modellers to show the progress made, and have an open dialogue with regulatory health authorities' representatives.

Regulators are increasingly open to advanced kinetic modelling and other modelling approaches for predicting vaccine stability and shelf-life, provided they are transparent, scientifically justified, and validated with real-time data. Initial claims can rely on accelerated studies and modelling simulating worst-case scenarios, with extensions supported by additional data. In urgent contexts, extrapolation from similar products or processes may be accepted if scientifically sound.

Platform-based extrapolation requires strong similarity, but product-specific data remain critical, as small formulation changes can alter stability. Simulation studies that demonstrate robustness and predictive accuracy enhance confidence.

Projects like Inno4Vac highlight Bayesian methods for formulation design, though formal guidance is limited. Regulatory scrutiny depends on model risk, with low-risk models probably still requiring justification. Transparent data practices, including justified handling of outliers, are essential.

Collaboration between regulators, industry, and academia remains key to advancing science-based innovation while ensuring product quality.

## 1. Introduction

The Inno4Vac consortium, funded under the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU), was launched in September 2021. Among its four key objectives is the development of an open-source, *in silico* simulation platform to support the design, scale-up, operation, and technology transfer of vaccine manufacturing processes, including stability testing [1]. The project centres on creating predictive models that accelerate vaccine bioprocess development while ensuring alignment with regulatory standards. Therefore, an early engagement with regulatory authorities was considered a priority.

An initial regulatory workshop was held on March 30, 2022, in Brussels, Belgium [2], bringing together model developers and international regulatory experts to discuss the regulatory criteria for acceptance of mathematical models for stability prediction and process optimisation for Chemistry, Manufacturing and Control (CMC) development, manufacturing, control, and dossier submission to authorities. Toward the end of the Inno4Vac project, a second workshop titled "Utilising *In Silico* Models to Expedite Vaccine Development, Testing, and Lifecycle Management" was held on May 27, 2025, in Brussels, Belgium, which provided an opportunity for modellers to show the progress made, and have an open dialogue with representatives of regulatory health authorities. This report presents a detailed summary of the key discussions and outcomes from the workshop.

## 2. Stability preparedness for rapid outbreak response

***Renske Hesselink***, Director of Manufacturing and Supply Chain Innovations at CEPI (Coalition for Epidemic Preparedness Innovations), presented an overview of CEPI's approach to "stability preparedness" for pandemic and epidemic response. Founded in 2017 following the West African Ebola outbreak, CEPI aims to accelerate vaccine development and ensure equitable access globally. While the COVID-19 vaccine response was a major scientific success, with vaccines developed in under a year [3], compared to the previous fastest timeline of four years, there remains an urgent need to be faster and better prepared for future pandemics.

CEPI's aspirational goal is to enable vaccine development within 100 days of pathogen identification [4]. During COVID-19, the 326-day vaccine development window allowed the pandemic to significantly spread, infecting millions before immunisation campaigns began. Modelling suggests that achieving the 100-day mission could have drastically reduced global mortality, particularly in low- and middle-income countries [5,6]. Achieving such rapid timelines depends on two critical pillars: prior knowledge of virus families and robust vaccine platform technologies.

Platform-based vaccine development allows for rapid adaptation by replacing only the antigen component, minimising impact on manufacturing processes and stability profiles. For example, mRNA vaccine platforms are versatile and well-suited to rapid response due to their modular design. However, mRNA-based vaccines face challenges such as limited thermostability and high cost [7,8], which constrain equitable access in low-resource settings. CEPI's response has included investments in technologies that enable rapid and scalable manufacturing, improve thermostability, and support cost-effective regional manufacturing, for RNA-, protein- and viral vector-based vaccines.

A significant challenge in rapid vaccine deployment is the availability of enough evidence to propose an expiry date (shelf-life) for newly developed vaccines. During emergencies, limited time and data hinder the establishment of a sufficiently long shelf-life for new vaccines, leading to difficulties in the supply chain which may result in a shortage of available doses. For instance, initial emergency use authorisations (EUAs) during COVID-19 often underestimated vaccine stability due to insufficient supporting data. Mis-evaluating the shelf life can lead to discarding valid doses, hence limit the availability for low- and middle-income countries. To address this, CEPI advocates for proactive stability preparedness: establishing platform-specific degradation models and defining the impact of variables such as RNA length, sequence, formulation, and manufacturing changes (Fig. 1). The goal is to build predictive models that can be rapidly validated and utilised during a pandemic response.

CEPI also underscores the importance of agile and flexible labelling practices. While field workers prefer clear and unambiguous storage guidelines, scientific realities demand a more dynamic approach. Real-time temperature monitoring and variable expiry labelling, possibly *via* QR codes or vaccine vial monitors, could enhance distribution efficiency without compromising safety, thereby increasing the availability of vaccine stocks.

Two CEPI-funded projects were showcased: one involving a thermostable RNA patch vaccine by the Australia-based company Vaxxas Pty. Ltd., and another exploring spin-lyophilised RNA formulations at Ghent University, Belgium. Both projects aim to improve stability profiles of RNA-based vaccines under standard cold chain conditions

(2–8 °C) or even higher, which is crucial for distribution in remote regions.

In conclusion, CEPI's vision of stability preparedness combines platform understanding, predictive stability modelling, and flexible regulatory frameworks. This integrated approach aims to make 100-day vaccine development a realistic and impactful objective, enabling rapid, equitable, and effective responses to future outbreaks.

## 3. Discussion

The 100-day mission aims to develop and deploy vaccines rapidly in response to severe pandemics but would only be applicable under exceptional circumstances involving highly contagious and lethal pathogens. In such cases, EUA might be granted based on limited data, with the understanding that the risk-benefit ratio justifies accelerated deployment. To support this, manufacturers are focusing on building well-characterised platforms with extensive safety data and the ability to quickly generate candidate-specific safety and immunogenicity information.

Batch release during such a scenario would be assessed on a case-by-case basis. While traditional processes like the EU's Official Control Authority Batch Release (OCABR) would still apply, additional testing requirements, like those imposed during COVID-19, could affect deployment speed and product shelf-life. Balancing urgency with the need for rigorous oversight will remain a critical challenge.

Shelf-life expectations would vary depending on the vaccine platform's known stability. In emergencies, a shelf-life of six to twelve months might be sufficient, especially if the vaccine is used quickly, as was the case during COVID-19. In remote or resource-limited regions, however, longer shelf-life and stable formulations would be more critical due to distribution delays.

On the regulatory side, alignment ahead of any outbreak is essential. Proactive engagement with global regulators aims to establish platform-based data standards and enable the submission of pre-approved master dossiers. This would streamline approval during emergencies and avoid time-consuming negotiations mid-crisis.

Finally, while the draft International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1 guideline reflects progress, more regulatory work is needed to establish platform-level stability as an accepted norm. Currently, product-specific data remains the standard, and further data generation and consensus-building will be necessary to support broader adoption of platform-based models.

## 4. Integration of stability models into industry workflow

**Caroline Forestieri** (Pharmalex) explained that traditional approaches rely heavily on ICH guidelines, notably ICH Q1A and Q1E, which outline requirements for stability studies, shelf-life estimation, and conditions for extrapolation. These guidelines emphasise linear modelling based on long-term storage data, typically over more than 6 months, and suggest extrapolation rules based on observed significant changes. However, such methods often fall short for biologics due to their complex degradation behaviours.

Conventional linear regression is widely used to model stability trends and predict shelf-life. These models often include pooled data from multiple batches, assuming shared slopes or intercepts. Under the actual ICH Q1A/Q1E guidance [9,10], statistical tests to determine whether data from different batches can be modelled with common or separate parameters must be done. Depending on the outcome, shelf-life estimates may be calculated using the worst-case batch or *via* a mean model. However, this fixed-batch approach assumes representativeness of the sampled batches (often limited to three single batches), which may not accurately reflect the variability of future production lots.

To address this limitation, mixed models (hierarchical models) have been used in stability modelling by many industries for years, and this concept has been recently introduced in the new ICH Q1E EWG draft guidance.

Unlike fixed models, hierarchical models treat observed batches as samples from a broader population, incorporating both fixed and random effects. This approach allows for more realistic modelling of batch variability and removes the need for rigid hypothesis testing. In practice, hierarchical models often yield more conservative shelf-life estimates due to the inclusion of additional variabilities pertaining to the batch and analytical run effects.

More recently, hierarchical models are fitted to stability data using Bayesian statistical methods. In contrast to frequentist approaches, they support probabilistic interpretations, such as the likelihood of remaining within specification limits over time. Another key advantage of Bayesian modelling is its flexibility in handling complex patterns, such as non-linear degradation profiles, which are common in complex biologics, but difficult to handle using frequentist approaches. For example, in one case study, a hierarchical mono-exponential model was necessary to adequately describe a protein degradation curve, as linear models were clearly not able to fit this data. In this context, obtaining valid confidence intervals using frequentist methods proved extremely challenging due to difficulties associated with degrees-of-freedom estimation in non-

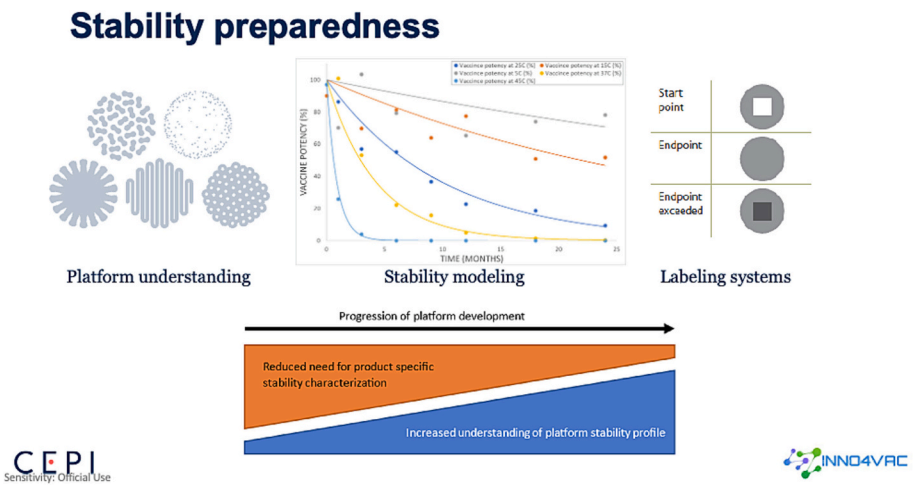



**Fig. 1.** Stability preparedness. Stability preparedness for rapid response is based on three pillars: 1) Platform understanding, including the impact of process and product factors on stability. 2) Stability modelling, to rapidly confirm the new vaccine candidate behaves according to platform expectations and to predict shelf life. 3) Labelling systems that are both flexible to integrate new data, and unambiguous to the end user. The greater the platform understanding, the lower the need for product-specific data.

linear hierarchical settings, while straightforward when the same model is implemented using Bayesian methods.Based on long-term stability data, the Bayesian approach improved the estimation of shelf-life. However, in some cases, such models fitted only on long-term data may fail to capture the multifaceted degradation pathways of biologics, emphasising the need to also consider data collected at higher temperatures (accelerated stability studies) and to use advanced kinetics modelling (AKM) [11–13].

The session concluded with a transition into accelerated stability modelling. Accelerated data, additionally collected at higher temperatures (*e.g.*, 25 °C and 37 °C), over shorter durations, were used to model degradation kinetics and to predict vaccine behaviour over long-term stability. These models can simulate long-term behaviour based on short-term accelerated studies, significantly enhancing the predictive power for products with non-linear degradation profiles compared to the methods only based on long-term data.

**Laurent Natalis** (Pharmalex) explored the technical and regulatory aspects of vaccine stability modelling, focusing on the evolution from traditional linear models to more complex mixed, Bayesian, and AKM approaches. Historically, stability predictions relied on simple linear models with only a few parameters (*e.g.* slope and intercept), often assuminguniform behaviour across batches (*via* the pooling rules from the ICH guidance, hereafter referenced as the fixed batches approach). More recently, the latest ICH draft guidance makes a notable step forward by recognising the use of hierarchical (mixed) models. These are particularly valuable for capturing variability across batches and for generating predictions that are more representative of the future vaccine production.

However, under its current form, the new draft regulatory guidance requires data from at least five batches to implement mixed models, while only three batches are required for the old-fashioned fixed-batch approach. This requirement can represent a practical constraint, especially in the early development stages of biological products, where the number of available batches is limited, and there is a significant pressure for a rapid submission of dossier to regulatory authorities. Requiring five batches may delay or deter the use of statistical methods that would better reflect the underlying variability of the process, while this requirement is not necessary from a statistical viewpoint. Indeed, fitting a mixed model with only threebatches does not invalidate the statistical consistency of the approach, but the resulting model uncertainty and its associated intervals will just be wider, which translates in shorter estimated shelf lives. This behaviour is statistically coherent and appropriately reflects that limited information results in more conservative decisions. Therefore, it is in the applicant interest to include more batches in mixed models to obtain a tighter interval, and to get a more advantageous shelf-life.

Consequently, the guidance as it is drafted may unintentionally discourage the use of more robust modelling approaches and limit the benefits that both applicants and health authorities could gain from mixed models, unless greater flexibility is introduced regarding the minimum number of required batches for implementing mixed models. Another key issue noted is the confusion between tolerance, confidence and prediction intervals in the draft regulatory guidance, which should be addressed in future updates. While the increasing recognition of batch-level variability and prior knowledge integration is encouraging, discussion of advanced kinetic modelling, high-throughput trend detection, and data automation remains limited and is not yet explicitly framed within the context of drug stability evaluation.

Current approaches for stability evaluation include:

1. Compliance approach: Shelf-life is based on the last time point meeting specifications. Requires long-term stability data and is very straightforward to compute. Even if this approach is currently accepted, this approach is conceptually flawed and should not be used to evaluate vaccine shelf-life.
2. ICH Q1 fixed-batch model: Applies a linear fixed model across batches, assuming common slopes or intercepts depending on the results of the poolability test(s). Requires long-term stability data and is straightforward to compute. Even if this approach is currently accepted, this approach is conceptually flawed and should not be used to evaluate vaccine shelf-life.
3. Mixed linear or non-linear models (fitted *via* frequentist or Bayesian methods): Introduce variability *via* random effects (analytical run, or batch effect) and is from a statistical perspective more appropriate than the two approaches above. Requires sufficient long-term data (*e.g.*, at least six months) and typically limited to long-term storage conditions data. Requires the help of a statistician to evaluate the shelf-life. Predictions should not be made over an extended period (*i.e.*, not more than within regulatory limits) because dealing with data from a single temperature may result in inaccurate long-term predictions, particularly for extrapolating reaction progress over time. Predictions may be only applicable up to the regulatory limits, and it cannot be excluded that a further drop may occur after a long period of time. If not enough long-term data at target conditions are available, it is wiser to consider resorting to accelerated condition data and the implementation of AKM approaches to support long-term predictions.
4. Advanced kinetic models: Useful for linear, non-linear degradation and multi-steps reactions. This approach is the only one that allows considering data from short-term accelerated studies to model the vaccine long-term stability. Requires advanced statistical tools and sophisticated data handling. When fitted with a frequentist approach, these models do not account for batch-to-batch variability, while errors associated with random effects (analytical run effect, or batch effect) can be propagated appropriately using Bayesian methods. While AKM refers to Arrhenius-based equation, known mechanistic models (*e.g.* 1st-order reaction with or without autocatalytic contribution) can be applied for well-known products. However, by default, AKM do not require assumptions on the type of kinetics. Instead, a phenomenological mathematical model is derived for fitting the reaction progress, without any mechanistic basis, allowing to model processes that show Arrhenius and non-Arrhenius behaviour.

The potential of the use of different approaches is showcased through real-world case studies (*e.g.*, GSK and Sanofi vaccines) [14–17]. Bayesian methods allow for providing flexible and probabilistic predictions of shelf-life based on long-term data. In cases where degradation is non-linear, traditional linear models cannot be used, while Bayesian and hierarchical approaches extend the modelling to non-linear models, to capture trends accurately at least up to the regulatory limits. These models can also generate predictions about the probability of remaining within specification limits over time, which supports better decision-making under uncertainty.

However, it was also shown that including accelerated stability data (*e.g.*, at 5 °C, 25 °C, 37 °C) and using AKM methods to model vaccine stability results in better estimations of the product shelf-life. It allows extrapolating reaction progress over time, even further than within regulatory limits, which is not possible when modelling only the long-term 5 °C data. One key insight from these cases is that AKM methods taking advantage of accelerated data (even over just 100 days) and Bayesian implementation, can offer more predictive power than years of long-term data and substantially refine shelf-life estimates, especially in biologics, where degradation often follows non-linear, multi-phase kinetics.

In conclusion, the integration of hierarchical models, Bayesian statistics, and accelerated kinetics represents a significant advancement in vaccine stability prediction. While regulatory frameworks are evolving to support these methods, ongoing collaboration and feedback from researchers and manufacturers during guidelines updates are crucial to ensure these guidelines are applicable and future proof. These models

aim to better predict vaccine shelf-life, especially under conditions where standard methods based on long-term data may fall short.

**Noémie Mansois** (Sanofi) discussed Quality by Design (QbD). QbD is a systematic approach to pharmaceutical development that emphasises the use of statistical, analytical, and risk-management methodologies to ensure product quality throughout the design, development, and manufacturing stages. A key objective of QbD is to identify, understand, and control all sources of variability within the manufacturing process. This proactive strategy aims to ensure that the final medicinal product (including vaccines) consistently meets predefined quality criteria, thereby achieving a 'right first time' outcome. QbD relies on multivariate analysis, often in conjunction with advanced process analytical technologies and knowledge-management systems. These tools facilitate a deeper understanding of critical material attributes and process parameters, supporting the integration of quality into the manufacturing process and promoting ongoing process and product improvement. However, no studies have yet documented the application of QbD principles for vaccine stability optimisation. The Inno4Vac project aims to develop Bayesian statistic-based approach to support the definition of the valuable stability design space of a vaccine. Exploration of the experimental space (*e.g.,* concentration range of each excipient in drug product) is done leading to best global stabilising region (design space).

## 5. Integration of upstream models into industry workflow - case study: bioreactor and metabolic modelling

**Antonio Gaetano Cardillo** (GSK) described a collaborative modelling project between GSK and Denmark Technical University (DTU), focused on upstream bioprocess development, particularly using *E. coli* for recombinant protein production. He emphasised the importance of data-driven model validation to support both kinetic and compartmental modelling. The models are intended to predict bioreactor behaviour and assess scale-dependent heterogeneity. The project focuses on the use of computational fluid dynamics (CFD) and compartment models to analyse fluid dynamics within bioreactors, using the Ambr 250 system at development scale and a 20-l Sartorius stainless steel fermenter as the pilot scale.

A key component of this work is the generation of a robust kinetic model. This required extensive experimental data gathered from parallel bioreactor runs based on a carefully designed Design of Experiments (DoE) protocol. The fermentation process involved an initial batch phase followed by fed-batch operation, with controlled variables such as temperature, pH, partial oxygen pressure ($pO_2$), and airflow. Induction of recombinant protein production was initiated upon reaching a specific optical density (OD), using isopropyl β-D-1-thiogalactopyranoside, and was further modulated by temperature, pH, and induction duration. The objective was to introduce deliberate process variations to capture dynamic behaviour and optimise productivity.

The DoE included variations in feed rate, induction timing (based on OD), and induction temperature. Key response variables were total biomass (pellet weight), expressed as grams per litre, and recombinant protein titre in kilograms per litre. Sampling at multiple time points provided data on metabolites (acetate, glucose, glycerol, ammonia, phosphate), gas exchange ($O_2$ uptake, $CO_2$ output), and critical culture conditions (temperature, pH, $pO_2$). These datasets formed the basis for model development and validation, supporting a predictive framework capable of simulating upstream fermentation dynamics.

The goal was to translate empirical observations into a comprehensive model that enables both scale-up and process optimisation. This required transferring the experimental data to DTU, where the modelling team worked on building a hybrid kinetic-compartmental model, aiming to reduce the reliance on empirical scale-up approaches by using validated simulation tools that can forecast fermentation outcomes across different scales and operating conditions.

**Xiyan Li** (Denmark Technical University) detailed the simulation methodology and practical benefits of integrating CFD with compartmental modelling in upstream bioprocessing. The core challenge in modelling bioreactors lies in addressing scale-specific phenomena: small-scale systems face diffusion limitations, while large-scale systems encounter mass transport and mixing heterogeneities. Full CFD simulations at large scale are computationally expensive, often requiring several days for short simulation windows. To overcome this, DTU implemented a compartment model approach that aggregates regions with similar fluid dynamics, significantly reducing computational complexity from millions of CFD mesh elements to hundreds of zones.

This approach enables the fast simulation of hydrodynamics and their integration with kinetic models. For instance, a 20-l fermenter CFD simulation was translated into a compartmental framework with fewer zones, preserving flow characteristics while allowing for quicker iteration. The compartment model supports simulations that can incorporate biological kinetics without the need to rerun expensive CFD calculations for every scenario.

The kinetic models injected into these compartments allow for precise analysis of biochemical processes, such as oxygen limitations, nutrient starvation, or overfeeding scenarios (Fig. 2). The platform developed by DTU allows users to upload CFD results and generate compartment models for testing. This was demonstrated using GSK's fermentation data, where different feeding strategies and oxygen transfer conditions were modelled to observe their effects on glucose and oxygen gradients in the reactor.

The platform is publicly accessible, allowing researchers to input their data, visualise simulation results, and validate compartmental representations [18] (https://platform-image-pfwhpn5qeq-ew.a.run.app/). Tracer studies within the model reveal how substrates like glucose disperse and how oxygen is consumed during feeding phases. Such insights are critical for troubleshooting, scale-up, and design space exploration. The approach offers a viable alternative to extensive wet lab experimentation, accelerating process development and supporting regulatory submissions by providing predictive simulations aligned with experimental data.

Overall, the integration of CFD with compartment and kinetic models provides a scalable, efficient, and data-driven method for understanding and optimising bioreactor performance across scales, reinforcing the use of *in silico* methods in modern bioprocess development.

## 6. Integration of downstream models into industry workflow – *in silico* modelling on chromatography & tangential flow filtration

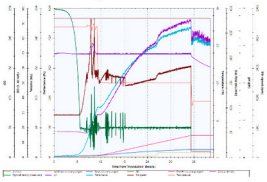
**Lea Girardon and Eric Calvosa** (Sanofi) focused on the application of *in silico* modelling and mechanistic modelling to streamline unit operations in vaccine manufacturing, particularly within Downstream Processing (DSP). While the methodology is currently being applied to a vaccine candidate in Phase II, the broader goal is to extend this approach across all manufacturing stages, including Upstream Processing (USP), thermostability assessments, and fill-finish operations.

The motivation for this work stems from the observation that a significant portion of vaccine production time is dedicated to quality control. By leveraging mechanistic models grounded in chemical engineering principles, and by integrating experimental design (DoE) and simulation data, development time and cost can be reduced while maintaining high safety and efficacy standards. The modelling approach allows for optimisation of unit operations during process development, mitigating risks before the manufacturing phase (Fig. 3).

A case study was presented involving two critical DSP steps: Chromatography and Tangential Flow Filtration (TFF). Classical mass balance models were developed for both unit operations. The chromatography model incorporated flow and adsorption kinetics, while the TFF model described membrane separation dynamics, focusing on protein retention and passage. Each model was calibrated using data from five experimental runs under varying initial conditions.

| BLOCK | n° Vessel | RUN | FACTOR 1 A: FLOW RATE ml/h | FACTOR 1 A: FLOW RATE ml/h per Lferm | FACTOR 2 B: OD ind. OD | FACTOR 3 C: TEMPERATURE ind. °C | CWW EoF (g/L) | rPtot Monomer mg/Kg Ferm. |
|---|---|---|---|---|---|---|---|---|
| Block 1 | 1 | 1 | 1,435 | 10,25 | 70 | 20 | 251 | 904,6 |
| Block 1 | 2 | 2 | 0,91 | 6,5 | 172 | 26 | 218 | 805,0 |
| Block 1 | 3 | 3 | 1,96 | 14 | 121 | 23 | 295 | 1184,2 |
| Block 1 | 4 | 4 | 0,91 | 6,5 | 172 | 26 | 224 | 788,9 |
| Block 1 | 5 | 5 | 0,91 | 6,5 | 70 | 26 | 130 | 674,3 |
| Block 1 | 6 | 6 | 1,435 | 10,25 | 121 | 26 | 213 | 648,4 |
| Block 1 | 8 | 8 | 0,91 | 6,5 | 70 | 20 | 212 | 630,8 |
| Block 1 | 9 | 9 | 1,96 | 14 | 172 | 20 | 371 | 841,4 |
| Block 1 | 10 | 10 | 0,91 | 6,5 | 70 | 26 | 146 | 635,9 |
| Block 1 | 11 | 11 | 1,96 | 14 | 70 | 23 | 256 | 1510,1 |
| Block 1 | 12 | 12 | 0,91 | 6,5 | 172 | 20 | 238 | 746,3 |
| Block 2 | 1 | 13 | 1,435 | 10,25 | 70 | 23 | 212 | 1241,5 |
| Block 2 | 2 | 14 | 1,96 | 14 | 172 | 26 | 263 | 726,4 |
| Block 2 | 3 | 15 | 0,91 | 6,5 | 172 | 20 | 253 | 565,6 |
| Block 2 | 4 | 16 | 0,91 | 6,5 | 121 | 20 | 260 | 670,5 |
| Block 2 | 5 | 17 | 1,96 | 14 | 70 | 20 | 315 | 865,1 |
| Block 2 | 6 | 18 | 1,96 | 14 | 121 | 20 | 334 | 693,3 |
| Block 2 | 7 | 19 | 0,91 | 6,5 | 70 | 23 | 179 | 712,3 |
| Block 2 | 8 | 20 | 1,96 | 14 | 172 | 26 | 268 | 682,8 |
| Block 2 | 9 | 21 | 1,96 | 14 | 70 | 26 | 176 | 843,9 |
| Block 2 | 10 | 22 | 1,96 | 14 | 70 | 26 | 174 | 1138,7 |
| Block 2 | 11 | 23 | 1,435 | 10,25 | 172 | 20 | 314 | 817,8 |
| Block 2 | 12 | 24 | 1,26 | 9 | 120 | 23 | 239 | 946,2 |

Data available for each fermenter run (i.e. U110_V1)



| Description | acetate (mg/L) | glucose (mg/L) | glycerol (mg/L) | ammonia (mmol/L) | phosphate (mg/ml) |
|---|---|---|---|---|---|
| T0 | 56.28 | 17489.6 | 56,20 | 35.408 | 11750.8 |
| 4h post feed start | 22.97 | 23.11 | 213.85 | 68.821 | 5884.36 |
| Induction | 25.52 | 45.29 | < 92.09 | 118.355 | 10407.7 |
| 8h post Induction | 52.73 | < 20.00 | < 92.09 | 102.202 | 8743.76 |
| 16h post Induction | 76.87 | < 20.00 | < 92.09 | 57.122 | 4817.46 |
| EoF | 101.32 | < 20.00 | < 92.09 | 39.393 | 3695.90 |

**Fig. 2.** Compartmental modelling in upstream bioprocessing: bioreactor data with different process variations. Sixty fermentation runs in total available, varying: OD to start induction; induction temperature; induction temperature and duration; feed flow rate; feeding strategy. CWW – Cell wet weight; EoF – end of fermentation; ind. – induction; OD – optical density; rPtot – total recombinant protein. (additional data available at Inno4Vac ST4 General – WP17 - Bioreactor - WP17 - Bioreactor))

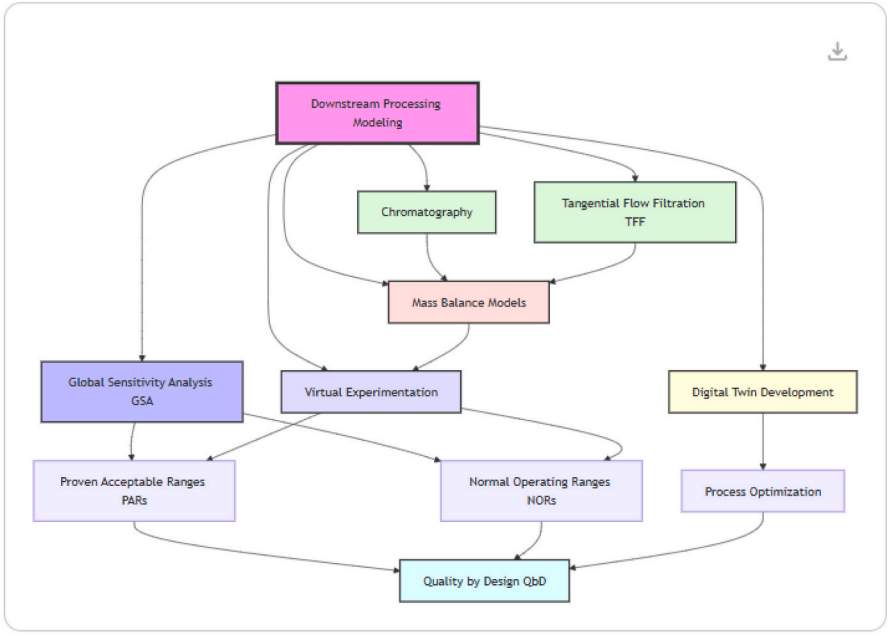



**Fig. 3.** Diagram of key components and relationships in the DSP modeling approach. 1. Downstream Processing Modeling is the central focus. 2. Global Sensitivity Analysis (GSA) is used to identify critical parameters. 3. Chromatography and Tangential Flow Filtration (TFF) are the main unit operations modeled. 4. Mass Balance Models are developed for both unit operations. 5. Virtual Experimentation is conducted using the validated models. 6. The analysis helps define Proven Acceptable Ranges (PARs) and Normal Operating Ranges (NORs). 7. Digital Twin Development is a key aspect of the modeling approach. 8. Process Optimization is achieved through the use of digital twins and virtual experimentation. 9. All these elements contribute to the Quality by Design (QbD) approach in vaccine manufacturing.

Once validated, the models were used for virtual experimentation, simulating a wide range of process conditions to predict outcomes such as purity and protein integrity. Importantly, the models were interconnected to assess how variability in the chromatography step could impact subsequent TFF performance. This interdependence supported the vision of building an end-to-end digital twin of the full production process—from fermentation to final formulation.

The *in silico* modelling framework was applied to quantify the influence of input parameters on key process outputs. This allowed identification of Proven Acceptable Ranges (PARs) and Normal Operating

Ranges (NORs), crucial for establishing a robust QbD foundation. The simplified visual representations generated from this analysis facilitated process understanding and helped define optimal conditions for consistent product quality.

Complementing this modelling effort, Sanofi's broader R&D strategy includes standardisation of both process and platform technologies across different vaccine types, such as recombinant proteins, live viruses, and combination products. Standardisation enhances the scalability, robustness, and cost-efficiency of manufacturing, while also enabling the integration of artificial intelligence (AI) and *in silico* process development tools. For instance, across *E. coli*-derived subunit vaccines, the use of standardised host strains (*e.g.*, VL21) and shared downstream strategies supports consistent model implementation.

A key challenge identified is the harmonisation and management of large-scale data across R&D and manufacturing. Effective digital infrastructure and user training are essential to ensure adoption of modelling tools by biologists and operational teams. Ultimately, the integration of mechanistic models into process design and regulatory documentation is seen as a strategic transition toward more predictive, flexible, and efficient vaccine development. The goal over the next 5–10 years is to move toward *in silico* process development as a standard, using digital twins and virtual experimentation to reduce physical trials and accelerate time to market.

**John Bagterp Jørgensen** (2-control ApS [2C] / MCT Bioseparation ApS [MCT]) explained the digitalisation of chromatography processes through the development of high-fidelity digital twins based on mechanistic modelling. These digital twins are constructed using a combination of physical, chemical, and biological principles (Fig. 4). At the core of this approach are mass transfer and adsorption models, which are parameterised using data from targeted tracer experiments, acid-base titrations, and protein-specific studies.

The digital twin development process begins in the wet lab, where key data such as UV absorbance profiles and average protein concentrations are collected. This data is uploaded to a cloud environment for parameter estimation. Here, the models are trained by combining empirical observations with *a priori* scientific knowledge. A key feature of this workflow is its capacity to separate system transport effects from other biochemical interactions, enabling precise model calibration.

To facilitate efficient modelling, MCT has employed tools such as CADET (Chromatography Analysis and DEsign Toolkit) and commercial simulation platforms. These platforms allow for high-speed dynamic simulations, enabling thousands of virtual experiments to be conducted within seconds. This capability dramatically improves process development efficiency by allowing rapid evaluation of process configurations and conditions, compared to traditional physical experimentation.

One of the main uses of these digital twins is to support process developers in real-time. By using limited in-process measurements, the model can provide immediate feedback on system performance and flag deviations through techniques such as extended Kalman filtering. This predictive capability ensures that errors can be detected early, minimising wasted time and resources on faulty process runs.

In addition to monitoring, the models are also used for process optimisation. For instance, case studies have demonstrated yield improvements exceeding 15% in chromatography by leveraging the model's [19,20]. A key insight from this work is that conventional assumptions (such as the use of linear gradients) may not be optimal. By removing such constraints and allowing the model to explore a wider range of conditions within defined boundaries, non-intuitive but more effective concentration profiles have been identified. In one case, this approach increased the yield from 89% to 94% while maintaining product purity.

To achieve such performance, MCT employed hybrid optimisation methods for complex model fitting. These methods account for parameter uncertainties and ensure the resulting model is robust across a broad operational range. Once validated, these models are used in virtual experimentation to assess the impact of different process parameters and to identify optimal conditions for scale-up.

Despite the power of these models, physical validation remains essential. Any model-driven recommendation is confirmed through laboratory experiments before regulatory submission.

In summary, MCT's digital twin workflow enables rapid, accurate, and flexible chromatography process development. It combines experimental data with mechanistic modelling, cloud-based computation, and real-time process optimisation. This approach enhances decision-making, increases process yields, and supports a move toward predictive, model-based biomanufacturing, with significant implications for vaccine production and regulatory strategy.

**Daniel Bracewell** (University College London, UK) discussed the


**Fig. 4.** Implementation of the Smart Biofactory. AI – Artificial Intelligence.

scale-down of centrifugation. Ultra Scale-Down (USD) technology facilitates efficient process development by enabling the preparation of small-scale samples (typically <50 mL) that accurately reflect full-scale manufacturing conditions. This approach provides valuable insights into how the production environment influences process materials, allowing for a deeper understanding of critical parameters much earlier than is typically achievable with conventional methods. By generating representative data at an early stage, USD helps to de-risk process development and supports robust, reliable technology transfer across different manufacturing scales.

In bioprocessing of *E. coli* for protein subunit vaccines, a critical intermediate step involves cell clarification, typically using centrifugation or filtration after cell homogenisation. This stage presents high complexity due to the release of intracellular components. Large-scale centrifuges impose high shear forces that may alter impurity profiles and affect downstream chromatography. To model and optimise this process at lab scale, researchers have developed methods combining small-scale shear devices and conventional centrifuges. These enable study of clarification efficiency and impurity release under varying conditions. The goal is to generate scalable, cost-effective data for process modelling, supporting QbD strategies.

## 7. A cloud-enabled open online platform for vaccine manufacturing modelling (COOP-VAMM)

**Hannah Lanzrath** (Forschungszentrum Jülich) discussed COOP-VAMM, short for Cloud-Enabled Open Online Platform for Vaccine Manufacturing Modelling, which is a collaborative initiative aimed at advancing digital tools to support *in silico* process development for vaccine manufacturing. The online platform, developed under the name CADET-Hub, addresses the technical and organisational barriers that currently limit the widespread adoption of model-based process design, particularly in non-assisted or low-resource environments.

The core objective of CADET-Hub is to provide a user-friendly, open-access, high-performance modelling environment that supports interdisciplinary collaboration and enables the application of QbD principles. The system is built on the open online platform JupyterHub, allowing users to develop, run, and share simulations through a web-based interface without requiring extensive local computational infrastructure (Fig. 5).

At the heart of CADET-Hub is CADET-Core [21], an open-source C++ simulation engine originally developed for chromatography modelling [22,23]. CADET-Core has since evolved into a modular, general-purpose simulation tool for bioprocesses, supporting a range of transport, binding, and reaction models. CADET-Hub integrates CADET-Core and extends its functionality with tools for probabilistic analysis, digital twin development, and optimisation, using the comprehensive process configuration, design, and analysis package CADET-Process [24].

The platform includes both frontend and backend components. The frontend allows users to interact with simulations *via* graphical user interfaces (GUIs), making complex modelling accessible to non-coding experts. Planned features include drag-and-drop simulation builders, data visualisation tools, and automated error analysis. The backend combines technologies such as Docker and Kubernetes to manage computational resources efficiently, supporting dynamic memory allocation for high-performance simulations. Secure user management and access control are implemented *via* MQTT (Message Queuing Telemetry Transport) protocols to ensure data protection and controlled collaboration.

A key feature of the platform is its support for collaborative workspaces, enabling multiple users to co-develop and share simulation projects in real-time. This is complemented by an integrated research data management system, CADET-RDM [25], which tracks simulation inputs, outputs, parameters, and software versions to ensure reproducibility and transparency across workflows.

Currently, CADET-Hub is at a working prototype stage with full CADET-Core and CADET-Process integration, user management as well as Python and R language support, while data management tools are actively tested. GUIs and additional backend features (*e.g.*, cluster connection and authorisation methods) are under development. The platform has already been applied in teaching and collaborative research, and ongoing work focuses on refining features through community feedback.

Importantly, the CADET-Hub is not designed as a fixed product but as a blueprint for other institutions to deploy their own modelling platforms. It provides modular, open-source components and documentation to facilitate adoption in both academic and industrial settings. Security features allow organisations to create user-specific environments and manage project access, making it suitable for use in regulated or proprietary research contexts.

In the near term, the development team will focus on testing

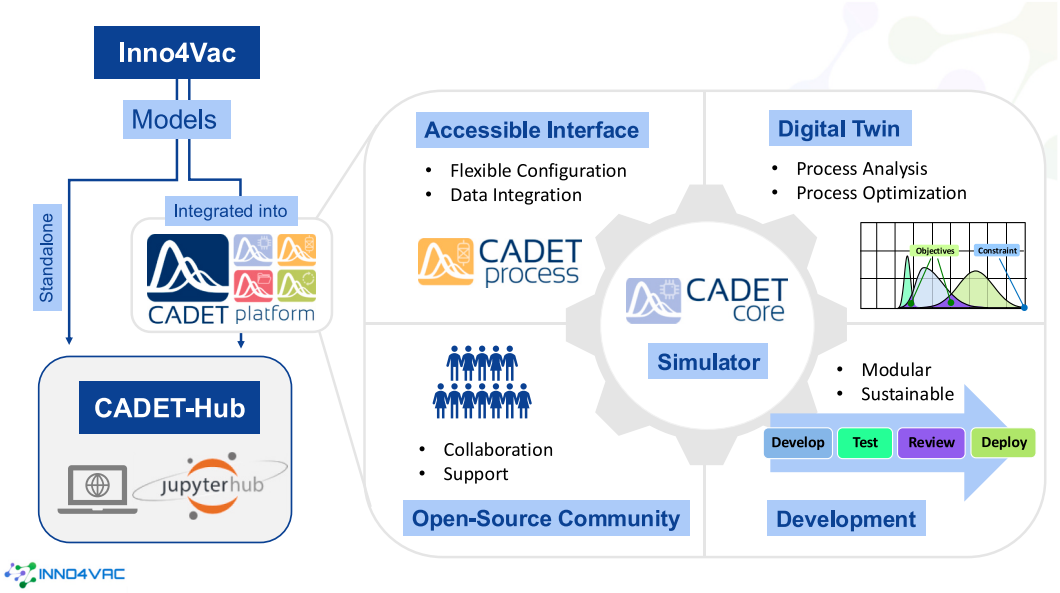



**Fig. 5.** Schematic representation of the CADET-Hub.

collaborative coding features and expanding GUI capabilities. Community engagement is strongly encouraged to ensure that the platform meets the practical needs of its users, especially those working on the front lines of vaccine development.

## 8. Discussion

The CADET-Hub open-source platform is designed to support integration of models, such as those built in R or Python, into a secure, collaborative environment, suitable for both academic and industry use. While individual deployments may remain closed-source, the core elements, including CADET-Core, CADET-Process, and the CADET-Hub blueprint, will be openly available. The platform includes user authorisation and data security features, making it suitable for sensitive industrial applications.

Built on JupyterHub, the platform offers a browser-based interface that allows users to easily upload, download, and interact with data and visualisations. This ensures that researchers and developers can access and reuse generated data and graphs without needing to manage the underlying infrastructure.

The key value for industry lies in the unified, collaborative workspace the platform enables. By supporting digital twin modelling, low-code interaction, and real-time collaboration, it brings together traditionally separate unit operations. This integration is especially valuable for vaccine development and rapid-response manufacturing, where speed, coordination, and cross-institutional cooperation are critical.

## 9. Concluding roundtable discussion

Following the presentations, a roundtable discussion was held, during which industry partners could pose general questions to the regulators. The panel of experts included Koen Brusselmans (Sciensano, Belgium), Arnar Gudjonsson (Norwegian Medical Products Agency, Norway), Julius Carl Pollinger (Paul Ehrlich Institute, Germany), Laura Rodríguez García (Spanish Agency of Medicines and Medical Devices, Spain), Sevda Şenel (Hacettepe University, Faculty of Pharmacy; the CMC committee at the Turkish Medicines and Medical Devices Agency, Ankara, Türkiye), Martin Spruth (Austrian Agency for Health and Food Safety, Austria), and Mats Welin (Medical Products Agency, Sweden). The main themes of the discussion are summarised below, while an overview of questions and answers is provided in Table 1.

Regulatory authorities are increasingly open to the use of AKM models and other modelling approaches for predicting vaccine stability and shelf-life, provided these models are clearly described, scientifically justified, and validated with sufficient batch data and real-time comparisons. While some companies use extensive historical data from 30 to 40 batches, others base models on only three batches, which poses interpretive challenges, particularly for new products. Developers must demonstrate that the model reliably fits observed data, especially in cases where product potency may decline or degradation may increase over time.

In urgent contexts, such as pandemics, regulators may accept stability data derived from similar products or processes, or even from alternative batches, if these provide a scientifically sound basis for setting shelf-life. The use of simulation studies to demonstrate model robustness, predictive accuracy, and sensitivity to variability is also supported, as they enhance confidence in the model's reliability. Initial shelf-life claims based on short-term accelerated data and AKM can be acceptable if the modelling includes the worst-case scenario. As more real-time data accumulate, regulators are open to shelf-life extensions, provided the updated predictions remain within scientifically supported and validated boundaries.

Platform-based extrapolation of stability data from one product to another is possible but context-dependent. High similarity in molecular properties or manufacturing processes is essential, and each case must undergo thorough risk assessment. However, product-specific data

**Table 1**
Summary of key discussion points from the second regulatory workshop.

| Theme | Question / topic | Summary of discussion / regulatory perspective |
|---|---|---|
| Stability Modelling | Use of Arrhenius kinetic models (AKM) | Acceptable if well-justified and supported by sufficient batch data. Models must demonstrate fit and predictive value. |
| | Initial shelf-life claim based on short-term data + AKM | Acceptable if worst-case scenario is claimed and extended with more data. Avoid overestimating initial shelf-life. |
| | Predictive models to accelerate review | Acceptable in emergencies. Prior knowledge and representative batches may support claims. |
| | Use of prior information and platform data | Minor changes in composition may strongly affect stability. This requires strong justification based on similarity of products and processes. Product-specific accelerated data (2–3 months) may help justify differences. |
| | Shelf-life exceeding ICH limits if supported by data | Future ICH Q1 revision may allow this. Models must be substantiated and aligned with real-time data. |
| | Simulation studies and robustness | Valuable for understanding variability. More batches increase model reliability. |
| | Industry collaboration and best practices | Dialogue with EMA and QIG encouraged. Involve Biologics Working Party for model-specific discussions. |
| Formulation Design | Bayesian modelling and QbD design space | Promising, but no specific regulatory guidance yet. May help identify optimal formulation regions. Applicable if justified and validated. |
| Upstream Modelling | Use of models for internal process development | Acceptable. Risk is low if used internally. Final process will be assessed by regulators. |
| | Use for process scale-up or tech transfer | Acceptable if models are supported by data. Usefulness depends on correlation with real-scale outcomes. |
| Downstream Modelling | Combining steps in DSP validation (centrifugation–chromatography–TFF) | May be acceptable if each step's contribution to |

(continued on next page)

**Table 1** (*continued*)

| Theme | Question / topic | Summary of discussion / regulatory perspective |
|---|---|---|
| | | quality is clear and modelling is well-justified. |
| | Real-time optimisation during manufacturing | Possible if within predefined ranges and consistently delivers quality. Sensors and automation must be validated. Increased regulatory scrutiny necessary due to higher risk. |
| | Standardised approaches to support SMEs | Helpful, but fundamental requirement remains - proving product quality and comparability. |
| Modelling for Regulatory Use | Acceptance of models in submissions | Increasing openness. Depends on model criticality, development phase, and data support. |
| | Use of models post-licensing | Acceptable if supported by data. Critical changes need more validation. |
| | Regulatory scrutiny of low-risk models | Less scrutiny expected, but all models must be scientifically defensible. |
| | Preferred statistical methods | No universal preference. Bayesian may be suitable but depends on product profile. |
| | Data access for modelling and AI | Still a barrier. Need for structured, accessible datasets. |
| | Modeller-regulator interaction | Documentation must be improved. Cross-functional communication encouraged. |
| | Shipment modelling | Possible, but needs more variables (*e.g.* shaking, humidity). WHO interest likely. |
| | Multiple models for validation (*e.g.* hybrid + AI) | Acceptable if validation outcome is sound and reproducible. |
| | Outlier removal in data preparation | Must be scientifically justified and pre-defined. Avoid arbitrary filtering. |
| | Extrapolation *via* platform strategy | May be possible if molecules and processes are highly similar. Requires strong justification and risk assessment. |
| | Enhancing collaboration across EU ecosystem | National scientific advice and QIG-type forums promote early alignment without compromising independence. |

AI – Artificial Intelligence; AKM - Arrhenius kinetic models; DSP – Downstream Processing; EMA – European Medicines Agency; EU – European Union; ICH - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; QbD - Quality by Design; QIG - Quality Innovation Group; SME – Small- and Medium-sized Enterprises; TFF - Tangential Flow Filtration; WHO – World Health Organization.

remain critical, as even small formulation changes can significantly alter stability. Accelerated stability studies can help detect whether a product behaves differently from its platform or analogues early in development.

Industry is encouraged to engage proactively with regulators, such as through the European Medicines Agency's Quality Innovation Group (QIG), to support the adoption of science-based approaches. For instance, the Inno4Vac project explores Bayesian methods for defining formulation design space, which regulators view as promising but still lacking formal guidance. Such modelling can support formulation development, but risks lie primarily with manufacturers if models prove inadequate. Post-licensing, models can support process changes or validation, but they must be substantiated with more comprehensive data depending on the model's criticality. Low-risk models generally receive lighter scrutiny but must be defensible, especially during inspection. While regulators do not prescribe specific statistical methods, modelling techniques (*e.g.*, Bayesian) must suit the product's specific stability profile. Data access remains a bottleneck for developing robust models, especially for AI-driven approaches, highlighting the need for more systematic data-sharing strategies.

In upstream and downstream development, modelling is considered low risk when used internally for process development or scale-up. For downstream processing, combining unit operations in a single validation (*e.g.*, centrifugation–chromatography–TFF) may be acceptable if the combined model clearly demonstrates consistent quality output. Any online or real-time adaptations of manufacturing must still meet predefined, validated parameters.

Data preparation practices, including outlier removal, must be grounded in predefined scientific criteria. Arbitrary removal, such as excluding 5% of data using a 2-sigma rule, requires clear justification to avoid bias or perceived data manipulation.

Finally, enhancing collaboration between regulators, industry, and academia is key to accelerating access to innovative medicines. Early scientific advice and initiatives like QIG offer structured avenues for dialogue, helping align expectations and promote innovation while maintaining regulatory independence.

## CRediT authorship contribution statement

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**Rodríguez García:** Writing – review & editing, Writing – original draft. **Sevda Şenel:** Writing – review & editing, Writing – original draft. **Martin Spruth:** Writing – review & editing, Writing – original draft. **Mats Welin:** Writing – review & editing, Writing – original draft. **Ole F. Olesen:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Eric Calvosa:** Writing – review & editing, Writing – original draft, Conceptualization.

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This communication reflects the authors' views, and neither IMI nor the European Union, EFPIA, or any Associated Partners, regulatory authorities or international organisations are responsible for any use that may be made of the information contained therein.

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## Declaration of competing interest

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## Data availability

No data was used for the research described in the article.

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