Expert View

ENABLING DELIVERY OF LYOPHILISED BIOLOGICS VIA SIMULATION-LED DEVELOPMENT OF DUAL-CHAMBER SYSTEMS

Dr Sahab Babaee of Sanofi and **Dr Matthew Hancock** of Veryst Engineering discuss the potential of using modelling and simulation when designing dual-chamber injection devices, which can enable device designers to investigate the complex interactions that take place within a dual-chamber system without a physical prototype and discover potential failure modes much earlier in the design process.

Biologics, including monoclonal antibodies, antibody-drug conjugates, peptides, proteins and vaccines, now represent a large and growing share of the pharmaceutical pipeline. There has been considerable growth in BLAs and approvals over the last several years, with a market size projected to be over US$1 trillion (£740 billion) by 2035.[1,2] Formulation stability challenges are a key factor in developing these molecules – many of them are not stable in liquid form for the shelf lives required by regulators and markets, and must be freeze-dried, or lyophilised, to preserve their structure and potency.[3,4] It is estimated that over 60% of biologics on the market today would not be possible without lyophilisation.[5] As the number of lyophilised biologic and vaccine candidates continues to grow, so too does the need for delivery systems that can reconstitute them reliably, safely and with minimal burden on the patient or caregiver.

"IN PARTICULAR, DUAL-CHAMBER DELIVERY SYSTEMS HAVE EMERGED AS PROMISING PLATFORMS TO ENABLE INTEGRATED RECONSTITUTION AND SELF-ADMINISTRATION OF LYOPHILISED DRUG PRODUCTS WITHIN A SINGLE COMBINATION PRODUCT."

WHY DUAL-CHAMBER DELIVERY SYSTEMS?

Historically, reconstituting a lyophilised drug for parenteral administration has consisted of several manual steps and components: withdrawing diluent, injecting it into a vial, swirling or inverting to dissolve the cake for robust reconstitution and then drawing the reconstituted solution into a syringe prior to injection. Each step is an opportunity for a dosing error, contamination or delay, along with other human factors-related use errors. Furthermore, the process assumes a level of manual dexterity, training and confidence that may vary across care settings.These challenges are particularly concerning for emergency-use products, paediatric and geriatric populations, and self-administered chronic therapies.[6]

These constraints have driven sustained industry interest in delivery devices that can automate reconstitution rather than delegating it to the user. In particular, dual-chamber delivery systems have emerged as promising platforms to enable integrated reconstitution and self-administration of lyophilised drug products within a single combination product.[7,8]

Autoinjectors with dual-chamber cartridges (AIDCs) respond directly to this unmet need. A single cartridge stores the lyophilised drug and liquid diluent in two compartments separated by a plunger stopper. Upon activation by the patient, a spring-driven mechanism moves the diluent into the drug chamber via a bypass channel, mixes and dissolves the lyophilised drug, then primes the needle and injects the ready-to-use solution, all resulting in one continuous, patient-triggered process.[7,9]

This approach offers a range of substantial advantages, including automated reconstitution and injection in a single platform, reduced user burden and training requirements, potential for at-home administration rather than in-clinic dosing, improved usability and treatment adherence, protection of sensitive drug products until the point of use and applicability across biologics, vaccines and emergency-use products alike.[6,8]

THE ENGINEERING COMPLEXITY BEHIND AIDCs

However, this simplicity for the patient is bought with considerable engineering complexity for the developer. An AIDC must execute a precise sequence of physical events, in the right order and within a tight time window, using a single drive spring or gas canister and no external power source – transfer diluent into the lyophilised drug chamber via a bypass channel, ensure that the lyophilised cake fully wets and dissolves, attach and prime the needle, and inject into tissue at an acceptable rate and within an appropriate timeframe.[9] The spring, two stoppers, bypass design, air compression, fluid motion and tissue backpressure all interact,[9,10] and AIDC-specific failure modes – missed stopper-position targets causing the stopper to fail to allow or prevent bypass flow, and incomplete reconstitution resulting in an inhomogeneous drug solution – can arise from interactions that simply do not exist in single-chamber syringes or autoinjectors.[9]

WHY CONVENTIONAL DEVELOPMENT APPROACHES ARE NOT ENOUGH

The conventional response to this complexity has been iterative prototyping: build a device, test injection time and force, redesign, retest.[11] This approach becomes disproportionately slow and expensive for AIDCs, because:

- The design space is larger and multi-dimensional, with multiple contributing parameters – including spring force, stopper friction and insertion depth, bypass channel design, chamber air volumes, cake formulation, diluent volume and tissue backpressure – all being interdependent.
- Some failure modes only reveal themselves late in development after experimental reconstitution and injection testing.
- Small dimensional tolerances in needle geometry translate into disproportionately large swings in injection force (via the fourth-power dependence of Poiseuille flow on needle radius), yet many early-stage models simulate only nominal geometry and friction conditions rather than sampling realistic manufacturing tolerances.[11]

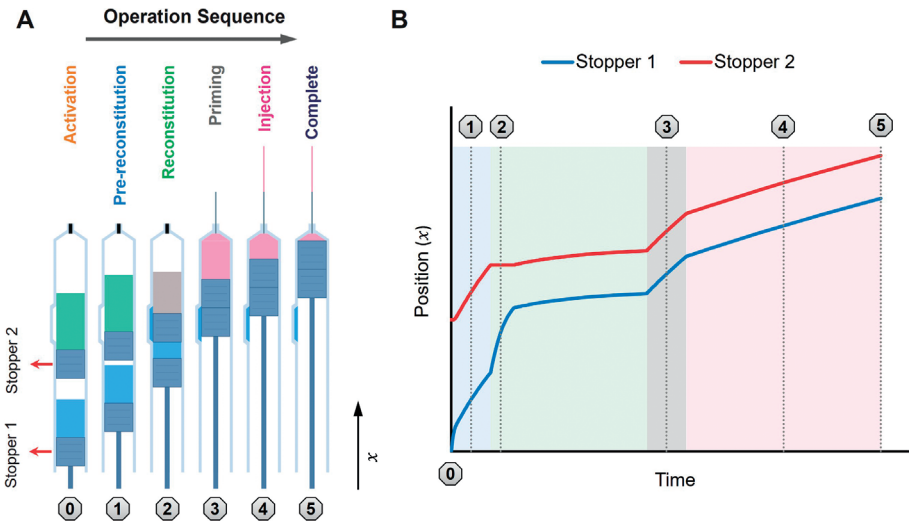

Figure 1: (A) Schematic illustration of the five-stage operational sequence of an AIDC, including: (0) activation, (1) pre-reconstitution, (2) diluent transfer into the front injection chamber via bypass channel and reconstitution of the lyophilised drug, (3) needle priming and (4) injection. (B) Model-predicted transient AIDC response, showing stopper positions throughout AIDC operation stages corresponding to the representative snapshots illustrated in A.

Simulation-led technical due diligence can change this dynamic. Physics-based and reduced-order models let developers explore spring stiffness, stopper friction, chamber air volumes, diluent volume, bypass design, cake properties and tissue backpressure ranges computationally, evaluating device and formulation configurations virtually and narrowing the design space to a small number of high-confidence candidates before committing to tooling or running full physical or clinical verification.[12,13]

This approach does not eliminate physical testing, but rather changes its role – from broad exploratory search to targeted confirmation – consistent with the risk-informed credibility principles in American Society of Mechanical Engineers Verification & Validation (V&V) 40 and the US FDA's Computational Modelling and Simulation (CM&S) credibility guidance, both of which recognise that adequately validated models can reduce the burden of physical verification for well-defined contexts of use.[13–15] The FDA's 2016 reporting guidance further standardises how a CM&S study should be documented, including governing equations, system properties, numerical methods, validation and limitations, so that a reviewer can judge whether a model's credibility matches its intended decision-support role, and a similar risk-based credibility framework has been applied to assess model risk for other device classes.[16,17]

A PHYSICS-BASED FRAMEWORK FOR PREDICTING AIDC PERFORMANCE

A modelling framework applicable to a broad class of spring-driven AIDCs for lyophilised drug and vaccine delivery makes this possible in practice. Consider a reduced-order model, developed and experimentally validated for AIDCs, that has been explicitly structured around the following stages (Figure 1A):

- Activation
- Pre-reconstitution, with drive-spring preload and initial stopper positions
- Bypass-enabled diluent transfer into the front injection chamber and lyophilised cake reconstitution
- Needle priming
- Injection.[9]

The equations of motion for the AIDC's two stoppers are coupled to the ideal gas law for the chamber air pockets and to

an experimentally derived stopper-friction-versus-glide-speed relationship, giving predictions of the stoppers' trajectories (Figure 1B), reconstitution, injection and priming time, as well as injection flow-rate time profile, peak tissue backpressure and failure modes, such as missed stopper-position targets causing the stopper to fail to allow or prevent bypass flow.[9]

This AIDC modelling framework does not require advanced simulation software to run. A snapshot of an HTML implementation is shown in Figure 2, highlighting the input variables incorporated into the model and the resulting predictions of AIDC behaviour, including the essential performance requirements across its stages of operation.

The stopper friction was found experimentally to follow a power law with glide speed rather than a classical constant or linear friction law, consistent with a lubricated stopper-barrel interface (i.e. silicone oil between a siliconised elastomer stopper and glass barrel, rather than dry solid-on-solid contact). A hybrid modelling framework built for precisely this interface captures the resulting Stribeck-type behaviour, where friction shifts between boundary, mixed and hydrodynamic lubrication regimes as glide speed changes, adding a data-driven component to describe what purely mechanistic friction laws miss.[9,18] Validation against measured injection times across a range of formulation and device configurations showed good agreement between predicted and experimental behaviour.[9]

"AS THE MODEL LINKS EVERY STAGE EXPLICITLY, IT CAN FLAG COMBINATIONS OF SPRING FORCE, DILUENT VOLUME, STOPPER FRICTION, CHAMBER AIR VOLUMES AND RECONSTITUTED DRUG SOLUTION VISCOSITY THAT WOULD OTHERWISE ONLY REVEAL A FAILURE MODE AFTER PHYSICAL TESTING."

Understanding the Interplay Between Formulation and Device Design

As the model links every stage explicitly, it can flag combinations of spring force, diluent volume, stopper friction, chamber air volumes and reconstituted drug solution viscosity that would otherwise only reveal a failure mode after physical testing.[9] As an illustrative example, increasing spring force can shorten reconstitution time by accelerating diluent delivery into the cake, but at the cost of higher injection forces or greater cavitation risk;[9,19] a gentler reconstitution profile may be kinder to the cake and formulation but push total patient-facing time (i.e. reconstitution plus injection) beyond a comfortable window. Mechanistic reconstitution models developed for formulation science, describing wetting, capillary penetration, cake disintegration and dissolution can be coupled directly to device-level bypass flow rate, turning cake microstructure and diluent delivery rate into explicit design variables alongside spring force and bypass design, rather than a lumped, black-box delay.[3,4,20–22]

Two further refinements would sharpen these predictions. First, coupling to finer-grained numerical dissolution models, such as particle- or continuum-scale simulations that move beyond classical one-dimensional dissolution formalisms.[23] Second, replacing the current constant-viscosity assumption with the shear-thinning, non-Newtonian rheology that many concentrated antibody formulations actually exhibit, where viscosity drops sharply at the higher shear rates seen in narrow-gauge needles.[24]

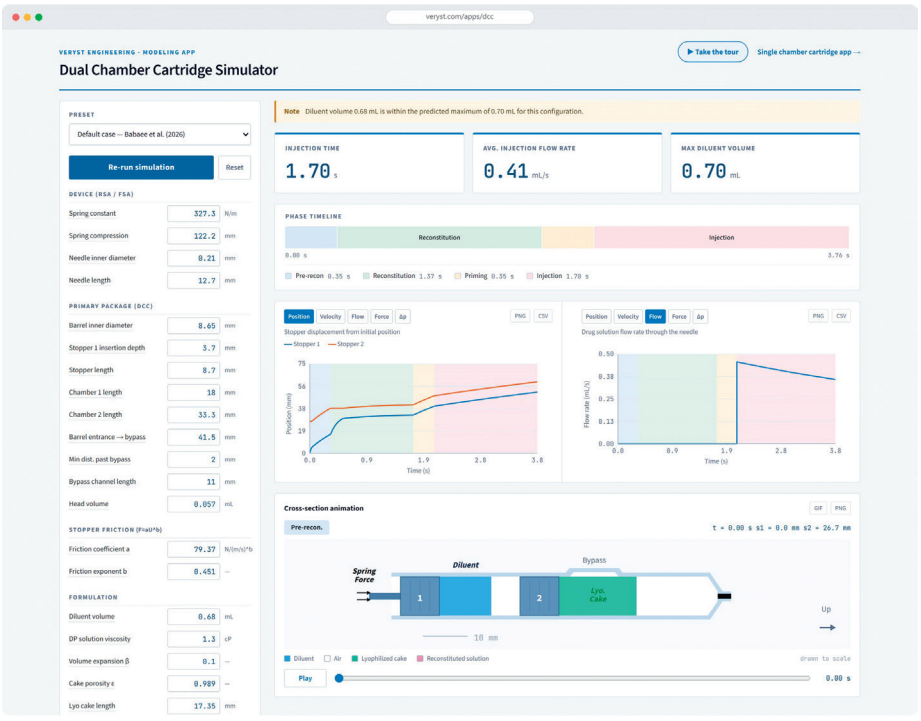

Figure 2: Snapshot of an HTML implementation of the AIDC model simulator.

DIGITAL DEVELOPMENT AND MODEL-INFORMED DEVICE DESIGN

Dual-chamber delivery systems are particularly well-suited to digital development because of their complex, multiphysics behaviour – no single test rig or bench measurement captures the full interaction between spring, stopper friction, air compression, bypass flow, reconstitution kinetics and tissue response. The industry is increasingly adopting model-informed drug device development, digital twins, virtual prototyping and simulation-based design optimisation as standard tools for precisely this class of problem, and has

begun to explore artificial intelligence (AI)-based methods for accelerating parameter identification and design search. Any such AI-assisted step would itself need to sit inside the same verification, validation and uncertainty quantification credibility framework described above before it could inform regulatory-facing decisions.[13,14]

Future Opportunities for Dual-Chamber Delivery Platforms

As the biologics and vaccines pipeline diversifies, dual-chamber delivery platforms are well placed to serve high-concentration biologics, messenger RNA (mRNA) and next-generation vaccines, long-acting injectables, emergency-use products, personalised medicines and connected or smart autoinjectors that log dose and adherence data. Each of these applications adds its own formulation and device constraints, and simulation offers a practical way to explore them before committing to a fixed platform. A further extension worth pursuing is coupling AIDC-specific models to tissue-level outcomes downstream of the needle, including depot formation, interstitial flow and absorption kinetics, as well as how patient variability in body-mass index and tissue composition shapes them, as injection conditions and device parameters can influence depot shape and, potentially, drug absorption and tolerability.[25,26]

"AS THE BIOLOGICS AND VACCINES PIPELINE DIVERSIFIES, DUAL-CHAMBER DELIVERY PLATFORMS ARE WELL PLACED TO SERVE HIGH-CONCENTRATION BIOLOGICS, MRNA AND NEXT-GENERATION VACCINES, LONG-ACTING INJECTABLES, EMERGENCY-USE PRODUCTS, PERSONALISED MEDICINES AND CONNECTED OR SMART AUTOINJECTORS THAT LOG DOSE AND ADHERENCE DATA."

CONCLUSION: FROM DEVICE SELECTION TO CLINICAL READINESS

As dual-chamber delivery systems become increasingly important for enabling self-administration of lyophilised biologics, development success will depend not only on device innovation but on the ability to understand and predict complex formulation-device interactions.[9] Simulation-led technical due diligence and model-informed development offer a practical framework to accelerate platform selection, reduce experimental burden and improve confidence in clinical and commercial success – turning dual-chamber development from a series of expensive physical iterations into a structured, model-informed path from device selection to clinical readiness.[13,14]

ABOUT THE COMPANY

Veryst Engineering is a Boston-based engineering consulting firm, providing PhD-level expertise across fluid and solid mechanics, materials science and physics. Veryst helps combination product and drug delivery device teams accelerate development, diagnose product problems and de-risk complex design challenges on an industrial timeline. For combination products specifically, the firm's work spans autoinjector performance, injection modelling, lyophilisation, drug product drying and container closure integrity. Veryst's methods are grounded in engineering and physical fundamentals and all resulting methods, models and IP are transferred directly to the client.

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