Interview:
Rethinking Drug Delivery for Increasingly Complex Therapies

In this interview, **Ram Halthore** of **Kaléo** discusses the demands of newer classes of injectable drugs and the trend towards self-administration of conventional drug delivery systems, the requirements innovative systems must meet and the importance of selecting a delivery system early in formulation development, as well as the roles that robust human factors engineering and high reliability should play in device development.

Q What new demands are large-molecule biologics, glucagon-like peptide-1s (GLP-1s) and antibody-drug conjugates (ADCs) placing on drug delivery systems compared with previous generations of drugs?

A The rapid and continued expansion of biologics, antibody-drug conjugates and peptide-based therapeutics is placing increasing demands on drug delivery systems because their formulations have higher concentrations, higher viscosities and larger delivery volumes compared with previous generations of drugs. With these formulations, the inherent challenge is generating and controlling the force needed to deliver these formulations at high flow velocities, keeping injection times short and delivering a consistent injection profile to assist with patient comfort. The required force must be achieved without negatively affecting the drug or the container – for example, by minimising shear-related effects that may contribute to protein degradation or aggregation – while maintaining reliable device performance.[1]

The evolving requirements around large-molecule therapies have become increasingly difficult for conventional drug delivery systems to meet. This has prompted drug developers to evaluate delivery platforms that are designed to provide greater flexibility in how the force is generated and how the flow velocity is controlled throughout the injection. The challenge for developers is no longer simply delivering the drug, but selecting a delivery platform capable of supporting increasingly complex formulations while maintaining the intended product quality and performance characteristics.

"THE EVOLVING REQUIREMENTS AROUND LARGE-MOLECULE THERAPIES HAVE BECOME INCREASINGLY DIFFICULT FOR CONVENTIONAL DRUG DELIVERY SYSTEMS TO MEET"

Ram Halthore
Vice-President, Development
T: +1 804 545 6360
E: ram.halthore@kaleo.com

Ram Halthore is Vice-President, Development at Kaléo, where he leads device and drug development activities from early design through manufacturing transfer. His responsibilities include developing the company's human factors engineering programme, leading integrated drug-device product development and overseeing the company's intellectual property portfolio development. Mr Halthore has more than 25 years of experience spanning medical devices, pharmaceuticals, biologics and combination products, including autoinjectors, prefilled syringes, inhalation devices, implants and on-body injectors. His previous experience includes leadership roles at Merck, Teva, Amgen, Johnson & Johnson and 3M.

Q How are more complex formats, such as combination therapies and formulations requiring component separation, lyophilised products and dual liquids, reshaping thinking around drug delivery?

A For patients and caregivers, combination therapies, dual-liquid systems and lyophilised drugs can provide important treatment benefits, but they can also make administration more complex and challenging. When a therapy involves two drugs or separation of two formulation components, the delivery system must help users prepare and administer the dose safely and reliably in an at-home administration environment.

Lyophilisation can improve drug shelf life, but it can add a significant number of steps to the preparation and administration process. Because lyophilised products must be reconstituted with a sterile diluent before injection, the process can take more time due to these added steps and can increase the probability of use errors. Dual-chamber autoinjectors can help reduce this burden by streamlining preparation and administration for patients and caregivers.

Combination therapies are becoming an increasingly common approach intended to improve therapeutic benefit to the patients. These therapies often require two drugs to be administered together. Combining two drugs into a single injection may not be possible due to incompatibility, formulation challenges or manufacturing constraints. In these situations, dual-container, dual-chamber and dual-injection systems make administration possible, as well as more practical and patient-friendly.

Dual-container systems, where both containers hold the same drug, can also be used as large-volume injectors. A dual-injector device in combination with a dual-container system enables distribution of the delivered volume across a broader surface area. Together, these formats are shifting drug delivery towards more patient-centric design. Development processes often benefit from managing formulation complexity while also helping patients and caregivers to administer their therapies safely, reliably and conveniently.

Q Historically, device selection has often come late in development, with the molecule adapted to fit an existing platform – is that approach still viable?

A That historical model of device selection is not as viable as it once was, partly because the formulations for biologics and other large-molecule therapies are more difficult to adapt or retrofit to an existing platform downstream in the development process. Development programmes can benefit from identifying the delivery architecture that is best for the molecule, and ultimately for the patient, early in the development process, rather than adapting the molecule to an existing platform later. Determining if and which autoinjector is most appropriate should be part of early development decisions – there are multiple reasons why this approach may help improve development efficiency and product optimisation.

"LYOPHILISATION CAN IMPROVE DRUG SHELF LIFE, BUT IT CAN ADD A SIGNIFICANT NUMBER OF STEPS TO THE PREPARATION AND ADMINISTRATION PROCESS"

First, no single drug delivery architecture is optimised for every therapy. Selecting one advantage often means accepting trade-offs elsewhere in formulation compatibility, stability, usability, manufacturability or lifecycle flexibility. The goal is to identify the right delivery system for the right drug, the intended patient population and the intended use environment.

Second, different delivery architectures solve different problems. Dual-chamber systems, dual-container systems, dual-injection technology and other delivery technologies should be viewed as complementary options available to the formulators rather than as competing technologies.

Finally, delivery architecture decisions made early in development influence nearly every downstream activity, from formulation strategy and human factors (HF) engineering to manufacturing, regulatory planning and lifecycle management. Device selection is therefore often most effective when integrated alongside formulation and process development rather than as a separate downstream activity.

Early collaboration helps formulators balance speed to clinic by integrating device development with drug development early in the development process. Leaving device selection until late in development can cost the formulator in terms of time lost researching available device options, potential changes in the drug's formulation or manufacturing to work with the selected device, delays in entering the clinic and, ultimately, a longer time to market.

Q What role should HF engineering play in device development and where do companies typically get it wrong?

A The trend towards at-home administration means that patients and caregivers will no longer rely on assistance from a trained healthcare professional but instead need to become self-reliant. Less frequent dosing increases the possibility that users may not recall instructions from one injection to the next. Both trends underscore the importance of a device that manages technical complexity behind the scenes with an intuitive design, clear use instructions and guidance that do not presume the user's familiarity, along with clear user feedback during correct operation to create a simple, streamlined experience for patients and caregivers.

This is where robust HF engineering comes into play. HF engineering begins with understanding the intended user, intended use and intended use environment. HF studies provide valuable insights into how patients and caregivers may interact with injectable drug delivery systems in the real world and under a variety of real-world circumstances, such as low-light settings, high-pressure or emergency situations, and limited-dexterity scenarios.

"HF STUDIES PROVIDE VALUABLE INSIGHTS INTO HOW PATIENTS AND CAREGIVERS MAY INTERACT WITH INJECTABLE DRUG DELIVERY SYSTEMS IN THE REAL WORLD AND UNDER A VARIETY OF REAL-WORLD CIRCUMSTANCES, SUCH AS LOW-LIGHT SETTINGS, HIGH-PRESSURE OR EMERGENCY SITUATIONS, AND LIMITED-DEXTERITY SCENARIOS."

In short, robust HF engineering drives usability and helps ensure that products are developed for real people, not just ideal lab conditions.

I can speak on Kaléo's approach and some important lessons we've learned along the way. One lesson we've learned is that a device should have features designed to solve real use-related challenges, not simply add functionality. Audio and visual guidance, for example, can help provide step-by-step administration guidance for first-time users and especially users in emergency situations, when urgency, fear and hesitation may make it difficult for them to think clearly or remember instructions.[2,3]

Q How does Kaléo's experience with emergency-use devices and designing for high-stress, emergency-use scenarios translate into broader development applications?

A Kaléo recognises the importance our emergency-use devices can have to the people that use them, whether they are military, police, emergency responders, parents, caregivers or patients. We are proud that our reliability studies have shown that, at the time of manufacture, 99.999% of Kaléo's autoinjectors work as intended, thus meeting the "five nines" reliability threshold established by the US FDA's draft guidance for emergency-use autoinjectors.

We bring a patient-first perspective to our work. As a company founded by patients, we understand that successful drug delivery is about more than technology; it is about helping ensure people can use a therapy when they need it most. As we've learned, that level of reliability is designed into a product long before it reaches the patient.

Designing for high-stress, emergency-use situations has taught us to anticipate the real-world factors that can challenge successful drug delivery, from variability in users and environments to the potential for human error, and to address those factors early in development. Those principles extend well beyond emergency medicine. Whether a therapy is used in an emergency, at home for a chronic condition or in another setting, patients need to be able to use it correctly.

Have we set the reliability bar exceptionally high for ourselves? Yes. But it means that Kaléo brings that same focus on reliability to all products we develop for others that we bring to our emergency-use autoinjectors. The patient-centric mindset we bring to the various stages of developing and manufacturing drug-device combination products means considering reliability, usability and the real-world needs of patients from the beginning. Ultimately, our experience designing products people can depend on in high-stress situations informs how we approach each development programme, whether on our own or for someone else.

REFERENCES

1. *Le Basle Y et al, "Physicochemical Stability of Monoclonal Antibodies: A Review". J Pharm Sci, 2020, Vol 109(1), pp 169–190.*
2. *Kessler C et al, "Usability and preference of epinephrine auto-injectors: Auvi-Q and EpiPen Jr". Ann Allergy Asthma Immunol, 2019, Vol 123(3), pp 256–262.*
3. *Zhang E, Sicherer S, Agyemang A, "Proper use of epinephrine autoinjectors is related to device type, prior physical demonstration, and sociodemographic factors". J Allergy Clin Immunol Pract, 2025, Vol 13(2), pp 418–420.e1.*

Kaléo
10900 Nuckols Road
Suite 200
Glen Allen
VA 23060
United States
www.kaleo.com