



LARGE VOLUME INJECTION – BEYOND VOLUME AND VISCOSITY

Large volume injectors are likely to have a growing impact on the delivery of parenteral therapy in the future. In this article, James Blakemore, PhD, Senior Consultant at Cambridge Consultants, uncovers the underlying reasons that drive the use of large volume injectors and make the case for a more extensive use of such devices based on the broader-than-expected purposes they can serve.

The use of large-volume injectors (LVIs) is predicted to have a significant impact on the parenteral drug delivery device landscape¹ in the near future. Medical device manufacturers including Unilife (York, PA, US), West Pharmaceutical Services (Exton, PA, US), BD (Franklin Lakes, NJ, US) and Insulet (Billerica, MA, US) are already active in this space and have developed devices capable of delivering a wide range of formulations.

“LVIs play a role that is far more important than enabling delivery of high-volume drug formulation as they differentiate drugs, make them safer to use, reduce the injection workflow and facilitate self-administration.”

Similarly, pharmaceutical companies – such as AbbVie (North Chicago, IL, US) and Amgen (Thousand Oaks, CA, US) – have started introducing LVIs alongside their medicinal products (Table 1).

To date, the case for LVIs has been relatively one dimensional and can be

summarised in one sentence: R&D pipelines are dominated by biologics, biologic formulations can be viscous or in large volume, and hence LVIs are bound to play a key role in the future.

The fundamental reasoning of this case is correct. Biologic drug formulations, particularly those containing monoclonal antibodies (mAbs), are viscous at high concentration. Therefore, increasing the volume assists with the development of formulations that are ideal for infrequent dosing or depot administrations.

Nevertheless, LVIs can fulfill far wider demands than those usually discussed. Indeed the role of LVIs is in fact far broader than enabling the delivery of high-volume drug formulations, as they differentiate drugs, make them safer to use, reduce the injection workflow and facilitate self-administration.

LVI BENEFITS IN COMBINATION MEDICINAL PRODUCTS

Looking at a handful of marketed and pipeline combination products, we can derive insights into the wider benefits that an LVI device may facilitate (Table 2).

Slow Release

Infusion site reactions are a common issue with biologic formulations. Reactions may be typified by local swelling and pain, and



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Brand	Trevyent™	Neulasta® Onpro™	Herceptin® SC	Repatha® Pushtronex™
Generic name	Trepostinil	Pegfilgrastim	Trastuzumab	Evolocumab
Therapy area	Cardiovascular	Cancer	Cancer	Cardiovascular
Delivery time	Slow release ³	45 minutes ⁴	7 minutes ⁵	9 minutes ⁶
Drug manufacturer	SteadyMed	Amgen	Roche	Amgen
Device	PatchPump®	Omnipod® (design variant)	Single Injection Device	SmartDose®
Manufacturer	SteadyMed	Insulet	Roche	West Pharmaceutical

Table 1: Examples of LVIs and associated therapies.

may lead to systemic effects such as nausea, headache and fever.

To mitigate this risk, such therapies are administered by slow infusion for up to several hours, requiring the patient to remain in the infusion clinic for long periods. The ability to transfer these types of formulations into a suitable LVI that delivers its dose at a similarly slow flow rate enables ambulatory drug delivery, and has potential to improve the experience of both patients and healthcare professionals (HCPs) significantly.

One such example is Trevyent®, which has been reformulated for presentation in the PatchPump® device from SteadyMed (San Ramon, CA, US). It is under development for the treatment of pulmonary arterial hypertension. The device permits slow release of the drug which minimises the risk of infusion site reactions – an otherwise common side effect of the drug when administered via subcutaneous (SC) infusion line.

Timed Release

As a concept, delayed release of drug therapies is well-established, particularly for oral formulations. Translating this concept across to biologic therapies is more challenging, given that such formulations usually require parenteral administration. The introduction of timed release of biologic drugs brings about clinical benefit.

An example illustrating this benefit is Neulasta® Onpro™, marketed by Amgen for the treatment of chemotherapy-induced neutropenia (low white blood cell count). It consists of the drug in a single-use on-body injector. The system is designed to delay administration of the drug for up to a day following chemotherapy so that it can exert its therapeutic effects at the right time.

In doing so, the system avoids the need for the patient to present to the physician the next day after chemotherapy for their treatment. Practically, the system avoids dose-limiting side effects typically associated with chemotherapy as it is common for the

patient to feel too sick to come back to the hospital for further treatment. Significantly, this novel presentation disrupts the care pathway, which otherwise requires the patient to present to the clinic.

Patient Self-Administration

Certain care pathways, particularly in oncology, require the patient to present to the infusion clinic on a regular basis over an extended treatment period to receive drug therapy. This is because many oncology products are given by intravenous (IV) or SC administration, which requires HCP supervision and suitable facilities for infusion.

Although being in an infusion clinic setting provides back-up if there are adverse events to deal with, once a maintenance therapy phase is established, this requirement to present to the clinic becomes a significant burden on the patient. The ability for patients to self-administer in a home environment would reduce this burden.

An example of this is provided by a SC formulation of Herceptin® (trastuzumab), which is under development by Roche (Basel, Switzerland) for delivery via its proprietary Single Injection Device (SID) platform. The drug has been reformulated and contains a novel excipient (Enhance®, from Halozyme, San Diego, CA, US) which permits bolus SC administration of large volumes. Typically, Herceptin® is administered weekly for up to three years, requiring the patient to present to the infusion clinic each time. Reformulation of the drug and its incorporation into a device permits patient self-administration, providing greater convenience to the patient and the basis for improved patient compliance.

Furthermore, a study by De Cock demonstrated that this SID presentation of Herceptin® reduces drug preparation and administration time in the infusion clinic, compared with the infused presentation.² Since infusion chair or bed “real estate”

Trevyent™	Neulasta® Onpro™	Herceptin® SC	Repatha® Pushtronex™
Slow release – continuous infusion	Facilitates dose scheduling / administration	Allows less frequent administrations e.g. every three weeks	Differentiation against other PCSK9 inhibitors
Reduces pain experience	Decreases IV- associated infection risk	Time saving during hospital administration ²	Use allows a traditionally injection-free TA to maintain its patient convenience
Minimises risk of infusion site reaction		Self-administration	Allows less frequent administrations e.g. monthly
Self-administration			

Table 2: Summary of LVI benefits in selected combination products.

is such a premium in infusion clinics, any intervention that reduces HCP workflow and patient time should have a positive commercial impact.

Reduced Dosing Frequency

It is common for biologic therapies with similar mechanisms of action to receive similar approval times. In these cases it is difficult for manufacturers to establish a material basis for product differentiation, other than perhaps incremental safety or efficacy claims. A favourable change in dosing frequency may be a principal route by which a drug could be differentiated from the competition.

For example, Amgen's Repatha® Pushtronex™ system comprises evolocumab, a novel PCSK9 inhibitor, packaged into a variant of West Pharmaceutical Services' SmartDose® electronic wearable injector. The system provides monthly dosing of evolocumab as an adjunct for statin therapy and as a primary treatment of hypercholesterolaemia, which improves patient convenience.

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Sales of Repatha® are low, as expected in a field where statins are, on the whole, perceived by physicians as an adequate cholesterol-lowering class. Therefore, the Pushtronex™ system provides Repatha® with a means of differentiation against competitor PCSK9 inhibitors, notably Sanofi's Praluent®. The Pushtronex™ system will likely drive compliance of Repatha®

which may in turn increase the chance of capturing data that proves better outcomes; ultimately the proof for improved outcomes data will push Repatha towards being positioned as a first-line therapy option.

Finally, it is worth noting that patients in this therapy area are likely to be needle agnostic. An LVI may be seen by pharmaceutical companies as presenting the less risky option to promote an injectable drug.

BENEFITS OF GREATER DIVERSITY IN LVI DESIGN

As seen in the above examples, it is not just volume and viscosity challenges that LVIs have the potential to address, but rather a wider set of clinical benefits. The benefits demonstrated in the therapy areas above apply equally to other therapy areas, particularly chronic diseases such as autoimmune disease, where regular dosing of increasingly biologic therapy classes is required.

In many cases, drug reformulation is required to facilitate a shift from IV to SC delivery by a LVI. Therefore, the application of suitable formulation technologies is a key technical and commercial consideration prior to the development of drugs for LVI administration.

LVIs provide a basis for product differentiation, through improving either safety, efficacy, tolerability or convenience. It is unlikely, however, that payers will acknowledge the value of LVIs through reimbursement until it can be demonstrated that these properties translate into significant improvement in patient outcomes.

Innovator pharmaceutical companies should take note of the wider benefits of LVIs as they plan lifecycle management strategies, particularly in terms of implementing biosimilar defence strategies. Likewise, generics companies that are focused on biosimilars development should consider LVIs as a basis for differentiation against both originator product and competitor biosimilar products.

The evidence above highlights that we

should not expect the current crop of LVIs to satisfy the broad range of clinical needs; each patient's requirements are different for each therapy area. Therefore, we should expect rapid expansion in the LVI class, including bespoke design variations, in order to meet these clinical needs.

ABOUT THE AUTHOR

James Blakemore is a Senior Consultant in the Medical Technology division at Cambridge Consultants. He specialises in market strategy and transaction support within the pharmaceutical and drug delivery device markets. He manages drug delivery device development projects bringing together commercial insight and technical expertise. Prior to working in the healthcare consulting industry, Dr Blakemore worked in a number of business development and licensing roles for speciality pharmaceutical and biotechnology companies, working towards the identification, validation and commercialisation of broad new therapies. He holds a PhD in Molecular Biology from King's College, University of London, UK.

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