The use of large-volume injectors (LVIs) is predicted to have a significant impact on the parenteral drug delivery device landscape 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.

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...
the PatchPump® device from SteadyMed has been reformulated for presentation in 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, requiring 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”

Table 1: Examples of LVIs and associated therapies.

<table>
<thead>
<tr>
<th>Brand</th>
<th>Trevyent™</th>
<th>Neulasta® Onpro™</th>
<th>Herceptin® SC</th>
<th>Repatha® Pushtronex™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name</td>
<td>Trepostinil</td>
<td>Pegfilgrastim</td>
<td>Trastuzumab</td>
<td>Evolocumab</td>
</tr>
<tr>
<td>Therapy area</td>
<td>Cardiovascular</td>
<td>Cancer</td>
<td>Cancer</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Delivery time</td>
<td>Slow release³</td>
<td>45 minutes⁴</td>
<td>7 minutes⁵</td>
<td>9 minutes⁶</td>
</tr>
<tr>
<td>Drug manufacturer</td>
<td>SteadyMed</td>
<td>Amgen</td>
<td>Roche</td>
<td>Amgen</td>
</tr>
<tr>
<td>Device</td>
<td>PatchPump®</td>
<td>Omnipod® (design variant)</td>
<td>Single Injection Device</td>
<td>SmartDose®</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>SteadyMed</td>
<td>Insulet</td>
<td>Roche</td>
<td>West Pharmaceutical</td>
</tr>
</tbody>
</table>

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 Sevices’ 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.

“**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.**”

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.

**REFERENCES**

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