**RESEARCH ARTICLE**

# Developing the Subcutaneous Drug Delivery Route

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**Abstract**

Biopharmaceuticals and biosimilars now represent the majority of the top 10 selling drugs. High development costs and requirement for most to be administered intravenously are noted drawbacks. Recent advances in subcutaneous drug delivery methods offer a viable alternative route for parenteral drug administration. Comparison studies have highlighted equivalent drug efficacies coupled with substantial cost savings. Allied to these developments are new closed-loop drug delivery systems which have the potential to revolutionize the biopharmaceutical sector through active patient engagement. First demonstrated in the insulin marketplace, these efforts represent formal embodiments of the precision medicine approach to disease management. This review will highlight key considerations for subcutaneous drug delivery, including patient preferences, drug formulation and needle and device design. We also provide an overview of the market evolution of subcutaneously administered drugs, highlighting those currently in clinical development, and predict areas for future innovation.

**Keywords:** Subcutaneous, closed loop, interstitial matrix, hyaluronidase, biologics, drug development, personalized medicine, syringe and needle technology

Biopharmaceuticals represent a $160BN market that is the fastest growing component of the pharmaceutical sector.[1] Based on pharmacogenomics and systems biology targeting, new drug approvals emerge at an impressive rate as they offer real potential to respond to the precision medicine initiative.[2] Many of these agents are curative and are increasingly targeted by employing patient stratification techniques based on genomic markers.[2] Despite their promise, development costs remain high with current estimates suggesting up to $2 BN per new chemical entity (NCE).[1] These rapidly escalating costs are naturally reflected in drug pricing.

Though such targeted therapeutics offer unquestioned benefit in disease management, they have also led to controversy, as some health care providers have established caps on permissible annual treatment costs. For example, the UK's National Institute of Health Care and Excellence (NICE) has set a ceiling of £30k (approx. $44,000) for annual treatment costs, precluding access to a considerable number of life saving biopharmaceutical drugs.[3] In an effort to impact costs of biopharmaceuticals in the USA congress enacted the Biologics Price Competition and Innovation Act (BPCIA) in 2012, to establish a regulatory pathway for biosimilar versions of innovator drugs.[4] It is estimated

 

that some $50BN of innovator drugs will come off patent on the next five years, and while the degree of cost reductions remains to be determined, the first drugs approved through the pathway are now entering the market.[1]

Along with drug cost itself, a major factor for the administration of most biologics is the requirement for patient delivery through intravenous injection, as the protein based products are incompatible with oral delivery. This is typically conducted at hospitals or infusion centers contributing to expenditures, where drug administration can approach 50% of the total treatment cost.[5] Studies have been conducted comparing costs of parenteral drug delivery using different modalities and identified considerable savings with the subcutaneous (SQ) route,[5] which has now become the focus of considerable development.[6] Based on historical innovations in the patient-administered insulin sector, in addition to cost savings and convenience to the user, this route of administration also has the added benefit of actively engaging the patient in the decision making process. By monitoring a circulating biomarker (blood glucose) levels, the decision when to inject drug (insulin) and dose thereof is responsive to the patients' individual profile and parameters (diet, exercise etc.). Given trends in digital medicine and electronic monitoring devices worn by patients, such homeostatic management principles can be expected to produce benefits in many additional therapeutic areas. More generally, the move towards SQ injection routes can be expected to lead to improvements in patient quality of life, obviating the need for frequent time consuming visits to healthcare facilities, deriving economic benefit as an added consequence.

**Subcutaneous Delivery**

When considering alternates to conventional IV administration the volume of the formulated drug to be injected constitutes a major consideration. Slow IV infusions administered over large time periods may be inconvenient but are capable of delivering large volumes (>10 ml) with ease. Typical SQ administrations of insulin are in the 1-2 ml range, requiring deep analysis to adapt for the delivery of the larger volumes needed for biologics. Based on this consideration, SQ appears the only viable alternative to IV delivery, as other transdermal methods suffer from volume constraint.[7] Exacerbating the volume problem is the fact that the majority of biologics administered SQ would need to be uptaken via the lymphatic system once introduced to the interstitial matrix (Figure 1). This is a consequence of the high molecular mass of the drugs (e.g. monoclonal antibodies) precluding direct uptake to systemic circulation. Though not the case with the relatively low molecular weight insulin, most biologics require consideration of both drug pharmacokinetics and stability, which relates to lymphatic drainage and eventual translocation to systemic circulation via the subclavian vein (Figure 1).[8] Myriad factors govern the movement of biologics from the interstitial matrix to the lymphatic capillaries including so called 'Starling' forces [8, 9, 10] which are impacted by the physicochemical properties of the drug substance (e.g. pI, charge, molecular mass etc).[11] Another consequence of injecting large volumes are injection site reactions and events. These include, swelling, edema, erythema, bleb formation, and pressure buildup, which in turn can impact pain experienced.[12, 13] These phenomena are compounded with increasing injected volumes, and it has been suggested that 20 ml represents the realistic upper limit for SQ injection.[14] Accordingly, considerable work has been conducted in an attempt to minimize site reactions by reducing injected volumes and co-formulation with additives which can help mitigate site reactions.

 

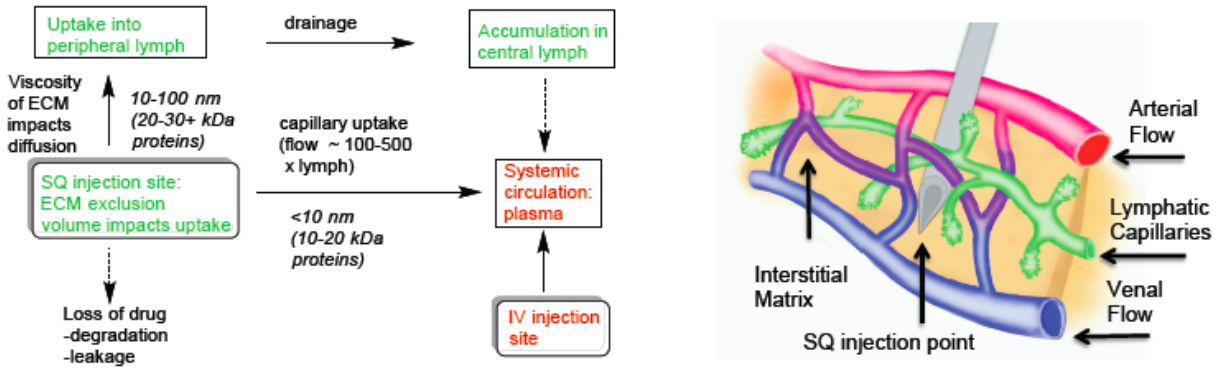


**Figure 1.** Factors Governing Uptake and Distribution of Subcutaneously Administered Drugs

Reducing volumes per se results in highly concentrated solutions with high viscosity. This presents an additional problem in that mechanical forces and back pressure on the delivery device (syringe needle and drive assembly) may result in vastly increased injection times. A potential remedy explored has been the use of crystalline forms of drugs suspended in solution, thereby reducing viscosity but increasing effective concentration.[15] Another approach is to aid dispersion of the injected bolus, thereby reducing local effects. Methods evaluated include ionto and ionophoresis, sonophoresis and ultrasound.[16] Chemical additives can also play a role, by improving the transport properties of the injected drug to enhance distribution. Buffers such as phosphoserine have been suggested,[17] as have albumins,[18] and chimeric constructs which stimulate uptake through the neonatal receptor.[19] The utility of albumins has also been attributed to their capacity to act as so called volume expanders, allowing dispersal of the bolus from the injection locus. A similar approach led to the application of hyaluronidase enzymes, which function by degrading the hyaluronic acid embedded in the interstitial matrix (Figure 2). A number of naturally derived versions of this enzyme have been used to good effect,[20] and a recombinant version was later developed.[21] Co-administration of such results in marked reduction in localized volume within minutes,[22] and PK studies confirm comparable drug availability to that obtained under IV administration.[23] Clinical trials have delivered impressive results,[24] and a number of drugs are now in development using this technology (Table 1).[25] This will greatly expand the volumes permissible for SQ delivery of biologics, and volumes of 250 mL have been demonstrated for rehydration.[26]

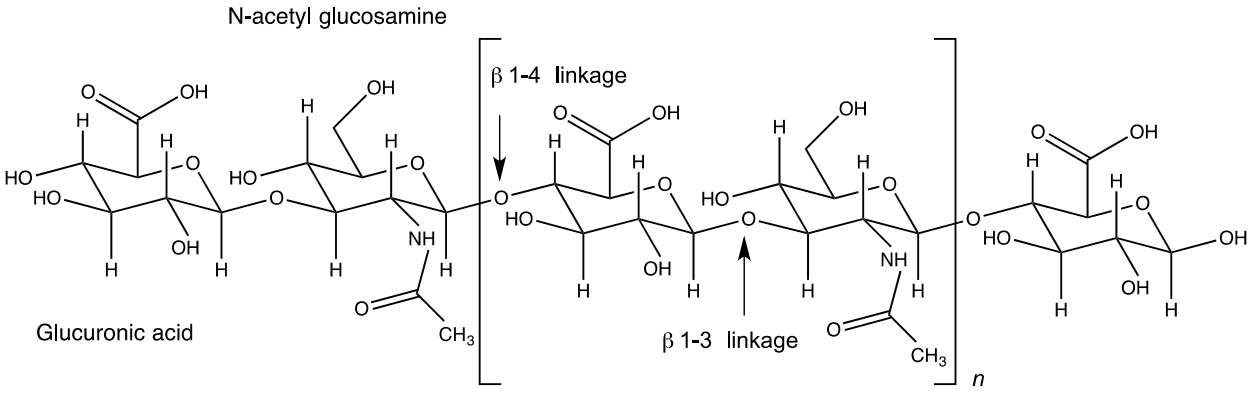


**Figure 2.** Chemical Composition of Hyaluronic acid with β 1-4 Hyaluronidase Cleavage Site Highligted

 

Independent of such strategies, considerable research is being conducted comparing the impact of multiple sequential injections versus single larger injections of the same volumes. One such study with a monoclonal antibody drug revealed no impact on the pharmacokinetics between single and multiple injected volumes. [27]

Encouraged by these findings, major opportunities now exist for innovative approaches to SQ delivery. Given the pathway for systemic administration of biologics requires lymphatic uptake and trafficking, imaging methods are important tools for this method of drug delivery. At the injection site, scanning electron microscopy has been used to examine the morphology of the SQ basement membrane and septa, and also the injection puncture sites.[28] X-ray CT (using radio-opaque dyes as vehicle) has been used to model plume architecture,[29] differentiate plume signatures in muscle and SQ tissue[30] and verifying that plume distribution correlates well with classical histological approaches.[29] Other useful imaging modalities include SPECT/PET and scintigraphy (using radiolabeled sub-strates),[31] fluorescent imaging employing near IR dyes or quantum dots to visualize lymphatic trafficking,[32] echography to define the boundaries of injected boluses,[9] and MRI for anatomical imaging. At the molecular level, use of innovative mass spectrometry imaging methods, principally desorption electrospray ionization mass spectrometry (DESI), allows tracking of molecules in the sub-dermal layers at atmospheric pressure.[33] Using these approaches, insightful studies can be designed which map SQ injected solution mobility as a function of critical key parameters in the drug delivery design space.

**Table 1. Selected Drugs in Development for SQ Delivery**

| Drug | Trade Name | rHu20PH | Company | Indication | Phase |
|---|---|---|---|---|---|
| Insulin | Lantus | x | Sanofi | diabetes | IV |
| Bortezomib | Velcade | x | Takeda | oncology | IV |
| Lanreotide | Somatuline | x | Ipsen | oncology | IV |
| Ceftriaxone | Rocephin | x | scPharmaceuticals | antibiotic | II/III |
| Enoxaparin | Lovenox | x | Sanofi | anticoagulant | IV |
| Morphine | Roxanol |  | multiple | analgesic | I |
| Deferoxamine | Desferal | x | multiple | hemochromatosis | IV |
| Trastuzumab | Herceptin |  | Roche | oncology | IV |
| Rituximab | Rituxan |  | Roche | oncology | IV |
| Adalimumab | Humira | x | AbbVie | RA | IV |
| Etanercept | Enbrel | x | Amgen | RA | IV |
| Human IgG | Hyqvia |  | Baxter | immunodeficiency | IV |
| PCSK9 inhibitor | Bococizumab | x | Pfizer | cardiovascular | III |
| Selectins | Rivipansel |  | Pfizer | sickle cell | II/III |
| C1-esterase inhibitor | Cinryze |  | Viropharma | angioedema | I |
| Adalimumab | Humira |  | AbbVie | RA | I |
| CD38 | Daratumumab |  | Janssen | oncology | I |

 

**Design of Next Generation Devices**

The rapid technological advances witnessed in the insulin market has seen development from pre-loaded syringes, pens, mechanical pumps, and now integrated 'closed loop' systems composed of an embedded glucose sensor connected to an infusion pump through a wireless link. [34] Introduced to the marketplace in 2017,[35] such a breakthrough concept could lead to application of the concepts in a number of other indications.[36-37] For example, detection of analyte biomarkers in tears,[38] saliva,[39] and skin[40] has been demonstrated, and the potential to connect remote monitoring sensors to a drug delivery auto injector device is attractive.[41] One of the principal limitations of closed loop systems using analyte detection in serum / tissue is the use life of embedded sensors and the administration port of the drug delivery component.[42, 43] Embedded needle tips suffer from the foreign body reaction (FBR) wherein fibrous tissue can foul the surface and also induce inflammatory response.[44-46] The current use life of such systems is in the range of 3-7 days following which needle tips are exchanged, and some degree of wound management conducted by the patient or care provider. Efforts to extend this period are a topic of active investigation, as extending e.g. to a monthly regimen would offer considerable flexibility and convenience to the user.[47] Among potential interventions are coated sensor tips,[48-53] needles composed of synthetic materials,[54-56] and the administration of anti-fouling agents[57-58] anti-inflammatory agents[59-60] and preservatives[61-63] at the point of skin penetration. In concert with these efforts, systems which utilize *ex vivo* sensing of biomarkers in biologic fluids potentially offer superior flexibility but require patient interaction e.g. collecting swabs of saliva[64] or tears[65] and insertion to an assessment device connected to the closed loop framework. In terms of drug delivery, innovations in both device and syringe technology continually advance. In the case of the latter, choice of needle design can play a role in drug dispersion and pain nociception. Following on from studies on needle size,[66] it will be interesting to see if multi-beveled tips,[67] and irrigation needles,[68] and sprinkler needles[69] can enhance or modulate PK of SQ administered biologics either in the presence or absence of spreading agents such as rHuPH20 (Figure 3).

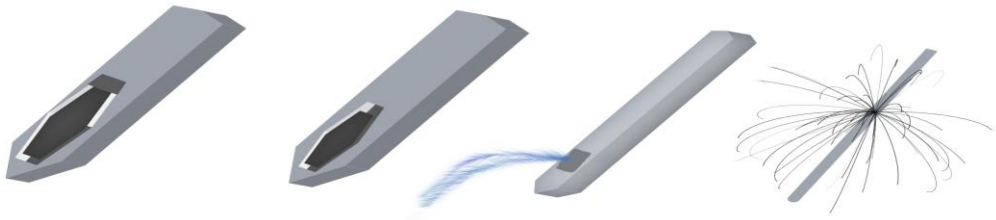

**Figure 3:** Impact of needle architecture on injection performance indicators
(l-r 5 point bevel tip, 3 point bevel tip, side-ported irrigation tip, 'sprinkler' tip)

**Patient-Focused Approaches**

Through developments in drug formulations and delivery device technology, SQ administration of biologics can now offer patients real choice.[70] Several comparative clinical trials have been able to demonstrate the effectiveness of the SQ route [24-25] and additional comparative trials have established patient preference for the route.[6,71] A variety of different SQ delivery options are available, including conventional syringe, single injection device, and auto-

 

injector. One of the primary considerations is perceived pain experienced by patients, and factors to be considered include injection locus (abdomen reported as less painful than thigh), solution viscosity,[9] volume injected, and speed of injection. One study noted patient preference for longer injection times with larger volumes,[72] and a variety of studies outline the benefits of injection site rotation.[73] Other studies suggest that tissue massage,[74] or electrical stimulation[75] may have potential to improve pain tolerance and could be useful for design of future comparative clinical trials. Other advances could involve modification of the form factor of the delivery device to conform to patient morphology. Experience in the design of patch style transdermal drug delivery systems could inform these approaches, with contoured reservoirs developed which are capable of housing large volumes of formulated drug product. It could be expected that such innovations would confer market advantage on the basis of personalized solutions, influenced by patient lifestyle parameters.

## Expected Developments

With the advent of closed loop systems and progress in digital medicine, there is much anticipation for growth in the SQ delivery market. Given reported enhancement in both patient experience and regimen compliance,[76-78] one can expect impact in terms of health provision.[79] As the space develops it will be guided by considerations of health care providers, and this in turn will be influenced by patient derived outcome measures in clinical trials. Given the potential for substantial cost savings in switching patients from IV to SQ drug delivery regimens,[80] it is likely that this will drive the discussion in the near future. Allied to this are directives from the regulatory sector. In the USA, guidelines on the classification of biomarkers have been issued by a joint working group from FDA and NIH.[81] The guidelines (referred to as Biomarkers EndpointS and other Tools or BEST),[82] classify various biomarker types which will inform sensor design in closed-loop systems (e.g. monitoring biomarkers, diagnostic biomarkers) as well as next generation biologics based on companion (Dx/Rx) diagnostics.[83-84] Rapid innovation in the development of biologics is now occurring, and the market sector is also experiencing competition in the form of biosimilar drugs, as innovator products launched in the past decades come off patent.[85] It will be interesting to monitor which innovator and biosimilar drugs are introduced for subcutaneous delivery. The variety of new user friendly devices including bolus injectors, single use pre-filled syringes and auto-injectors could be expected to appeal to patient preferences and drive the market adoption.[6,71,86-88] Equally, it could be expected that biosimilar developers may opt to repurpose innovator drugs designed for IV delivery as subcutaneous offerings, either through the 351k or BLA pathway.[89] In cases where co-administration of the rHuPH20 hyaluronidase enzyme is desired, shelf-life of the co-formulated product either in pre-filled devices or in reservoirs in closed-loop systems will be a factor to establish, guided by appropriate analytical studies.[90] These key opportunities and challenges are likely to drive the agenda in the near future. Addressed appropriately, the subcutaneous drug delivery route has the potential to render a marked impact in managed healthcare, and is thus expected to sustain itself a high growth area of investigation in the years ahead.

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