TRANSFORMING PARENTERAL DELIVERY: KEY CONSIDERATIONS FOR SC AND IM FORMULATION DEVELOPMENT

Jeff Clement of **PCI Pharma Services** looks at the changing landscape of parenteral delivery, considering the pros and cons of intravenous, subcutaneous and intramuscular formulations and considers how new technologies are reshaping the drug delivery landscape.

The pharmaceutical landscape is constantly evolving as patient-centric care and innovative drug delivery methods reshape treatment paradigms. Among these advancements, the transition of many traditional intravenous (IV) therapies to subcutaneous (SC) and intramuscular (IM) formulations stands out as a pivotal development. A report by Roots Analysis has estimated that the global subcutaneous biologics market for approved drugs will reach US$233 billion (£176 billion) by 2035, with this significant growth bringing tangible benefits for patients, healthcare systems and manufacturers.

THE IMPERATIVE FOR TRANSITION: WHY SHIFT FROM IV TO SC AND IM?

The change from IV to SC or IM administration is driven by multiple factors, including patient centricity and self-administration to aid convenience, the increased availability and wider acceptance

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of drug delivery devices, a focus on reduced healthcare resource use and costs, and an overall objective to improve therapeutic adherence for better patient outcomes.

Traditional IV therapies often require prolonged infusion times in controlled clinical environments, imposing a logistical burden on patients and healthcare providers. SC and IM formulations, however, can be self-administered or administered in outpatient settings, reducing hospital visits and improving patient quality of life.

For pharmaceutical companies, SC and IM formulations extend product lifecycles and intellectual property (IP), enhance market differentiation and align with value-based care models. Notably, the exponential growth of glucagon-like peptide-1 (GLP-1) therapies has accelerated interest in alternative patient-centric delivery mechanisms, highlighting the importance of decentralised care.

When transitioning from IV to SC or IM administration, it is important to consider the advantages and limitations of each delivery technique, as well as the need to balance pharmacokinetics, patient comfort and operational feasibility. Tables 1 and 2 show the advantages and disadvantages of each type of administration.

	Intravenous (IV)	Intramuscular (IM)	Subcutaneous (SC)
Use Case	For administration of drug products in emergency situations and drugs with poor oral absorption	Useful for formulations needing sustained release	Suitable for vaccines, biologics and patient self-administration therapies
Onset of Action	Rapid onset exposure	Moderate onset, typically 15–30 minutes	Slower onset due to absorption through subcutaneous tissue, can be 30 minutes to several hours
Bioavailability	100% bioavailability due to direct systemic delivery	High bioavailability, although slightly lower than IV	High but variable bioavailability depending on tissue perfusion
Pharmacokinetics	Rapid systemic absorption with consistent plasma concentration profiles	Depot effect possible for slow, sustained drug release	Slower uptake enhances duration of therapeutic effect
Volume	Minimum constraints, volumes can be up to litres	Moderate volumes (2–5 mL)	Typically small volumes (1–2 mL)
Dose Control	Optimised management of therapeutic concentration and titration parameters	Suitable for drugs requiring prolonged or sustained release	Allows for gradual drug absorption and sustained therapeutic effect
Patient Adherence	Healthcare administration ensures compliance	Can be administered by healthcare providers or in some cases self-administered	Easily self-administered by patient, enhancing compliance

Table 1: Advantages of IV, SC and IM administration.

	Intravenous (IV)	Intramuscular (IM)	Subcutaneous (SC)
Skill Required	Requires trained healthcare personnel	Requires knowledge of specific points on the body to avoid nerve damage	Easier to perform, but clear instructions for use and training needed
Formulation Challenges	Requires aqueous and sterile formulations compatible with blood	Sterile formulation should be well-tolerated and optimised for intramuscular uptake	Limited by volume, solubility and viscosity; must minimise local irritation
Stability Concerns	Maintains solution stability, with degradation risk introduced during administration	Stability for depot formulations may require advanced formulation strategies	Stability of proteins and biologics must be ensured over time
Convenience	Requires clinical setting and monitoring	Requires healthcare provider oversight	Ideal self-administration, increasing patient convenience and adherence
Cost	High cost due to hospital setting administration and required equipment	Lower cost than IV but more expensive than SC	Cost-effective for long-term treatments and self-administration

Table 2: Limitations of IV, SC and IM administration.

"SC TISSUE TYPICALLY HAS LOWER BLOOD FLOW COMPARED WITH MUSCLE, RESULTING IN SLOWER DRUG ABSORPTION, WHILE IM INJECTIONS CAN PROVIDE A FASTER ONSET OF ACTION DUE TO RICHER VASCULARISATION."

SCIENTIFIC CONSIDERATIONS IN FORMULATION DEVELOPMENT

Pharmacokinetic and Pharmacodynamic Profiles

Developing an SC or IM version of an existing IV formulation requires a thorough understanding of its pharmacokinetic (PK) and pharmacodynamic (PD) profiles. SC and IM administration introduce variability in absorption rates, which can impact drug bioavailability, time to peak concentration and therapeutic effect duration. Formulation scientists must evaluate:

- **Drug Solubility and Stability in Various Delivery Matrices:** For biologics, such as monoclonal antibodies, the molecular size can significantly affect diffusion through interstitial tissues and lymphatic absorption, necessitating tailored formulation approaches.
- **Targeted Tissue Absorption Characteristics:** SC tissue typically has lower blood flow compared with muscle, resulting in slower drug absorption, while IM injections can provide a faster onset of action due to richer vascularisation. Formulators must carefully design studies to model these pharmacokinetic differences and assess their clinical implications to ensure therapeutic equivalence.
- **Impact of Injection Site Variability on Systemic Exposure:** Physiologically based pharmacokinetic modelling is increasingly used to predict drug behaviour following SC or IM administration. Such models integrate several key parameters, including drug physicochemical properties, tissue composition and lymphatic transport. This predictive approach helps to refine formulation design and supports regulatory submissions by offering mechanistic insights into absorption kinetics.

Excipient Selection and Compatibility

Excipients play a crucial role in stabilising the formulation and modulating drug release. In SC and IM formulations, excipients must support drug stability while minimising injection site reactions. Common excipients include:

- Viscosity modifiers to facilitate diffusion
- Buffers to maintain pH, tonicity and stability
- Preservatives, where applicable, to ensure microbial safety.

Each excipient must meet regulatory standards for biocompatibility and safety while maintaining drug efficacy over the intended shelf life. Furthermore, excipients must be chosen to account for the physiological properties of the injection site. For example, osmolarity-adjusting agents are crucial for preventing local irritation. The choice of surfactants can also impact protein stability in biologics while minimising aggregation and immunogenicity.

Excipient compatibility testing should include forced degradation studies to identify potential interactions under stress conditions. Additionally, comprehensive extractables and leachables testing is required to ensure no adverse effects arise from the chosen container-closure system.

"ADVANCED FORMULATION STRATEGIES SUCH AS MICRO-EMULSIONS, LIPOSOMAL ENCAPSULATION AND NANOPARTICLE CARRIERS CAN ENHANCE DRUG SOLUBILITY AND REDUCE INJECTION VOLUME."

Volume and Viscosity Constraints

Unlike IV administration, which allows for larger infusion volumes, SC and IM delivery are volume-limited. Generally, SC administration is restricted to 1–2 mL per injection with the exception of some recent higher volume autoinjector systems in development, while IM injections may accommodate 2–5 mL. In high-concentration biological formulations, the antibodies or proteins "stick together" and can be very viscous, proving difficult to produce and administer with a syringe, impeding administration ease and patient comfort, therefore necessitating formulation optimisation. Techniques to address these challenges include:

- Concentrating the API
- Using viscosity-reducing excipients
- Exploring technologies for sustained release.

Additionally, advanced formulation strategies such as micro-emulsions, liposomal encapsulation and nanoparticle carriers can enhance drug solubility and reduce injection volume. Enzyme-based permeation enhancers, such as recombinant hyaluronidase, are also used to facilitate the diffusion of larger molecules through dense tissues, improving bioavailability.

Rheological profiling is essential for characterising the viscoelastic properties of high-concentration protein formulations. Optimising syringeability and injectability ensures that the formulation is compatible with available delivery devices and does not exceed acceptable injection forces.

Stability and Shelf Life

Maintaining stability throughout the product lifecycle is a significant challenge when transitioning from IV to SC or IM. Stress testing under various conditions is essential to evaluate the degradation pathways specific to the new delivery format. Proteins and biologics are particularly susceptible to denaturation

and aggregation during storage and administration. Critical areas to monitor include:

- Physical stability (e.g. precipitation, phase separation)
- Chemical degradation (e.g. oxidation, hydrolysis)
- Storage conditions (e.g. temperature sensitivity).

Innovative stabilisers, such as trehalose, can mitigate stability challenges and enhance the shelf life of temperature-sensitive formulations.

Analytical methodologies must be robust and validated, incorporating size-exclusion chromatography for aggregation detection and differential scanning calorimetry to evaluate thermal stability.

REGULATORY CONSIDERATIONS

Bridging Studies and Bioequivalence

Switching from IV to SC, or even from vials to device-based delivery, constitutes a major regulatory event. Regulatory authorities therefore require robust evidence demonstrating bioequivalence or comparable efficacy and safety between the new SC or IM formulation and the existing IV product. Bridging studies are designed to evaluate the pharmacological and clinical impact of transitioning between formulations while ensuring consistent therapeutic outcomes. Key elements of a bridging study include:

- **PK Comparisons**: Evaluate parameters such as peak plasma concentration (C_{max}), area under the curve and time to peak (T_{max}) to ensure similar drug exposure between IV and SC or IM routes.
- **PD Assessments**: Where applicable, analyse biological markers or clinical endpoints to confirm that the therapeutic effect remains unchanged.
- **Immunogenicity Evaluations**: For biologics, assess the potential for increased immunogenicity with the new route of administration, as altered absorption kinetics may impact immune responses.
- **Local Tolerability Studies**: Examine injection site reactions, pain, erythema and patient-reported outcomes to ensure acceptable tolerability.
- **Dose Conversion**: Evaluate appropriate dose adjustments accounting for absorption differences to maintain therapeutic efficacy.

Regulatory agencies may allow streamlined clinical programmes if sufficient similarity is demonstrated through PK and PD data and bridging study results, reducing time-to-market for new SC and IM formulations.

Device Integration and Human Factors Engineering

SC and IM formulations often require advanced drug delivery devices such as autoinjectors or prefilled syringes. Human factors engineering ensures device usability aligns with patient capabilities and regulatory expectations. Factors such as ease of handling, convenience and patient comfort are evaluated to determine which container and device type may be preferred by end-users.

"HUMAN FACTORS ENGINEERING ENSURES DEVICE USABILITY ALIGNS WITH PATIENT CAPABILITIES AND REGULATORY EXPECTATIONS."

With patient-centric focus, the interaction between users and the product as received is paramount. Understanding how patients and healthcare professionals interact with the packaging, instructions for use (IFU), and the device itself is vital for optimising usability, minimising user errors, and enhancing overall safety, efficacy and adherence for improved outcomes.

Conducting usability studies and incorporating human factors considerations early in the design process can help to identify potential issues and inform design modifications. Human factors and usability engineering is an integral component of regulatory submissions and essential for demonstrating the product's usability and user comprehension. Key design considerations include:

- **Needle Gauge and Length**: Optimised to balance drug viscosity, injection speed and patient comfort while ensuring appropriate tissue penetration.
- **Injection Force and Speed**: Device mechanisms must accommodate high-viscosity formulations without compromising injection time or causing undue patient discomfort.

- **Ergonomics and Usability:** Devices should be designed for ease of handling, especially for patients with limited dexterity or chronic conditions.
- **User Training and IFU:** Clear, comprehensive instructions must be developed and tested to ensure patients and caregivers can safely and effectively use the device.
- **Device Robustness and Reliability:** Ensuring consistent performance under varied environmental conditions and across multiple use scenarios.
- **Safety Features:** Incorporation of needle shielding, dose counters and error prevention mechanisms to enhance user safety.

DRUG-DEVICE STRATEGY CONSIDERATION

Considering the target product profile or quality target product profile, decisions can be made on whether there is a unique need for device innovation tailored to specific patient populations, or whether traditional, readily available platforms would be suitable. Selecting established platforms that have received regulatory approval as part of a drug-device combination product previously, may be deemed lower risk for a new programme. Table 3 shows the advantages and disadvantages of established versus proprietary programmes.

STRATEGIC BUSINESS ADVANTAGES OF SC OR IM TRANSITION

Transitioning from IV to SC or IM delivery offers a range of strategic business advantages for biopharmaceutical companies, spanning clinical development, commercial success, market differentiation and patient engagement, ultimately enhancing both competitive positioning and operational efficiency.

- **Improved Patient Experience and Adherence:** SC and IM delivery enables self-administration or fewer clinic visits, improving convenience for patients with chronic conditions, thereby enhancing treatment adherence and persistence, especially for long-term therapies.

	Advantages	Disadvantages
Established Platform	• Lower upfront costs • Use of existing capital infrastructure • Smoother regulatory path • Robustness of device uses currently in the market	• Limited product differentiation • Higher unit costs • Coemption of supply for popular devices
Proprietary Platform	• Product differentiation – competitive advantage • Custom design for specific applications • Extend IP life of the product • Lower unit costs when scale is achieved	• Higher upfront costs, including design, IP, capital, technology • Complex regulatory path

Table 3: Advantages and disadvantages of established versus proprietary platforms.

- **Reduced Healthcare Costs:** The transition to patient-centric, self-administered formats facilitates outpatient or at-home administration, minimising the need for infusion centre resources, nursing time and healthcare facility overheads – reducing overall treatment cost for payers and providers.
- **Faster Time-to-Market with Lifecycle Management:** Reformulating approved IV therapies for the SC or IM routes can extend product lifecycles, gain additional IP and support differentiation in crowded therapeutic areas. Transitioning enables bridging studies rather than full clinical programmes, accelerating development timelines.
- **Enhanced Competitive Differentiation:** SC and IM formulations offer a competitive edge in crowded biologics markets where multiple IV options exist. It differentiates products based on patient convenience, dosing frequency and administration route, which can influence prescriber and payer preference.
- **Broader Market Access and Global Reach:** Simplified self-administration enables deployment in resource-limited settings and global markets where infusion infrastructure may be limited, thereby increasing accessibility and enhancing commercial reach.
- **Manufacturing and Supply Chain Efficiencies:** Transitioning to SC or IM administration can reduce manufacturing and logistics costs associated with infusion services. Prefilled syringes, autoinjectors and long-acting injectables often have smaller fill volumes, enabling higher batch yields. SC and IM formats can also reduce cold chain complexity for some formulations and support more efficient logistics and packaging.

FUTURE OUTLOOK AND INNOVATIONS

As the pharmaceutical industry continues to evolve, a wave of innovative technologies are reshaping the landscape of SC and IM drug delivery, paving the way for more effective, patient-friendly and precision-guided therapies. Examples of some such emerging technologies accelerating SC and IM development include:

- **Nanoparticle and Liposomal Carriers:** These cutting-edge drug delivery systems are designed to encapsulate APIs, improving their pharmacokinetic and pharmacodynamic profiles by providing improved solubility and prolonged systemic circulation.
- **Long-Acting Injectables:** Formulations that slowly release drug product over extended periods, often weeks or months, are growing in relevance, as they improve chronic disease management with fewer administrations, maintain stable drug concentrations and reduce fluctuations that might lead to side effects.

As precision medicine advances, customisation of patient-specific formulations will become increasingly feasible, further enhancing therapeutic outcomes. Together, these developments are transforming SC and IM delivery from a traditional route into a dynamic, patient-centric platform for next-generation therapeutics.

CONCLUSION

Transitioning IV formulations to SC or IM delivery represents a transformative opportunity for pharmaceutical progress. While the path involves complex scientific, regulatory and operational challenges, the rewards include enhanced patient outcomes, market expansion and sustained product viability. By adopting a holistic development approach, pharmaceutical companies can drive meaningful advancements in drug delivery and shape the future of patient-centric care.

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