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Scalable Strategies for Parenteral Dosage Form Selection

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There are many parenteral dosage forms from which the pharmaceutical scientist can choose to develop their drug product. For primary pack choices, there are traditional vials, ampoules, cartridges, pre-filled syringes and complex containers such as the various types of dual chamber syringes. Additionally, there are newer dosage forms such as wearable injection devices or pump patches. Each have their own merits and advantages, but these advantages may not be realized until the product is marketed. Consideration must also be made on the form of the product within the container and the environment in which it will be used and needs to be (or is able to be) stored. The most desired form is normally an aqueous liquid which can be stored at room temperature; however, there are many perfectly acceptable products which are supplied in solid form such as lyophilized powder for reconstitution which need to be stored in refrigerated or even frozen conditions.

To make the right choices which can, and arguably should, change during the development life cycle of the product, the pharmaceutical scientist needs to employ a sound development strategy. In this article, the author discusses the choices available and strategies which can be employed at the different stages of development.

Importance of target product profile

At the beginning of the development program it is essential that the pharmaceutical scientist has clearly defined product attributes and development goals. One way this can be achieved is with a well-written Target Product Profile (TPP). The US Food and Drug Administration (FDA) has a draft guidance document[1] providing information on the purpose, advantages and use of a TPP, including guidance on completing a TPP and case studies demonstrating its usefulness. In the FDA document, it is pointed out that the TPP should provide a statement of the overall intent of the drug development program and information about the drug at a particular time in development. The agency also states that the TPP should be a dynamic summary that changes as knowledge of the drug increases. Lambert[2] has also described how the TPP should evolve over the product life cycle.

For the pharmaceutical scientist, the TPP should describe how the product will be used or taken by the end user, and hence, describe the critical attributes of that product. The TPP is a live document and should be reviewed and updated as changes occur throughout the development of the pharmaceutical product. Table 1 is an example of some of the key product attributes of a TPP for a parenteral product which are important for the pharmaceutical scientist to know and highlights how they may change during the development program. Many of these attributes will have an impact on the parenteral dosage form to be selected, whether that be the primary pack or the physical form, or indeed both.

1 US FDA, Draft Guidance for Industry and Review Staff. Target Product Profile – A Strategic Development Process Tool. March 2007.

2 Lambert WJ. Considerations in developing a target product profile for parenteral pharmaceutical products. AAPS PharmSciTech. 2010;11:1476–1481.

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In addition to the pharmaceutical product's specifications, technical challenges and requirements for clinical trials, the TPP must consider the business and financial constraints and requirements. For instance, depending on the project budget, the studies which can be performed may be limited, and hence, will have an impact on the development strategy. Likewise, the strategy will be very different if the business goal is to sell the product following successful Phase II clinical studies, rather than taking the product all the way through development to commercialization.

Table 1. Example TPP content and potential changes during development

Product Attributes	Potential Changes During Development	Possible Consequences for the Pharmaceutical Scientist
Indication	Additional indications may be added to the clinical program	Changes to the formulation, drug concentration and dosage form
Patient profile	Pediatric patients	New formulation
Route of administration	Changes from IV injection to SC injection	Probable re-formulation. Reduction in injection volume.
Dose range	Reduction in dose	New formulation, stability review
Dose frequency	Increase in frequency	Formulation review – determine if maximum daily doses of excipients are still within recommended limits
Primary packaging	Change from vial to pre-filled syringe (PFS)	Stability study, component compatibility
Single-dose / multi-dose	Change to multi-dose format	Preservative may be required if dosage form is to be multi-dose. Dosage form may need to change.
Dose preparation requirements	Dose prepared by a medical practitioner changed to a ready-to use-format	Dosage form change (e.g., vial to PFS) resulting in formulation development and stability study
Administration by patient or medical practitioner?	Change to self-administration	Dosage form change (e.g. vial to PFS) resulting in formulation development and stability study
Storage conditions	Change from frozen to refrigerated storage	Formulation development and stability study
Shelf-life requirement	Increase from six months to two years	Formulation development and stability study
Manufacturing location	Small-scale in-house manufacture to CDMO	Technology transfer and scale-up studies

Primary packaging considerations

When selecting the appropriate dosage form for a parenteral product, the pharmaceutical scientist has some unique challenges to overcome in terms of the requirements of the primary packaging. The packaging components need to be able to withstand sterilization prior to use and need to be able to maintain sterility throughout the shelf-life of the product. These are fundamental requirements of sterile products that do not change during the development lifetime. There are a number of primary packaging forms which would be acceptable for parenteral products. Table 2 shows some of the more popular primary packaging choices and the corresponding advantages and disadvantages of each.

Table 2. Advantages and disadvantages of different parenteral dosage forms

Format	Advantages	Disadvantages
Ampoules	• Single product contact material	• Old-fashioned format • Generation of glass particles upon opening • Risk of injury upon opening
Glass vials	• Wide level of acceptance • Flexibility of dosing • Availability of components • Established manufacturing methods • Wide choice of manufacturers	• Manipulation on dosing • Doesn't necessarily separate a company from the competition (not a concern in early development)
Plastic vials	• Wide level of acceptance • Flexibility of dosing • Robust packaging less prone to breaking than glass • Glass delamination not an issue	• Manipulation on dosing • More limited manufacturing options (than glass vials) • Need to address potential issues of interaction with the drug product
Pre-filled syringes	• Ease of end-use • Product differentiator • Patient compliance • Self-administration • Lower overfill than vials	• Lead times and costs for components may be an issue during development • Siliconization compatibility • More limited choice of manufacturers

Ampoules

Ampoules are traditionally one of the simplest dosage forms used for parenteral products and were originally the most popular primary packaging system for small volume parenterals (SVPs). Made of only glass with no other contact components, they may appear to be the ideal first choice in early development. However, ampoules are becoming frequently less desirable as a parenteral dosage, both during development and for commercial products due to the risk of injury from glass particles produced upon opening, requiring the use of a filter to withdraw the product.

During the development program, vials offer a good degree of flexibility in dosing, which may be taken advantage of, especially in early clinical trials.

Glass and plastic vials

For SVPs, vials are currently the most common primary packaging choice. They are a readily available format which is well understood by medical professionals. During the development program, vials offer a good degree of flexibility in dosing, which may be taken advantage of—especially in early clinical trials. Vials are most frequently made from Type 1 glass and generally have good compatibility with most liquid and freeze-dried injectables. If glass compatibility is a problem, however, there are other options available to the pharmaceutical scientist. This may sometimes be addressed during formulation development. For example, some therapeutic proteins are known to adsorb onto the surface of glass vials. This can lead to loss of active protein in the solution due to structural changes and inactivation due to aggregation. This is typically prevented or reduced with the use of a blocking agent through competitive binding to the glass surface. Common blocking agents are surfactants such as polysorbate 80 and 20, and Human Serum Albumin (HSA). Glass surface treatments may also be considered, such as ammonium sulfate treatment and baked on silicone to reduce glass/product interactions. Vials which have been subjected to an oxygen/plasma reaction resulting in an extremely inert SiO2 layer inside the vial are also commercially available. This layer serves as a barrier against ion leaching, making it a good choice for formulations sensitive to metal ions and unbuffered formulations. The SiO2 layer also reduces the risk of glass delamination by preventing corrosion of the glass by the drug formulation, potentially a problem for some drug formulations, particularly those with a high pH value.

Plastic vials may be considered a good alternative to glass vials. Plastic vials made of cyclic olefin polymer (COP) or cyclic olefin copolymer (COC) are now commercially available and look identical to glass vials. However, studies need to be conducted to address potential concerns of interactions with the drug product such as absorption, adsorption and leachables. Additionally, consideration should be given to product manufacturing. Glass vials are typically sterilized and depyrogenated in dry heat tunnels which transport the vials directly to the filling machine in the aseptic area. Plastic vials are typically pre-sterilized by the vial manufacturer; therefore, the product manufacturer needs to consider how the plastic vials can be aseptically transferred onto the filling line. This is not an easy option, particularly when compared to the way glass vials are automatically transferred via the tunnel. Plastic vials are also lighter in weight than the corresponding glass vial. While this can reduce transportation costs for the finished product, it does create challenges in the vial handling on high-speed filling lines. As a result, there are currently fewer options for the manufacture of finished products in plastic vials compared to the options for glass vials. This may be particularly important if a CDMO is to be used to manufacture the product, as there will be a reduced choice of CDMOs with this capability.

All vials–glass and plastic—need to be sealed after filling in order to produce an integral package protecting the product inside. This is achieved with a rubber stopper held in place typically with an aluminium overseal. There are many different options for the stopper, e.g., different rubber formulations, coated/uncoated stoppers and coatings which improve the machineability of the stopper on the filling line. Some considerations for choosing a vial stopper include single-dose versus multi-dose and compatibility of the drug product with the rubber formulation. For lyophilized products, the stoppers must not absorb moisture which could be released into the lyophilized cake on storage. The suppliers of the stoppers are often a great source of information on the use of their products and the pharmaceutical scientist would be well advised to contact them to seek their advice.

PFS are a very popular delivery system and are experiencing the greatest growth in market share of any parenteral dosage form.

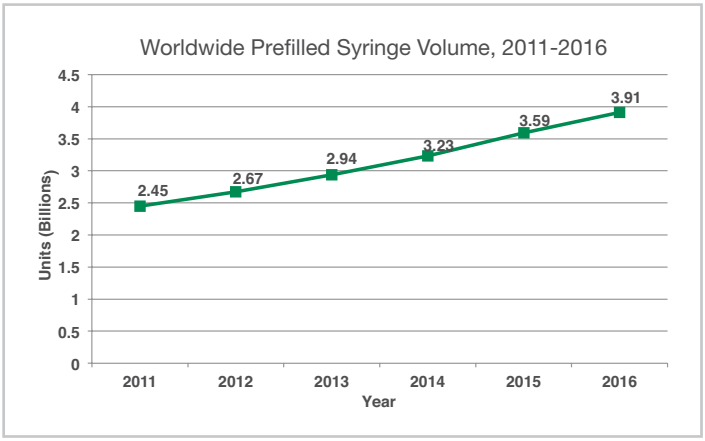
Pre-filled syringes

Pre-filled syringes (PFS) are a very popular delivery system and are experiencing the greatest growth in market share of any parenteral dosage form (Figure 1). Reasons for this growth include the convenience to medical practitioners and end-users and the lower probability of dosage errors. There are also advantages for the pharmaceutical manufacturer. Since the filling overage required in a PFS to deliver the labeled dose is very low, the manufacturing yield is typically much higher than for an alternative parenteral format such as a vial. PFS barrels can be either glass or plastic and are frequently supplied as pre-sterilized and ready-to-fill. This is very convenient for drug product manufacturers as often the filling equipment for PFS is the same regardless of the PFS barrel material of construction.

For the pharmaceutical scientist, a number of considerations need to be made if PFS is the chosen dosage form. Compatibility of the drug product with the syringe components needs to be assessed in the same way as for a vial product. A major difference though is the need to consider syringe functionality (or glide force), i.e., the force to initiate movement of the plunger in the barrel and the force required to maintain that movement throughout the barrel to the end of the syringe. Siliconization of the inside of the barrel is typically used to achieve the movement at an acceptably low force. However, excess silicone can be problematic with respect to the visual appearance of silicone droplets in the product and potential interactions of the drug with the silicone —especially protein aggregation. Syringe manufacturers have developed alternatives to siliconization, and these may need to be considered if compatibility is a problem.

There are more limited manufacturing options for PFS, and currently they are generally not as readily available as vials. As a result, the required size and/or format may need to be special ordered by the pharmaceutical scientist for the clinical trials. Depending on the format, this often requires a longer lead time than for vials and large minimum order quantities. Also, manufacturing scale needs to be considered. Although there is an increasing number of high-speed filling machines available to manufacture the increasing number of commercial products in PFS, these machines are not ideal for manufacturing the relatively small volumes of PFS required for the early-phase clinical studies.

Figure 1. Growth of the PFS market



Source: Pre-Filled Syringes: World Market Prospects 2012-2022, Visiongain

While the lyophilized form generally requires more formulation and process development initially, it is the most likely form to have an acceptable shelf-life for the clinical program without having to resort to frozen or refrigerated storage.

Stability considerations

Parenteral dosage forms aren't limited to the primary packaging. The drug product inside the primary pack may be either liquid or powder form. The pharmaceutical scientist needs to consider the advantages and disadvantages of each form in order to determine which is the most suitable for each stage of development. The advantages and disadvantages are summarized in Table 3. In almost every case, the most desired form for the commercial product would be a liquid product which can be stored at room temperature. This form is often the easiest to manufacture, the easiest to transport and store and the most convenient for the end-user, as there are fewer manipulations to prepare the dose when compared to a powder form. However, developing a liquid product isn't always possible, at least not without a significant amount of formulation development work, and even then may not be achievable. Consideration may then be given to storing the product under refrigerated conditions. This is less desirable than room temperature storage due to the slightly increased logistical complexity of storage and transportation but is still a realistic option. The pharmaceutical scientist may decide for early phase clinical studies to perform minimal formulation development and supply the product as a frozen solution, stored at -20°C (or even deep frozen at -70°C) in order to enhance the product's shelf-life. This could potentially reduce initial development costs and allow clinical studies to start sooner due to a decreased number of laboratory studies and simpler manufacturing requirements. Nevertheless, freeze/thaw studies would still need to be conducted to confirm that there is no impact on the product. Transportation and storage requirements are also significantly more complex and costly than for the room temperature stable product. The increased logistics complexities, although often acceptable (or at least tolerated) for early clinical trials, are very undesirable for a commercial product.

On the other hand, the pharmaceutical scientist may consider developing a lyophilized drug product form from the outset. While the lyophilized form generally requires more formulation and process development initially, it is the most likely form to have an acceptable shelf-life for the clinical program without having to resort to frozen or refrigerated storage. This can potentially help identify which drug candidates are worth investing in to develop as liquid products following successful clinical outcomes. Lyophilized products are perfectly acceptable as commercial products but are less desirable than liquid products by medical practitioners, as they require many more manipulations to prepare the dose than liquid products. Lyophilized products are also generally much more expensive to manufacture than liquid products due to the often lengthy lyophilization cycles required to manufacture the product.

Table 3. Advantages and disadvantages of liquid, frozen and lyophilized parenteral products

Option	Advantages	Disadvantages
Liquid product (room temperature or refrigerated storage)	• Typically lowest manufacturing cost and simplest option • Convenience of transport, storage and for the end-user • Easy to change primary pack (e.g., vial to a PFS) at a later stage	• May not be achievable • Risk that the product does not have sufficient stability to support the clinical program • May require significant formulation development resources to achieve the desired shelf-life

To advance the development program appropriately, the pharmaceutical scientist should effectively leverage the advantages offered by each pack and dosage form in order to balance the needs of the clinical trials with the needs of the business

Frozen solution	• Potentially minimal formulation development • Aids in getting to clinic quickly • Can minimize risk to product stability	• Less desirable for later product development/ marketed product • Added logistical complexity for transportation, storage and end-use • Potential risk to product stability with freezing/thawing
Lyophilized product	• Form most likely to achieve acceptable shelf-life for the clinical trial program • Convenience of transportation and storage	• Can add to timeline of development program • Relatively high initial cost • Added complexity of manufacture and at point of end use

Evolving strategy during development

The importance and impact of the advantages and disadvantages for each of the primary packs and dosage forms will most likely change during the development program. As stated earlier, the business strategy and budget will also impact the development strategy. The business strategy may affect the timing and pace of the development program—and the budget could dictate the amount of drug substance available for development studies and the number and type of studies which can be done—especially in the early phases of development. Therefore, to advance the development program appropriately, the pharmaceutical scientist should effectively leverage the advantages offered by each pack and dosage form in order to balance the needs of the clinical trials with the needs of the business.

Summary

The choices available to the pharmaceutical scientist developing a parenteral product are varied with many different and often conflicting and changing advantages. With careful planning and strategic foresight, these advantages can be leveraged to great effect during the development program, resulting in shortened development timelines and minimal drug substance use—especially during the early development phases.

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