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Review Article

Theme: Sterile Products: Advances and Challenges in Formulation, Manufacturing, Devices and Regulatory Aspects
Guest Editors: Lavinia Lewis, Jim Agalloco, Bill Lambert, Russell Madsen, and Mark Staples

Considerations in Developing a Target Product Profile for Parenteral Pharmaceutical Products

William J. Lambert[1,2]

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Abstract. A target product profile (TPP) describes how a product will be utilized by the end user. A systematically developed TPP can ensure alignment of objectives across company departments, accelerate development timelines, minimize development risks, and eventually lead to an optimal product. A TPP is particularly important for parenteral products due to the need for administration devices, the variety of possible end users (nurses, patients, pharmacists, and physicians), and requirements specific to sterile products. This manuscript describes key components of a TPP from a formulation development perspective and provides guidance on practical issues common to parenteral products.

KEY WORDS: freeze dried; injectable; lyophile; quality by design; sterile product; target product profile.

INTRODUCTION

Before work begins on the development of a new product, it is critical that the development scientist or engineer clearly defines the critical attributes of the product. In the popular Six Sigma approach, defining the design goals for a product is the first of the five phases (1). In the pharmaceutical industry, these product attributes are referred to as the target product profile (TPP). Ideally, the TPP describes how the product will be utilized by the end user. For the company, the TPP will help identify project goals and potential risks. It can serve as the basis for discussions between various groups within the company (clinical, development, drug safety, manufacturing, marketing, regulatory, research, and quality) before and during development. These discussions should occur from the candidate nomination stage through and after marketing approval. The development of pharmaceutical products is a lengthy and expensive exercise, often taking 10 years and costing over $1 billion (2). Given this time and expense, it is critical to ensure that the right product is being developed. The TPP is a key tool to help ensure the eventual product meets all expectations. In addition, the TPP document can be used for discussions between the company and the Food and Drug Administration (FDA) and, in fact, is considered a "critical path" tool by the agency (3).

The absence of a well-defined TPP can lead to a host of problems. For example, without a TPP, one group within a company may make certain assumptions about how the product will function, only to find out at a later and inopportune moment that the product does not meet that group's expectations. This can lead to inefficiencies in time and resources and may even result in failure of the product from a medical or commercial standpoint. A well-planned TPP can also be used to guard against unnecessary changes as new members are assigned to project teams. Ultimately, the TPP helps ensure that all parties are clear on what is and is not being developed.

The use of a parenteral pharmaceutical product has a number of considerations which may not apply to orally administered dosage forms. For example, administration generally requires a device such as a syringe, injection pen, catheter, *etc.* In addition, formulations often must meet specific requirements (*e.g.*, the use of an antimicrobial preservative in a multi-use container). Finally, there are a variety of end users for parenteral products. These include self-administration by the patient, preparation by a pharmacist, and administration by a nurse or physician, all of whom can introduce a variety of preferences. The use of a TPP for pharmaceutical development has previously been described (4,5). The purpose of this manuscript was to focus on those considerations that are specific to sterile products from a formulation development perspective. The importance of the customer's requirements and preferences is stressed. An example TPP will be provided in order to provide useful guidance to the reader.

KEEP THE CUSTOMER IN MIND

Development of the TPP must start with consideration of the end user's needs. How will they use the product? Are they already using a similar product? Product sales can be

[1] Pacira Pharmaceuticals, Inc., Pharmaceutical Development, 10450 Science Center Dr, San Diego, California 92121, USA.
[2] To whom correspondence should be addressed. (e-mail: BillL@pacira.com)

impacted if an unfamiliar device or technique is forced on hospital staff. If the company is entering a therapeutic area where it has limited experience, it may be useful for the marketing group to perform focus group studies with appropriate nurses and/or physicians to better understand their needs. If this is done, it is a good idea that the development scientist be involved so that technically relevant questions are asked and so the scientist can receive useful input.

The importance of understanding how the end user will want to utilize the product cannot be overstated. Consider the use of an anesthetic agent such as bupivacaine in a hospital operating room. It would be easy to assume that the surgeon takes a vial and removes the desired dose with a syringe. However, it is common practice for the stopper to be removed from the vial and the vial contents poured into a sterile surgical bowl containing a volume of saline appropriate for the given surgery. The bowl is then utilized to replenish the syringe used as the surgery proceeds. This insight might lead the development scientist to consider alternative packaging. For example, a tear-off seal could be utilized for the vial (rather than a traditional "flip-off" seal) in order to facilitate emptying of the vial.

In addition to the patients, pharmacists, nurses, and physicians, the needs of internal customers must also be considered. Pharmaceutical products generally have multiple internal customers, and often, each has certain requirements to ensure success for the product. The internal customers include groups such as marketing, clinical, legal, regulatory, quality, and manufacturing.

COMPONENTS OF A TPP

The TPP as described by the FDA (3) can encompass a fairly broad range of topics which may lead to inclusion in the product labeling. Topics can include dosage and administration, clinical studies, adverse reactions, and contraindications. For the present document, the focus will be on those aspects of the labeling which directly impact how the product should be developed from a formulation development standpoint. TPP topics such as indications and adverse reactions are outside the scope of this manuscript and are not addressed, except as they might impact the formulation. A list of product attributes which should be considered for inclusion in the TPP is provided in Table I. Many of the attributes relate to what the product will be used for and how it will be administered to the patient. Other attributes address the specifics of the product, its components, and how it will be packaged. Some address potential intellectual property issues. Finally, attributes which impact the manufacturing site are addressed.

"MUSTS" AND "WANTS"

During the development of the TPP, people will often describe what they feel are product "requirements." For example, "The product must be isotonic and formulated at pH 7.4" or "It must have a 2-year shelf-life." It is critical to differentiate what are minimally acceptable requirements (musts) from what are desired attributes (wants). Some companies may indeed have a commercial policy on having a 2-year shelf-life, and this is probably a reasonable requirement for many low-volume products in order to ensure stability through distribution and storage. However, if launching the company's next blockbuster with only an 18-month shelf-life is preferred over stopping development from a corporate standpoint, then a 2-year shelf-life is not a must. The TPP can be used to clarify such considerations.

It is generally useful to put quantifiable ranges on the musts and wants. The development scientist should make use of the literature to assist other project team members with regards to what product attributes are acceptable. For example, significant evidence exists that injectable products do not need to be formulated at pH 7.4, but rather, a fairly broad range of pH is found to be well tolerated in commercial use (6–10). Thus, one might define a pH range of 5–8 as preferred for a given product, with the stipulation that the pH must not be <3.5 or >9.5. When attributes are quantified in this manner, the development scientist has a clear direction how to proceed.

EXAMPLE TPP

An illustrative example of a TPP is provided in Table II. For this example, a hypothetical antifungal agent about to enter Phase 1 studies was used. Being an early stage compound, the final dose is yet to be determined. For the development scientist, this leads to uncertainty as to what the eventual formulation concentration will be and possibly whether the compound is sufficiently soluble. The TPP will aid in addressing these considerations.

The example contains several instances where the desired product attribute differs from the true requirement. For example, it may be desirable for marketing to launch in both a plastic bag and a bottle. However, the TPP captures the true requirement, which in this case is just one package type.

Flexibility has also been built in to the TPP. For example, at this stage in development, it may not be clear if a solubilizing agent such as a cyclodextrin is required. Since the use of a cyclodextrin could require a technology license, the potential impact of the license on cost of goods sold (COGS) is noted under "Freedom to Operate."

EVOLUTION OF THE TPP OVER THE PRODUCT LIFE CYCLE

The first version of the TPP may be a key document used in the decision process for taking a drug from research into development. TPPs have even been used at the discovery stage to help set research goals (11).

The TPP is considered the initial step in the "quality by design" approach to pharmaceutical development (12,13). As the formulation and process are developed and critical quality attributes are identified, the TPP should be revisited to ensure consistency. The TPP should be considered a living document. It should be updated throughout development as knowledge of the product increases or as new information becomes available (*e.g.*, knowledge of a competing product, changes in hospital use patterns).

Table I. Critical Components of a TPP from a Formulation Development Standpoint

Attribute	Comments
Drug-related	
Indication	Note if target population may have restrictions (*e.g.*, glucose and diabetics)
Route of administration	May impact acceptability of excipients (*e.g.*, intraspinal injections), deliverable volumes, *etc.*
Dose range	
Dose frequency	The volume, duration of treatment, and dosing frequency may impact the use of some excipients (are these outside the precedented use levels?)
Expected duration of treatment	
Infusion or injection rate/duration	
Volume per dose	
Drug concentration(s)	
Pharmacokinetic profile	Is toleration or activity associated with the plasma concentration or total exposure? For controlled release formulations, what is the desired profile?
Drug products which may be mixed or co-infused with this product	Are there potential incompatibilities?
Product-related	
pH	
Tonicity	
Excipients compendial, precedented, contain low levels of endotoxin?	
Need to dilute/reconstitute and with what?	
Single or multiuse container?	
Packaging type(s)	If more than one, will all be available at launch? Does the packaging work with existing equipment? Will there be a kit (with a diluent, device, *etc.*)? Are there disposal considerations (may vary from region to region)? Is functional labeling needed (*e.g.*, freeze indicators, able to be hung from an IV pole, anti-counterfeiting measures)?
Storage conditions	Include in-use stability requirements and constraints (*e.g.*, "do not freeze", need for secondary packaging to protect from light).
Shelf-life	
Shipping requirements	Are there unusual constraints (temperature excursions, susceptibility to shaking, *etc.*)?
Legal-related	
Freedom to operate	Does the product or process infringe any patents and applications?
Product intellectual property	The ability to patent the product, process, or method of use may be a critical attribute for drugs near the end of their patent life
Manufacturing-related	
Cost of goods sold	Include any royalties as appropriate
Equipment needed for manufacture	Will the process match existing equipment?
Product processing time	May be an issue for some processes (*e.g.*, freeze drying). Also, need to consider sterility assurance.

The development scientist should be aware of how new knowledge of the product will impact the TPP. For example, if it is discovered that the hydrochloride salt of a basic drug has limited solubility, it behooves the scientist to assess the solubility product constant (K_{sp}) of the salt and determine if this will impact its ability to be diluted in normal saline. If the ability to dilute with saline is considered a must in the TPP, the low solubility of the chloride salt needs to be communicated to the team. Thus, the TPP can be a useful tool for the scientist to use when communicating technical issues which might impact the use of the product.

It may also be useful to develop separate TPPs which are appropriate for products utilized in specific stages of development (having said this, the eventual commercial TPP must always be kept in mind). Thus, in the preclinical stage, it will be important to have a TPP describing the product to be used in the various drug safety studies. In this case, the dosing and administration may vary significantly from the human product. Other considerations may include the desire to introduce potential degradation products into the formulation in order to qualify these compounds. Likewise, the TPP for the clinical product may have more or less stricter requirements than the commercial TPP. As noted in the compatibility section above, administration sets can introduce a large number of variables. For this reason, one may wish to limit the number of administration sets which will be used for Phase 1 and 2 clinical studies, and the TPP for the clinical drug product may be used to effectively achieve this.

As intravenous formulations move into later stage clinical studies, the clinical sites will often want to co-administer the drug of interest with other medications,

Table II. Commercial TPP for a Hypothetical Antifungal Agent About to Enter Phase 1 Studies

Product attribute	Wants	Musts
Drug-related		
Indication	Treatment and prophylaxis of systemic candidiasis	Treatment of systemic candidiasis
Route of administration	IV	IV
Dose range	50–100 mg	<300 mg daily
Dose frequency	Once per day	No more than three times per day
Expected duration of treatment	1 week	2 weeks
Volume per dose	100–200 mL	<500 mL
Drug concentration(s)	0.25–1 mg/mL	>0.17 mg/mL
Product-related		
pH	pH 5–8	Greater than pH 3.5 and less than pH 9.5
Tonicity	Isotonic	Isotonic ±50%
Excipients compendial, precedented, contain low levels of endotoxin?	Yes	If not, will need endorsement by project team
Need to dilute and with what?	No (ready to use solution)	Dilution or reconstitution only if necessary; normal saline and D5W
Single or multiuse container?	Single	Single
Packaging type(s)	Glass bottle and plastic bag with ability to be hung	Glass bottle or plastic bag with ability to be hung
Storage conditions	Room temperature	Room temperature (long term and in-use)
Shelf-life	3 years or more	2 years or more; 24 h following dilution or reconstitution
Legal-related		
Freedom to operate	Yes	Will need to meet COGS requirements if a proprietary solubilizing agent is necessary
Product intellectual property	Formulation/process patent if possible	Formulation/process patent not necessary
Manufacturing-related		
Cost of goods sold	<10% of sales price	<30% of sales price
Equipment needed for manufacture	Standard equipment in facilities X and Y	If not standard equipment, will need endorsement by project team
Product processing time	Compound to fill in <16 h	To be determined

often through a "Y-site" or by direct addition of two or more of the drugs in one bag or bottle. There are many examples in the literature where the co-administration may lead to physical and/or chemical incompatibilities (14–16). Thus, it is critical to understand what drugs might be co-administered and capture these in the TPP in a phase-appropriate manner.

Project teams should review the commercial TPP at various milestones during development to ensure that all parties are still in agreement with the profile. Tebbey and Rink (17) have appropriately addressed the issue that given the fact that the TPP is dynamic, it is critical for the project team to assess how the current product being developed compares to the original vision of the product. They note that without such an evaluation, a company may unwisely invest in a drug product that does not meet marketing needs.

Following the product launch, the TPP can be utilized to assess life cycle management and product extension opportunities. Often, the product which is launched may meet the "musts" but fall short of the "wants," possibly as part of a strategic decision to shorten the development timeline. A second-generation product which can address these unmet desired attributes might lead to significant product value.

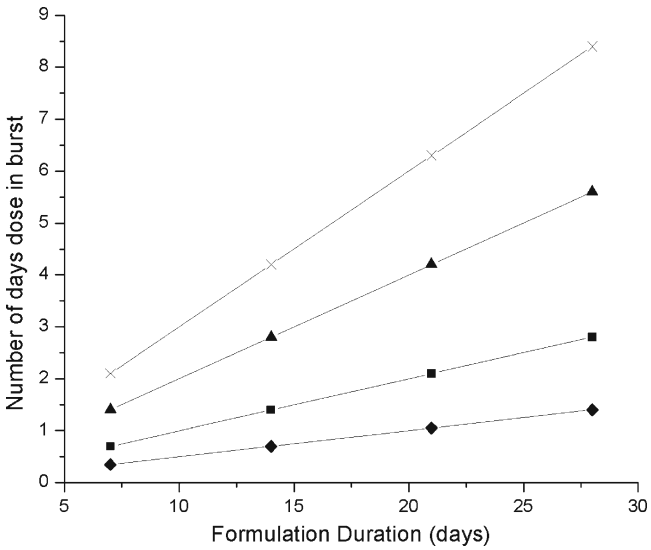

Fig. 1. Theoretical number of days dose released in an initial burst for a sustained-release dosage form as a function of the intended duration and the percent of the total drug content released in a "burst"; 5% (◆), 10% (■), 20% (▲), and 30% (X) burst percent

SPECIAL CONSIDERATIONS

As described above, parenteral formulations are unique in that they must be administered to the patient using some type of administration device. These devices as well as the primary packaging used for the product must be thoroughly considered when developing the TPP. In addition, if the product is a sustained-release formulation, the TPP should address attributes critical for such dosage forms. These considerations are discussed below.

Packaging. The primary packaging used for parenteral products should be considered integral with the formulation and thus deserves significant attention. Furthermore, how the product is packaged can provide a competitive advantage over existing or soon to be marketed products. It is important to address end user preferences, particularly for products entering a well-established therapeutic area. It must also be acknowledged that not all end users are alike, and thus, there may be a need to provide multiple packaging options. Consider an infusion product that will be used in the hospital setting. Not all hospitals are alike. Purchasing at a community hospital may look at the bottom-line cost per unit and may prefer simple vials. On the other hand, a busy teaching hospital might prefer prefilled bags or Add-Vantage® vials as a means to reduce pharmacy and nursing staff labor. The marketing strategy for these varying preferences needs to be factored into development timelines and the TPP.

Compatibility with Administration Devices. For intravenous (IV) formulations, it must be recognized that IV access is necessary. The product will generally not be given directly into the vein with a syringe and needle, but instead will generally involve the use of a catheter, placed either peripherally or into a larger central vein such as the subclavian vein. Some catheters are intended for long-term use and, in this case, may have antimicrobial substances such as antibiotics, silver sulfadiazine, or chlorhexidine on the lumen surface. If the product will be infused rather than given as a bolus, it may be placed in a bag or bottle and delivered through an IV set. The IV set may or may not utilize an in-line filter.

The development scientist must consider the potential for incompatibilities with all of these administration device materials. Common incompatibilities include loss of potency due to adsorption to or permeation into polymeric administration devices, loss of particulate-based systems to in-line filters, and electrostatic interactions between charged colloidal systems and charged administration set surfaces which may lead to aggregation of the product.

Sustained-Release Formulations. Sustained-release formulations necessitate significant discussion as to what is the preferred and required pharmacokinetic profile. Is there a goal of remaining above a certain therapeutic level in the plasma while remaining below a level which leads to undesirable side effects? Is there a maximum ratio of plasma concentration at its highest point to the average over the intended duration (C_{max}/C_{avg} ratio)? How will duration be defined? Given the complexity of developing-sustained release formulations, it is imperative that all interested parties agree on the desired pharmacokinetic profile.

Since many sustained-release systems are to be self-administered by the patient, a prefilled syringe or pen-type injector may be utilized. This added level of complexity with these devices might lead to a TPP just for the device itself. One item which does require attention is the gauge of needle. Advances in needle design in the last decade or two have led to narrow-diameter needles which do an excellent job of eliminating or minimizing pain. However, not all sustained-release formulations are compatible with needle gauges of 27 G or more. For example, the inside diameters of 27- and 31-G needles are typically 0.19 and 0.11 μm, respectively. Lumens in this size range will often clog with many microparticulate systems and present an impractical resistance for many viscous systems. This must be addressed early in development.

Finally, the preferred dosing frequency also needs to be considered. Superficially, it might appear that a once every 2-week formulation would be preferred over a once a week formulation. However, twice as much drug must be loaded in the former, which can lead to a variety of issues. First, the release characteristics of most sustained-release dosage forms are impacted by drug loading. In addition, an initial "burst" of release is often observed in the first 24 h. Such a burst of drug may result in undesirable side effects, particularly for drugs with a small therapeutic index. The longer the duration (requiring a higher total dose present in the dosage form), the more likely it is for this burst to become significant. This concept is exemplified in Fig. 1. If the burst releases 20–30% of the total dose, the patient will receive the equivalent of approximately 3–8 days of drug in the first 24 h for a formulation intended to be given every 2–4 weeks. For many drugs, this would not be an acceptable situation. On the other hand, a dosage form designed to be administered once weekly can have a 20% burst and yet only release a little over 1 day's worth of dose. Furthermore, patients have trouble remembering to take a drug every other Saturday *versus* just every Saturday. Thus, a once a week formulation may be preferred over one with a longer duration. This is an issue that the marketing group should consult on.

CONCLUDING REMARKS

The use of a TPP during development of the product provides a formal mechanism to ensure that the various disciplines needed to bring a drug to the market are communicating and working toward a common goal. When a project is initiated, the development scientist should schedule informal meetings with colleagues in key departments to begin development of the TPP. Often, project team members come away with a greater understanding of the challenges that their colleagues face during product development by going through the process of generating the TPP. Thus, the TPP should be viewed as a helpful tool for development team members. It is also critical to ensure that the TPP undergoes periodic review to verify that no changes in project direction have occurred which might impact the TPP. In the end, effective use of the TPP will benefit the project team, the company, and, eventually, the patient.

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