

## The Role of a Target Product Profile in Pharmaceutical Product Development

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In the last 10 years the drug development process has seen many new regulatory initiatives mainly aimed at improving quality. Examples include FDA and ICH initiatives such as Pharmaceutical cGMPs for 21<sup>st</sup> Century<sup>1</sup>, Quality by Design (QbD)<sup>2</sup>, Process Analytical Technology (PAT)<sup>3</sup> and the Quality Systems initiative<sup>4</sup>. While many pharmaceutical researchers may think these initiatives are the same old wine in fancy new bottle, we believe these initiatives have helped clarified many ambiguities, standardized terminology and provided a framework for a more structured approach to pharmaceutical development, manufacturing and quality control thus creating an environment that provides not only a better understanding of our products but also frees up pharmaceutical scientists and engineers to be more innovative. This article focuses on another initiative, the Target Product Profile ("TPP") initiative which is a comprehensive approach to product development.

So what is the TPP initiative? We all know the old saying "If you don't know where you are going you will probably end up somewhere else". In other words, action without a clear goal is usually unproductive. Although it is important to establish clear objectives of any undertaking, it is especially critical in pharmaceutical development which takes 7 to 10 years and costs hundreds of millions of dollars. TPP is a tool that will help you plan and therefore increase your odds of success.

The TPP concept was introduced in 1997 in a draft guidance document from FDA<sup>5</sup>. TPP originated from a Clinical Development Working Group composed of representatives from the FDA and the pharmaceutical industry that sought ways of improving industry and FDA interactions. The group recommended the use of a "template" that summarizes drug labeling concepts to focus discussion and understanding between FDA and the company. The purpose of the TPP was to begin with a goal in mind and use the TPP to convey the overall intent of the drug

development process. In this case the goal was the final product labeling that would be submitted in the New Drug Application (NDA) or the Biologics License Application (BLA) from the company to FDA. The objective of the TPP was for the company and the FDA to work backwards from the desired product labeling using the TPP document to guide preclinical and clinical research.

Although the initial TPP guidance document was focused on product labeling and studies required to support label claims, regulatory agencies and the some pharmaceutical companies recognized TPP as a tool which can be used to clearly define all aspects of the development pathway for drug development from start to finish. This tool can be applied to pre-clinical and safety studies, clinical development, marketing development and the development of a quality system. Everyone on the development team should have the final goals of the project in mind as they plan their own activities. The TPP can be a powerful tool even during drug discovery, which is the earliest start of the R&D process, because discovery scientists often become so involved with the interaction between potential drug candidates and specific targets that they forget to consider critical features of the final product. A TPP keeps researchers focused on the endgame - a pharmaceutical product that will be taken by a patient. ICH Q8(R1)<sup>4</sup> recommends the following five major elements as a minimum in pharmaceutical development:

1. Defining the target product profile as it relates to quality, safety and efficacy, considering for example the route of administration, dosage form, bioavailability, dosage, and stability.
2. Identifying critical quality attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled.
3. Determining the quality attributes of the

drug substance, excipients etc., and selecting the type and amount of excipients to deliver drug product of the desired quality.

4. Selecting an appropriate manufacturing process.
5. Identifying a control strategy.

A well-written TPP can serve as an excellent briefing document for internal meetings, development partners and with regulatory agencies. It is a multidisciplinary tool and includes detailed information about drug manufacture, safety, pharmacokinetics, pharmacodynamics, and statistics. Regulatory agencies can easily assess the development strategy for a product and provide accurate advice on whether the strategy will satisfy all necessary requirements for registration<sup>5</sup>. To regulatory agencies the target product profile forms the basis of the overall design for the development of the drug product<sup>4</sup>.

The TPP concept has also been used by non-profit organizations to define their goals and objectives for product development of drugs for neglected diseases. These TPPs detail acceptance criteria for early stage projects and the ultimate goals for commercial products. Examples include the World Health Organization ("WHO") that developed a TPP to define its goals for development of pneumococcal vaccines<sup>7</sup> and One World Health that published a TPP to define its goals for the development of drug products to treat acute secretory diarrhea.<sup>8</sup>

Used properly the TPP can play a central role in the entire drug discovery and development process. This role includes (1) optimization of drug candidates (2) design of clinical research strategies, (3) decision-making within the organization, and (4) constructive communication with regulatory authorities<sup>5</sup>. A TPP can also be used as part of the development of a quality system. A Quality Target Product Profile ("QTTP") is a very useful and important tool during development of the Chemistry, Manufacturing and Control ("CMC") section

of a regulatory submission. A QTPP is valuable not only in the development of a new chemical entity, but also for a generic drug product and in life cycle management. The focus of this article is on the QTPP, however, the discussion is relevant to the use of a TTP in other areas of pharmaceutical development. A QTPP is a detailed prospective, dynamic, living document enlisting all the key quality product characteristics from early dosage form design through product launch and ongoing commercialization. The QTPP is the road map to design and develop a drug product with the desired safety, efficacy and quality profile.

Specific key elements of a QTPP include the following:

- Dosage form/strengths and route(s) of administration, rate of administration, and desired in vitro and in vivo release of the drug.
- Phase 1 study results on tolerance, absorption, clearance, and bioavailability and other pharmacokinetic parameters.
- Phase 2 and 3 study results including the minimum efficacious dose (new strength/size), patient/clinician feedback (e.g convenience), and adverse events.
- The clinical condition to be treated (e.g. acute versus chronic, severity of the condition and target duration of treatment)
- Target patient population (e.g. age, sex, general health, mental awareness, and any cultural factors) Drug product quality criteria appropriate for the intended marketed product including product specifications, stability data and proposed expiration date.
- Manufacturing information including any specialized processing equipment requirements and the site(s) of manufacturing.
- Product packaging information including descriptions of the primary and secondary packaging components and the packaging sites.

The QTPP document should contain the following general sections which are common to all products under development:

## Objectives:

To drive strategic alignment between R&D, Operations, Quality, and Commercial in the product development cycle and provide a strategic roadmap for executing manufacturing operations throughout product development lifecycle.

## Goals:

To establish a mechanism to formally and consistently define and achieve an up-front development & manufacturing strategy.

Capture and gain agreement on development and manufacturing strategy.

## Benefits:

By using the QTPP, the following benefits are desired:

- All stakeholders are informed, understand and agree to project goals early in development
- Establishes a "baseline" for the strategy on manufacturing operations
- Provides a single source to go to for strategic direction
- Leads to successful and timely development of the commercial product that meets commercial expectations
- Provides a mechanism to document changes in a product profile and the impact of any changes on the overall goals of the project
- Optimizes resources and provides direction
- Provides a tool/process to align Technical Teams to create a roadmap for execution

To provide an overall picture of a QTPP, we have generated a model QTPP for a hypothetical oral tablet formulation (XYZ 50 & 100 mg) which is presented below. This is just an illustration to provide a template for QTPP and the information should not be used for any real application.

## Model Quality Target Product Profile for XYZ 50 & 100 mg Tablets

### Target Product Profile for XYZ 50 and 100 mg Tablets

**Scope:** 50 mg and 100 mg tablet strengths

#### Section 1. Recommended Timing:

The target date for completion for both strengths is January 1, 2011

The Project Team is composed of the following representatives

- Mr. A from manufacturing
- Ms. B from Quality Control
- Mr. C from Marketing
- Dr. D from R&D etc.

#### Section 2. Clinical Target Profile

- Indication: Treatment of general pain
- Clinical pharmacology/ pharmacokinetics:  
Mode of action: CNS  
Biological half life: 6.5 hrs  
Oral bioavailability: 70%

Metabolism: primarily by conjugation with about 50% of the drug excreted unchanged

Cmax: 30 minutes

Food effect: none

- Efficacy: The phase III dose was 100 mg once daily, with or without food.
- Safety: The main adverse reactions in patients taking 100 mg were nausea, dizziness, and decreased appetite.

#### Section 3. Regulatory Assessment

- Registration of the 50 and/or 100 mg XYZ tablet will require regulatory approval in all markets.
- New Quality Risk Management (QRM) and Quality by Design (QbD) documents will be developed and approved.
- The current specifications and Critical Quality Attributes (CQAs) have been established
- Stability plan: three batches of each strength with a minimum of 3 months accelerated and long term data to support desired expiration date of 24 months.
- BSE/TSE: All raw materials used for manufacture are of non-animal origin, meeting corporate BSE/TSE requirements.
- Regulatory Risk Assessment/Mitigation Plan: Reduced shelf life approved due to limited stability data (i.e. 3 or 6 months) provided in submission. Obtain FDA agreement to provide additional stability data during the review period (i.e. 6 months) and request a 24 month shelf life. Confirm implementation of extended shelf life based on real time data obtained on 3 commercial scale batches in the submission.

#### Section 4. Target Markets, Filing Plans and Anticipated Approval Timing

Submission strategy for the XYZ 50 and 100mg will be

Country	Filing Target	Approval Target
USA	1Q2011	3Q2012
Japan	2Q2001	4Q2012

#### Section 5. Drug Product/Drug Substance

Active Pharmaceutical Ingredient (API) Characterization:

- **Solubility & Permeability:** BCS Class II (high solubility and low permeability)
- **Polymorphism:** Two different crystalline forms with Form 1 being the preferred.
- **Chemical Stability:** extremely stable drug substance at ambient and accelerated conditions
- **Particle Size:** The particle size distribution of the API received from Chemical Development generally varies from 10 to 50 microns in diameter.

### Phase III Formulation

Exipient	Standards	Functions
Lactose monohydrate	USP/NF, PhEur	Diluent
Magnesium stearate (vegetable grade)	USP/NF, PhEur	Lubricant
Microcrystalline Cellulose	USP/NF, PhEur	Diluent
Povidone	USP/NF, PhEur	Binder
Opadry OMB*	Non-compendial	Coating agent

\*50 mg tablet - light pink

\*100 mg tablet - dark pink

### Section 7. Technology Platform

- Wet granulation technology platform with moisture barrier coating
- Manufacturing unit operations include dry blending, wet granulation, lubrication, compression and aqueous film coating
- Critical process parameters and critical quality attributes will be evaluated as part of QbD studies including formulation/process range studies and confirmation of Critical Quality Attributes

### Section 9. Stability

API considerations:

Three batches of XYZ drug substance, manufactured by Chemical Ltd., have completed stability testing at:

- 36 months at 25 C/60% RH
- 6 months at 40 C/75% RH conditions
- One batch was also exposed to ICH Option 2 light conditions
- Batches were tested for physical appearance and description, identification (IR), strength and purity (by HPLC), water (by KF) and crystallinity.
- All tests results were satisfactory and within specifications with no changes noted over time at any storage condition.

### Clinical Trial Supplies:

The 2 batches of 50 and 100 mg tablets used in phase I, phase 2a/2b have been on stability for 18 months. All results are within stability limits with no changes noted over time at any storage condition. Primary package: HDPE bottle and cap.

The 2 batches of 50 and 100 mg tablets used in phase III studies were packaged in HDPE bottles and caps as well as in PVC/PVDC blisters. Samples were tested at 3 months under accelerated conditions (40C/

75%RH) and up to 6 months at Climatic Zone II (25C/60%RH). All tests results were satisfactory and within specifications with no changes noted over time at any storage condition.

### Section 10. Proposed Commercial Trade Dress:

Round light and dark pink color scored round tablets with XYZ engraved on one side and strength on the other side.

### Section 11. Packaging

*Bottles*

- 60cc HDPE Bottles (50 mg and 100 mg) - 30 and 90 count tablets
- 28 mm DPG Closures

*Hospital Unit Dose*

- 250 micron PVC/PVDC film, clear
- 25 micron paper-backed soft foil
- 3" x 1.5" Inserts
- Blisters are sized at 115 x 70.55 mm.
- Full prescribing information leaflet is placed into inside pocket of card

*Blisters*

- 250 micron PVC/PVDC film, clear
- 20 micron hard-tempered foil
- Blisters are sized at 63 x 109 mm globally; 14-count blister is configured in 5-4-5 pattern
- Cartons are sized at 116 x 68 x 27 mm

### Section 12. Tentative Cost of Goods

Current projections for cost of goods (COG) for drug product are acceptable.

Material costs, direct labor and overhead costs were considered in cost of goods analysis. Production standards for current commercial strengths were used as reference for determination of labor and machine hours for 50 and 100mg. No specialized equipment or material handling conditions are required for this product.

### Section 13. Commercial Site Selection

To be manufactured and sourced from both the Palo Alto, California and Puerto Rico sites

In conclusion, a TPP is an important document in the drug development process, which can serve as an excellent briefing document for meetings with regulators and to keep track of development strategy internally. It is a living document and should be updated on an ongoing basis to reflect the current status of product development.

A QTPP is a prospective and dynamic

summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and hence the safety and efficacy, of a drug product is realized. An example of a QTPP for solid oral tablets was illustrated. A similar QTPP can be developed for other dosage forms.

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