Emerging Life Sciences Series

MaRS | ENTREPRENEUR WORKBOOKS

Defining Your Target Product Profile: Therapeutics

MaRS is a member of ONE Ontario Network of Entrepreneurs

Introduction

What is a target product profile?

A target product profile (TPP) is a key strategic document that provides a summary of the following:

- the product under development
- the product's desired characteristics and features
- the studies and activities that must be completed to demonstrate the product's performance, efficacy and safety
- the features of the product that provide a competitive advantage

A well-designed TPP provides a structure to ensure that a company embarks on a product development program that is efficient and yet defines a listing of all relevant medical, technical and scientific information required to reach the desired commercial development outcome. Historically, the US Food and Drug Administration (FDA) developed the concept of a TPP to facilitate the communication strategy regarding a particular drug development program. However, many of the objectives provide sound guiding principles for the development of diagnostic products or medical devices.

Benefits of a TPP

If used properly, a TPP can help address issues early in the product development process and prevent late-stage development failures. A TPP also provides various parties and stakeholders (e.g., management, board members, employees, advisors, investors, regulatory authorities, strategic partners) a clear statement of the desired outcome of the product development program. This can be used later to help assess elements of the process and track progress. The TPP is a dynamic strategic document that should be revisited during the course of development. Much of the information discussed in the TPP should be incorporated into your business plan.

A TPP serves as a:

- strategic planning tool
- communication tool for discussions with regulatory authorities
- communication tool for discussions with investors, partners, employees and other stakeholders
- tool for communicating, supporting and tracking changes during the lifecycle of the development program

The FDA document was specifically developed for therapeutic products to provide a format for discussion between a sponsor and the FDA. It was designed for use

throughout the entire drug development process, including pre-investigational new drug application (pre-IND); investigational new drug application (IND); phases I, II and III of drug development; post-marketing programs; and the pursuit of new indications or other substantial changes in labelling.

Read the FDA's document, "Guidance for Industry and Review Staff: Target Product Profile—A Strategic Development Process Tool." *You can view it at http://tinyurl.com/2cky5d6.*

This workbook will help you put together a *modified* TPP for therapeutic products (mTPP-Rx); the goal is to provide early-stage companies and new entrepreneurs with a streamlined version of the FDA's TPP as well as experience in preparing such a technical document.

While a full TPP includes up to 17 different sections, the MaRS mTPP-Rx features seven key sections. The mTPP-Rx zeroes in on the following areas:

1. Indications and usage
2. Dosage and administration
3. Contraindications
4. Adverse reactions
5. Clinical pharmacology
6. Non-clinical toxicology
7. Clinical studies

These seven sections were selected based on their importance when developing a business plan. Several sections provide opportunities to describe the key differentiating features and competitive positioning of your product. The focus on competitive positioning will assist your company in communicating the value proposition as you embark on raising capital and preparing for strategic discussions with partners.

How to use these workbooks

1. Make it a team exercise—but make it quick!
We believe that much of the information you need is already known to your management team and advisors, so we recommend that you make the creation of your mTPP-Rx a team effort. Remember, time is of the essence for high-tech start-ups; we encourage you to complete the workbook template thoroughly yet efficiently. The first version of your mTTP-Rx should be no longer than eight to 12 pages. Use bullets and lists to speed your work.

2. Record and test your assumptions
As you go through the exercises, record and highlight key assumptions. Identify

assumptions that will be tested (and validated or invalidated) through further market research, as well as assumptions that will be tested through pre-clinical or clinical studies.

3. Use the icons for help
The MaRS workbooks are structured under the assumption that this is the first time you, the reader, has undertaken an exercise in of this nature. To help provide context for some of the ideas in these workbooks, we have clarified the ideas by defining key terms and offering real-world examples. In addition, we have provided links to articles provided by MaRS through the Entrepreneur's Toolkit. For this reason, you may find it easiest to use these workbooks on a computer with an Internet connection.

Look for these icons:


denotes a key industry term that will recur in these workbooks


indicates an example drawn from a real-world business in order to illustrate an important idea


denotes a link to a more in-depth online article


appears wherever you are asked to record something while completing the exercises

Before you start

The following six steps will help you gather the data you need in order to start these workbook exercises.

1. Broadly list all the potential indications and usages of your proposed therapeutic. Rank the indications and select an initial indication. The selection of the initial indication is one of the most critical strategic decisions for an early-stage therapeutic development company. Criteria to consider when selecting the initial indication include:

    a. Will the indication validate the product's clinical benefit(s)?
    b. Will the indication clearly demonstrate a competitive advantage?
    c. Does the indication provide an efficient path to regulatory approval?
    d. Does it lay the foundation for leveraging expanded clinical indications in the future?
    e. Does the indication target a real market opportunity with revenues that will support the company's future growth?

While you may not be able to answer all of these questions initially, the exercise of defining a TPP provides a structured platform to test the initial indication against key metrics.

2. Once you have selected an initial indication, identify the competitive products indicated for the same conditions. Contact your MaRS advisor for assistance. MaRS has access to Life Science Analytics' MedTRACK database, which can retrieve lists of potential competitor therapeutics at various stages of development. Research your competitors based on disease indication, mechanism of action, chemical or biological class, or a combination of disease and mechanism of action. Results can be filtered by the phase of the clinical trial.

3. After collecting the names of currently approved products that target the indication, navigate to the Drugs@FDA section of the FDA website at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. The site allows you to search drugs and therapeutics by drug name, active ingredient or application number. Searching for a specific drug will allow you to view therapeutic equivalents, approval history, letters, reviews and related documents, and, perhaps most importantly, label information. The label information is the same as what is included with the package insert for prescription drugs and therapeutics. By convention, it provides information concerning indications and usage, dosage and administration, contraindications, adverse events, clinical pharmacology, pre-clinical toxicology and clinical experience. (These seven key areas comprise the mTPP-Rx.)

4. Review a number of competing products [see above] and highlight the areas where these competitive products have limitations and where your product is designed to offer improved benefits.

5. Determine the pre-clinical and clinical studies needed to demonstrate your competitive differentiation. Even if you don't yet have a complete clinical development plan, we recommend you outline how many trials you will need, the anticipated outcome from those trials and a prospective development timeline.

Note that the above approach applies to potential therapeutic treatments where competitor products exist. Nevertheless, creating an mTPP-Rx for an orphan drug indication is a worthwhile exercise as it will help you organize your thoughts, outline the studies and clinical trials you will have to undertake, and define milestones related to fundraising.

WORKBOOK:
Defining Your Target Product Profile: Therapeutics

1. Indications and usage

In completing this section of the mTPP-Rx, you will create a concise summary of the proposed product. This section is not about a technology platform or broad descriptions of opportunities across a range of indications and diseases. In response to the following questions, keep your answers brief and focused:

- What is the drug product?
- Is it for treatment or prevention?
- What disease/condition does it target?
- Who are the target patients?

In the corresponding section of the workbook template, write one or two brief sentences in response to the questions above. List assumptions and studies that will validate (or invalidate) the assumptions.

On the following page, review the example of Genentech's Herceptin® with regard to indications and usage.

Example: Indications and usage—Herceptin®

The pharmaceutical company, Genentech, has developed a highly successful breast cancer drug called Herceptin.

The indication and usage section for Herceptin reads, "Herceptin is a HER2/neu receptor antagonist indicated for the treatment of HER2 overexpressing breast cancer."[1]

Herceptin is a monoclonal antibody targeting HER2 and had been shown, in both *in vitro* assays and in animal studies, to inhibit proliferation of human tumours that overexpress HER2. Appropriately, Genentech focused the clinical development program for Herceptin by targeting the HER2 overexpressing sub-population of breast cancer patients, which represented about 25% of all breast cancer patients.

The initial labelling for Herceptin was limited to the treatment of women with metastatic, HER2 overexpressing breast cancer. Following FDA approval for the narrower indication of metastatic breast cancer, Genentech completed additional studies that demonstrated the clinical benefit in the adjuvant setting as well. The combination of the two studies significantly expanded the market for Herceptin and provided the basis for a broad-label indication for a targeted patient population.

[1]*Source:* http://www.gene.com/gene/products/information/pdf/herceptin-prescribing.pdf

Consider the following points (if applicable) with regard to your own product:

- Does your proposed indication meet an unmet medical need?
- Will the target indication require any pre-clinical studies, such as carcinogenicity, that might significantly delay time to market entry?
- If you are pursuing an orphan indication, have you considered the challenges associated with enrolling a sufficient number of patients in the required clinical development studies? Do you have plans to mitigate the risk?
- How might the first clinical indication offer an opportunity to gain early initial approval of the drug?
- Will you be able to leverage the first successful approval and expand the market to additional indications?

Review the example of Amgen's Vectibix® with regard to indications and usage.

Example: Indications and usage—Vectibix®

The pharmaceutical company, Amgen, has developed Vectibix to treat colorectal cancer.

The indications and usage label for Vecitibix reads, "Vectibix® (panitumumab) is indicated as monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens."[1]

Vectibix provides an example of the increasing importance of biomarkers in targeting drugs and the importance of patient selection in the emerging era of personalized medicine.

In the case of Vectibix, not only must the cancer be overexpressing EGFR (the target) but a secondary marker (non-mutated [wild-type] KRAS) must also be confirmed prior to treatment of the patient. The phase III clinical studies had clearly demonstrated that Vectibix has no effect on progression-free survival in patients with KRAS mutant tumours, but a positive effect in patients with tumours bearing the non-mutated KRAS.

More recently, Amgen has reported that mutations in NRAS, another member of the RAS gene family, are also associated with lack of response to Vectibix, suggesting further refinements to patient selection for optimized response.

[1]*Source:* http://pi.amgen.com/united_states/vectibix/vectibix_pi.pdf

Consider the following points (if applicable) with regard to your own product:

- How well characterized is the mechanism of action of your therapeutic product?
- What biomarkers could be used to select the most likely responders to the new therapeutic?
- Will there be a companion diagnostic required for the new drug?

2. Dosage and administration

Doses can be prepared with varying amounts of active ingredient in various formulations, and can be administered by a wide variety of routes including non-invasive strategies such as oral, transdermal, transmucosal and pulmonary inhalation, or invasive strategies such as intravenous, subcutaneous or intramuscular injections.

Dosage and administration can offer significant opportunities to develop a competitive strategy or a series of line extensions for a new therapeutic product.

Multiple formulations can be beneficial; however, in selecting the first formulation, choose something that will demonstrate efficacy with limited risk of causing side effects though the chosen route of administration.

In your development program, select the route of administration that offers the best balance for rapid market entry and acceptable market adoption risk. Options for alternative routes can be used as line extensions; however, the most convenient route might not be required for first approval and first market entry if your product is clearly superior in other clinical areas.

In completing this section of the mTPP-Rx, you will create a concise summary of the proposed dosage and administration. In response to the following questions, keep your answers brief and focused:

- How much drug is required?
- How is it administered?
- How often is the treatment?
- What is the duration of treatment?

In the corresponding section of the workbook template, write one or two brief sentences in response to the questions listed above. List assumptions and studies that will validate (or invalidate) the assumptions.

On the following page, review the example of Roche's Boniva® with regard to dosage and administration.

Example: Dosage and administration—Boniva®

Roche has developed Boniva, a product for the treatment of osteoporosis in postmenopausal women. It is available as an oral tablet to be taken once a day, as an oral tablet to be taken once a week, and in an intravenous form to be administered once every three months.

While patients might prefer daily or monthly oral administration, dosing instructions for oral administration require the following:

- the tablet must be taken 60 minutes before the first food, beverage or medication of the day
- patient may only drink water for 60 minutes after taking the tablet
- patients must not lie down for at least 60 minutes after taking the tablet

In contrast, the quarterly intravenous product is positioned as a quick 15- to 30-second route to administer medication that eliminates the need for pre- and post-dose fasting. It also provides an attractive alternative to patients with difficulty swallowing or those who suffer gastrointestinal side effects with the oral form.

[1]*Source:* http://www.gene.com/gene/products/information/boniva/pdf/pi.pdf

For the clinical indication selected for your new therapeutic product, review the current therapeutic offerings and their routes of administration. Determine if the administration route for your product is:

i. similar (no change in clinical practice)
ii. more convenient (offering a significant competitive advantage)
iii. more complicated or more invasive

If your product falls into the third category above, you will need to identify other benefits of the product (greater efficacy, improved safety) that will mitigate the perceived risk of market adoption.

3. Contraindications

A contraindication is a symptom or condition that makes a particular treatment or procedure inadvisable.[1] The FDA's TPP guidance document lists situations in which the drug might be contraindicated that include "increased risk of harm because of age, sex, concomitant therapy, disease state"; other "adverse reactions which would limit use"; and "known, not theoretical, hazards."

Even in early stages of development, it is possible to identify patients who might be harmed if treated with the drug. This information can be determined from an understanding of the mechanism of action, an understanding of class effect (if the new drug belongs to an existing class of drugs) or toxicity studies that identify potential risk factors.

In completing this section of the mTPP-Rx, you will address and provide a concise response to the following question: Which patients should not be treated with this drug?

In the corresponding section of the workbook template, write one or two brief sentences in response to the question above.

On the following page, review the examples of Lipitor® and Accutane® with regard to contraindications.

1Medline Plus. (2009, February 23). *Contraindications*. Retrieved January 3, 2011, from http://www.nlm.nih.gov/medlineplus/ency/article/002314.htm.

Example: Contraindications—Lipitor® and Accutane®

- Lipitor, Pfizer's blockbuster drug for lowering cholesterol, is contraindicated for use in patients with active liver disease, and for pregnant and lactating women.[1]

- Accutane (isotretinoin) is a prescription medication marketed by Roche and others and indicated for severe recalcitrant nodular acne. It is contraindicated for female patients who are or may become pregnant, as there is "an extremely high risk that severe birth defects will result if pregnancy occurs while taking Accutane in any amount."[2]

Sources:

[1] http://www.pfizer.com/files/products/uspi_lipitor.pdf

[2] http://tinyurl.com/2cbycf6

Consider the following points (if applicable) with regard to your own product:

- Which patients might be harmed by your product? This information will inform decisions on which patients to exclude from upcoming clinical studies, and will mitigate the risk of generating adverse events in future clinical studies.
- Can you identify any contraindications that might be due to your drug's mechanism of action or its metabolism?
- Are there any base therapies that may interfere with your proposed therapeutic, and could these base therapies constitute a contraindication?
- Have you checked the product monographs of similar products or product classes to identify potential contraindications?

4. Adverse reactions

An adverse reaction is a result of drug therapy that is neither intended nor expected in normal therapeutic use and that causes significant, sometimes life-threatening, conditions. Adverse reactions are considered side effects, and can be observed in some subset of a population undergoing treatment. The objective of therapeutic development programs is to minimize the incidence of adverse reactions while maximizing therapeutic benefit.

In completing this section of the mTPP-Rx, you will create a concise summary of the possible adverse reactions associated with your product. In response to the following questions, keep your answers brief and focused:

- What adverse effects might be anticipated based on results of pre-clinical studies?
- What adverse effects might be expected due to drug class?
- What adverse reactions have been observed in clinical studies?

In the corresponding section of the workbook template, write one or two brief sentences in response to the questions listed above. List any assumptions and studies that would validate (or invalidate) the assumptions.

Review the example below of Bayer's Precose® with regard to adverse reactions.

Example: Adverse reactions—Precose®

Adverse events do not need to be life-threatening but might contribute to poor compliance with a drug therapy and render therapy ineffective. For example, during clinical trials, patients treated with Precose (a drug developed by Bayer Healthcare Pharmaceuticals and indicated as an adjunct to diet and exercise for patients with type 2 diabetes) experienced significant gastrointestinal symptoms, including abdominal pain (19%), diarrhea (31%) and flatulence (74%). These gastrointestinal effects were a manifestation of the mechanism of action of Precose. Bayer provides guidance on dietary strategies to mitigate the side effects, but if the prescribed diet is not observed during treatment with Precose, the intestinal side effects may be intensified.

Source: http://www.drugs.com/pro/precose.html

Review potential side effects based on your drug's mechanism of action, its metabolism and animal toxicity profile, and, for targeted therapeutics, the expression of the target on specific organs or tissues. Evaluate the potential side-effect profile of your new therapeutic drug and make sure to continuously update this section of your mTPP-Rx (and later your TPP).

Consider the following points (if applicable) with regard to your product:

- What are the adverse event profiles listed in product monographs of competitive products and products of the same class? Identify potential opportunities for your product to reduce the incidence of adverse events.
- What are acceptable thresholds for the incidence of adverse events based on benefit/risk ratios and the precedent(s) from existing therapeutic strategies?
- Are there any opportunities to demonstrate a superior safety profile for your new therapeutic product?

5. Clinical pharmacology

Clinical pharmacology includes mechanism of action, pharmacokinetic information, distribution and pathways for transformation.

Clinical pharmacology offers multiple opportunities for product differentiation and competitive advantage. The elements of clinical pharmacology are usually the subject of extensive pre-clinical research and early phase I clinical development.

In completing this section of the mTPP-Rx, you will create a concise summary of the clinical pharmacology of your proposed product. In response to the following questions, keep your answers brief and focused and list the related studies (completed or planned):

- What is the mechanism of action?
- How fast does the drug reach the target organ(s)?
- How is the drug distributed through the body?
- How long does the drug persist?
- How is the drug cleared from the body?

In the corresponding section of the workbook template, write one or two brief sentences in response to the questions listed above. List assumptions and any studies that will need to be completed to support those assumptions.

An important aspect of clinical development is to ensure that clinical pharmacology is aligned with the desired clinical outcome. Improvements in any aspect of the clinical pharmacology can provide a competitive advantage. On the following page, review the examples of Zomig® and Frova®.

Examples: Clinical pharmacology—Zomig® and Frova®

Both zolmitriptan (Zomig, marketed by AstraZeneca) and frovatriptan (Frova, marketed by Endo Pharmaceuticals) belong to a class of drugs called triptans that are indicated to treat migraine headaches. Both drugs are available in oral doses of 2.5 mg. Upon administration, frovatriptan takes approximately three hours to reach maximum blood plasma concentration, whereas zolmitriptan reaches maximum blood plasma concentration in half that time.[1] All else being equal, a patient suffering from a migraine would likely prefer a treatment that is absorbed, and thus potentially effective, in a shorter period of time.

Source: http://www.drugs.com/pro/precose.html

Consider the following (if applicable) with regard to your product:

- What are the limitations (if any) of competitive treatment modalities?
- Is there a need to formulate the drug to increase the onset of action or increase the duration of action to benefit the patient or decrease drug interactions?
- Does the mechanism of action offer more selective treatments with better efficacy and potentially fewer side effects?
- Which studies characterize and potentially differentiate your new therapeutic product from existing or competitive products in development?

6. Non-clinical toxicology

Clinical trials alone cannot always assess the potential long-term effects of a therapeutic on a person, and thus regulatory bodies rely on animal study data to assess a treatment's long-term carcinogenicity, mutagenicity or its effect on reproduction or cardiovascular and respiratory systems. Regulatory agencies have developed specific guidance documents related to core toxicology studies. The sequencing of these studies must be carefully planned to ensure that they are appropriately completed for different stages of clinical development. A core group of studies is required prior to the first-in-human study. Make sure that you are familiar with the requirements for your selected indication and that you identify the key studies required for various stages of clinical development.

Read more about toxicology requirements for clinical studies.

In completing this section of the mTPP-Rx, you will create a concise summary of the non-clinical toxicology of your proposed product. In response to the following questions, keep your answers brief and focused and list the related studies (completed or planned):

- What is the safety profile of the drug based on cells, tissues and organ systems assessed through *in vitro* and *in vitro* animal studies?
- What is the maximum tolerated dose in animals?
- What would be a safe starting dose in human studies?
- What are the effects of long-term exposure?

In the corresponding section of the workbook template, write one or two sentences in response to the questions listed on the preceding page. List any assumptions and the studies that will validate (or invalidate) those assumptions.

While a variety of animal toxicology studies are listed as requirements for a marketing application, not all studies are required to gain approval for all indications.

For example, drugs intended for acute use in life-threatening indications might not require carcinogenicity studies. The anticipated duration of treatment in clinical practice will also dictate the recommended duration of repeated-dose toxicity studies to support various stages of clinical development and, ultimately, the marketing of the product.

Consider the following (if applicable) with regard to your product:

- If your new product offers an opportunity for an enhanced safety profile as a result of a novel mechanism of action or a highly targeted therapeutic, what is the non-clinical study that would support the hypothesis? What comparator drug will you use as a control arm in your toxicology studies?
- What GLP (Good Laboratory Practice) non-clinical studies are required for different stages of clinical development for your target indication?
- What is the anticipated duration of exposure to your new drug in the target clinical indication? Does your plan include the appropriate non-clinical toxicology studies?
- Do the non-clinical studies address specific questions and concerns that may be related to your drug? Recognize that standard GLP toxicology panels might not suffice to address specific questions and that more specialized animal models or analytics might be required.

7. Clinical studies

For regulatory approval, clinical studies must demonstrate a drug's efficacy by achieving a statistically significant improvement compared to a placebo, while also achieving an acceptable safety profile. Ideally, design studies so that they demonstrate a statistically significant improvement over the existing standard of care. These active comparator studies require careful planning and are not usually undertaken as initial studies. However, active comparator studies, if successful, provide compelling evidence and accelerate market adoption of the product.

The design of clinical trials to support the marketing submission requires very careful planning and strategic consideration. These studies often incur great expense and can make or break a development program. Investment of time and resources into the design process is key to success, and clinical advisory boards, comprised of experienced clinical researchers, can provide strategic and tactical guidance. Suggestions from advisory boards should be reviewed and aligned with the requirements set forth by various regulatory agencies.

In completing this section of the mTPP-Rx, you will create a concise summary of the proposed studies in relation to your proposed indication and usage. In response to the following questions, keep your answers brief and focused:

- What is the clinical evidence to support the indication claims?
- How strong is the evidence?
- What is the safety profile?
- How will the endpoints in the study support the competitive positioning and marketing strategy for the new drug?

In the corresponding section of the workbook template, create bulleted summaries in response to the questions listed above. List any assumptions and studies that will validate (or invalidate) the assumptions.

Read about the following:

- *the key aspects of developing a regulatory strategy*
- *the clinical trial application process in Canada, the US and the EU*
- *the application process for the approval of a new drug in Canada, the US and the EU*

Consider the following and implement as applicable in the design of your clinical studies:

- Plan carefully, as a poor design of clinical trials can significantly delay the development of even the most promising drugs.
- Invest time and effort to review clinical studies that have been completed and reported for competitive products.
- Review the Summary Basis of Approval (SBA) for competitive products. These SBA reviews are available through the FDA and provide a wealth of information on the strengths (and weaknesses) of various clinical development programs.
- There are many guidance documents available on major regulatory websites (e.g., EMA, FDA). Some are specific to therapeutic areas of development.
- Seek guidance from statisticians to ensure that your studies will include sufficient numbers of patients to demonstrate the selected endpoints.
- Consider meeting with regulatory authorities to discuss the clinical development of your product. This is an option any time prior to your first-in-human study and also at the end of phase II.
- Select and include endpoints that not only will achieve regulatory approval but will differentiate the product from the competition and support your marketing efforts.
- Evaluate the viability of your path toward clinical development. For example, if your product is only minimally more effective than the standard of care, you will require thousands of patients (or multiples of thousands) to demonstrate this. Is this realistic? Bear in mind that differences in safety can be very difficult to validate statistically if the incidence of adverse events with existing drugs is low.