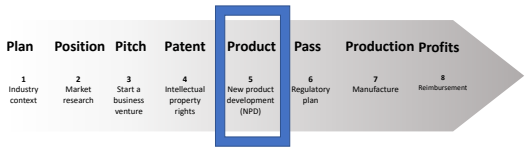

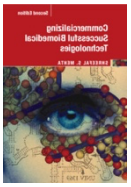

Chapter 5: Practical Tips on Product Development

Q. What is a target product profile (TPP) and how is it useful ?

- The TPP is a key document, capturing the value proposition of the proposed product, its market focused key characteristics and its regulatory strategy. This document is typically owned by the project leader or product manager but has inputs from regulatory, marketing, engineering/pharmacology, clinical, manufacturing etc.

- The TPP provides a framework that ensures that a company's product development program is efficient, by defining all relevant medical, technical, and scientific information required to reach the desired commercial outcome.

- Most important part of the TPP is the identification of the primary indication planned to addressed by the product.

- The TPP also defines key characteristics of the product and its development context – such as specific desired dosing characteristics (once a day vs thrice, oral vs injected, etc.)

- The TPP also specifies key claims or benefits (safety/ efficacy) over competitors or the existing standard of care (key differentiations), details mechanism of action, and finally lists the desired clinical outcomes or end- points for human trials for registration.

- Economic value of indication and claims are also usually included in the TPP, which can be thought of as a business plan for the product but with more technical details than might be typical of a business plan.

- To see sample outline of a TPP document, refer to Box 5.9 on page 187 of the book.

Q. What regulatory and ethical requirements will we need to fulfil in the path of developing a regulated product ?

- Animal studies - If you plan to have your own animal study facility, you will need to put together your Institutional Animal Care and Use Committee. This committee acts as an IRB for animals and reviews protocols for animal studies and needs to approve each study planned.

- Human studies - An Institutional Review Board reviews and approves any study protocol that involves interactions with human subjects. You will have to submit your clinical study design to an IRB at the clinical trial centers or a centralized IRB if the center accepts that. Rather than trying to appoint your own IRB, it is much more efficient to

work with the IRB at the clinical trial center or one of the professional IRBs (e.g. Western IRB). The IRB ensures the rights and welfare (safety) of the subjects participating in a clinical trial and it also verifies that the sponsor has obtained all necessary permissions from the FDA.

- Safety and OSHA – Appoint a safety officer for the company operations whose job it is to ensure a safe working environment for the staff and ensure compliance with OSHA regulations. In a laboratory built up by the company, it is useful to get an OSHA consultant to walk through and do a mock visit with reports provided to the company so they can fix issues before an actual OSHA visit happens. Check with your local government economic development group or small business association who might provide funding to have such consultants do a facility review.

Q. What pitfalls should I watch out for in product development ? What are common reasons for failure seen in the industry sectors of drugs and devices?

- ***Factors that prevent drug candidate molecules in development from reaching the market:***
    - Poor ADME characteristics – absorption, distribution, metabolism and excretion are all factors that influence the drug levels and kinetics of drug exposure to the tissues and hence influence the performance and pharmacological activity of the compound as a drug. For example, if the drug product is metabolized rapidly, then not enough of the drug will stay in circulation to have the desired effect. Many oral drugs show rapid clearance and thus very short half life in the circulation – modifications to the drug molecule or formulation are then considered and risk vs reward must be balanced at each step of product modification.

    - Lack of efficacy – this failure can occur during statistical evaluation of the clinical trial of efficacy in humans, but many compounds also fail in early development where the binding to the target has low potency or animal studies fail to show significant enough improvements. s

    - Toxicity – toxicity studies are critical to ensure safety of the patients and always must fall within the reasonable risk reward benefit of the drug product. Any toxicity expected from the target pathway perturbation must be investigated thoroughly,

    - Market or business reasons – market adoption sometimes fails to develop after approval of the drug. A recent example is Aduhelm, approved by the FDA for Alzheimers' but rejected by most of the prescribers and payers. Another example is inhaled insulin developed by Pfizer, which was taken off the market a year after it was approved by the FDA. (see book for details). Business reasons also

include lack of funding, strategic reasons eg. acquisition of another company with competing product or business decision to drop that therapeutic area from portfolio.

- ***Factors that prevent <u>medical devices</u> (all types) from reaching the market:***
    - Failed to meet efficacy – clinical trials in medical devices need careful design as control arms are sometimes difficult to achieve. Efficacy is determined also as improvements over current state of the art (competitors, alternatives) and increasingly, efficacy needs longer term clinical outcome measures, especially for success with payers.
    - Safety, toxicity or instability in device behavior/mechanics
    - Biocompatibility – e.g in one case while basic component materials tested as being biocompatible, a sharp corner in the product design resulted in adverse inflammatory reactions and fibrosis in the surrounding tissue. In general, note that material selection and supply chain quality control checks must be rigorously implemented and continuously monitored.
    - Business or market reasons

- ***Factors that prevent <u>in vitro diagnostics</u> from reaching the market:***
    - Lack of clinical utility – finding a new biomarker that shows a different reading in disease versus healthy subjects does not mean that there is clinical usefulness in that diagnostic test. Is the patient care or disease resolution significantly influenced as a result of this diagnostic?
    - Needed sensitivity/specificity of the assay not verified in subsequent clinical studies – reproducibility is at the heart of product development and many biological or environmental factors can influence the assay performance. Hence, good product development will carry out flexibility tests with failure risks paramount in mind
    - Repeatability and precision not achieved
    - Wrong test principle
    - Wrong test format
    - Test is too complicated versus existing format – just because the test can measure with greater sensitivity or accuracy does not mean it will fit into clinical flow. If the new test requires new behaviors of caregivers or patients, the benefit

must be significantly different or else caregivers will resist the new more complicated test format.

- Nonlinear response of assay in clinical use – when a larger variety of samples or wider range of testing conditions comes into the assay, linearity can be affected leading to incorrect interpretations of the readings. Here, again flex tests which look at assay outcome over wide ranges of conditions must be a part of assay development

- Patents are not comprehensive or valid