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Constructing target product profiles (TPPs) to help vaccines overcome post-approval obstacles

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Abstract

As history has demonstrated, post-approval obstacles can impede a vaccine's use and potentially lead to its withdrawal. Addressing these potential obstacles when changes in a vaccine's technology can still be easily made may improve a vaccine's chances of success. Augmented vaccine target product profiles (TPPs) can help vaccine scientists better understand and anticipate these obstacles and galvanize conversations among various vaccine stakeholders (e.g., scientists, marketers, business development managers, policy makers, public health officials, health care workers, third party payors, etc.) earlier in a vaccine's development.

Keywords

Vaccines; Development; Target product profiles; Market

1. Introduction

Although the majority of vaccines fail at the pre-clinical and clinical trial stages, reaching the market does not guarantee success; post-approval obstacles can impede a vaccine's use and potentially lead to its withdrawal. The underutilization or discontinuation of an important vaccine can have longstanding detrimental consequences to global health as well as waste valuable time and resources. Over the past several decades, post-approval obstacles have prevented some promising vaccines from achieving their full potential. As seasoned pharmaceutical executives will emphasize, a vaccine's technology must be good enough not only to garner approval but also to stay on the market and ensure adoption. Early in a vaccine's development when the market appears far away, it is tempting to focus on getting a vaccine past the next developmental and regulatory hurdle without fully considering how the technology will interact with all aspects of the future market. But early in development is also when a vaccine's technology is most adaptable to be tailored to the market. Many post-approval obstacles might have been surmountable had developers been able to anticipate the obstacles and adjust their strategies early enough in the development process.

To maximize a vaccine's chance of success, vaccine developers need to anticipate and formulate a strategic plan to overcome post-approval obstacles well before the vaccine hits the market. Biotechnological and pharmaceutical companies have long used target product profiles (TPPs) to plan their research and development processes [1]. The TPP is essentially an organized "wish-list" of characteristics, features, and attributes that one would like to see

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in a newly developed medical product once it reaches the market. This “wish-list” presents optimistic, realistic, and minimal goals for stakeholders in the drug development process and helps all stakeholders focus on the same aims and understand the potential end results of their efforts. The attributes in a traditional drug development TPP are usually limited to those seen in a typical drug label (e.g., target disease, mechanism of action, comparative efficacy, routes of administration, possible side effects, contraindications, etc.) but may not address many of the post-approval issues that have beleaguered vaccines in the past. Each vaccine characteristic can have a complex impact on vaccine adoption, distribution, and administration. Creating TPPs that incorporate how vaccine technological characteristics may interact with a wider array of strategic, marketing, operational, epidemiological, and public health market issues can lead to vaccines and vaccine strategies that are more likely to succeed and benefit everyone globally. Carefully constructed predictive models can offer important insight into how to best tailor vaccine characteristics and the accompanying strategic plan. With the increasing size of many vaccine developers and increased functional specialization, organizational barriers can prevent needed communication among people in pre-clinical and clinical development, marketing, business development, and safety. Understanding the vaccine market can help scientists involved in vaccine development better tailor their vaccines for commercial success. What follows are seven points to consider when putting together TPPs for future vaccine development, each derived from a vaccine that faced a different major post-approval obstacle.

2. Points to consider

2.1. Account for and engage all potential stakeholders early in a vaccine’s development

Whenever a new vaccine reaches the market, it enters into an “ecosystem” of many diverse stakeholders from the public and private sectors (e.g., physicians, physician groups, governments, non-governmental organizations, public health officials, insurance companies, and other manufacturers). The success of a vaccine depends on its place within this ecosystem and the cooperation and support of these diverse stakeholders. Failure to engage any one of these stakeholders could threaten a vaccine’s success or even doom it to failure, regardless of the vaccine’s technological merits.

2.1.1. Example: Merck’s Human Papilloma Virus (HPV) vaccine—Although Merck’s Gardasil has been a financial success since its approval for 9–26-year-old females in June 2006, its adoption has hit impediments. Gardasil was the first approved vaccine against HPV strains associated with cervical cancer, precancerous genital lesions, and genital warts. In 2007, Merck’s aggressive lobbying of state legislatures throughout the United States helped motivate 41 states and the District of Columbia to introduce HPV vaccine-specific legislation, such as mandating HPV vaccination as a condition for school entry, requiring insurance companies to cover HPV vaccine, or allocating state funds for vaccination or to promote awareness of the vaccine [2,3]. The intense legislative initiatives spurred a backlash against HPV vaccination, raising concerns that state governments were being coercive, overstepping their authority, and potentially infringing upon individual rights [4–6]. The sheer speed and urgency of the legislative movements only exacerbated concerns about the “Big Brother” government trying to control its citizens before adequate scientific, economic, and legal discourse occurred. Prior vaccination mandates (e.g., smallpox) had taken much longer times to pass. Critics contended that the HPV legislative initiatives were unconstitutional since HPV is not immediately life threatening, does not qualify as a public health threat, lacks a strong enough link to cervical cancer, is preventable by other means, and does not pose equal risk to all individuals [7]. HPV’s link to sexual behavior heightened concerns. Critics argued that HPV vaccination mandates violated the rights of parents to make choices for their children, promoted sexual promiscuity as

vaccinated females would falsely assume protection against all sexually transmitted infections, and discriminated against females since males did not have comparable requirements [8]. Merck's aggressive lobbying led many to believe that profit-making interests were superseding public health good and would divert already limited funds from other more important programs. Ultimately, mounting criticism convinced Merck to transition from active lobbying efforts to educational campaigns.

This experience highlighted the dangers of focusing on some while neglecting other stakeholders. In hindsight, moving too quickly and aggressively and focusing on State legislatures may have antagonized other stakeholders in the HPV vaccination ecosystem. More gradual and earlier engagement of stakeholders may have ultimately won their acceptance. When constructing a TPP, it is important to understand and project how a vaccine's technology may be received by different stakeholders. When possible, modifying characteristics based on stakeholder interests may facilitate acceptance. At the very least, anticipating different stakeholder responses can assist launch and marketing campaigns.

2.2. Forecast the effects of vaccine pricing

Determining a vaccine price is complicated with substantial short- and long-term adoption consequences. Although increasing a vaccine's price does not alter the number of people at risk for an infectious disease (i.e., true population demand is price inelastic), it may decrease vaccination compliance, potential purchaser interest, and third party payor coverage of the vaccine (i.e., realized population demand may be elastic) [9,10]. Of course, lowering the price per dose may erode a manufacturer's profits if demand remains unchanged [11].

2.2.1. Example: MedImmune's FluMist influenza vaccine—Pricing problems hampered adoption of FluMist, a live attenuated influenza virus intranasal vaccine. In May 2003, FluMist achieved FDA approval for healthy individuals between 5 and 49 years of age. MedImmune and its partner Wyeth were optimistic that its needle-free, painless nasal spray formulation would make FluMist very popular, especially among children. MedImmune and Wyeth projected initial year sales of 4–6 million doses, invested $50 million in marketing and advertising, and established a $40–$70 per dose price, over four times that of the intramuscular vaccine [12]. FluMist's first year on the market was a commercial failure with first year sales falling short of a quarter of initial projections [13]. Saddled with a massive unsold vaccine inventory, MedImmune eventually unloaded doses at deep discounts. Major insurers balked at covering the high-priced vaccine, and Wal-Mart canceled a plan to stock its stores with FluMist. MedImmune then severed ties with Wyeth in April 2004 and cut FluMist's price to $23.50 per dose for the 2004–2005 influenza season [14].

In retrospect, FluMist's technological advantages could not overcome its higher price and other market obstacles. Potential customers were particularly price-sensitive since a well-established alternative (inactivated influenza virus vaccines) already existed, influenza vaccination was not mandatory, and skepticism remained about a live virus vaccine's safety. The errant launch left MedImmune and FluMist reeling for several years, whereas a stronger first year could have catapulted them towards greater success, especially with the influenza vaccine shortages of 2004 and 2005. Sacrificing first year revenues by accepting a lower price may have secured a greater initial market share, which in the long-run may have facilitated adoption.

This experience emphasized the critical role of pricing in new technology adoption and why target prices may be an integral component of a vaccine TPP. Constructing comprehensive economic models early in a vaccine's development can help forecast the impact of different vaccine price points and establish appropriate target price ranges. Such models should

capture all the potential complex epidemiological, clinical, and operational effects of different pricing. While manufacturers usually construct pricing models prior to a vaccine's market launch, all stakeholders may want to construct, share, and compare pricing models earlier in a vaccine's development. Although establishing pricing targets early in a vaccine's development may raise concerns about price fixing, prices that impede adoption ultimately hurt manufacturers. Knowing price targets earlier in development may offer more time to overcome potential obstacles and warn important stakeholders. Ultimately, selling larger volumes of a lower priced vaccine trumps selling relatively small volumes of a higher priced vaccine.

2.3. Identify multiple potential purchasers

Identifying a vaccine's potential purchasers early in development can facilitate eventual market success. Depending on a single purchaser, even a large seemingly stable one, can place a vaccine manufacturer in a precarious position not only in the short-term but also in the long-term.

2.3.1. Example: Wyeth's adenovirus vaccine—From 1984 to 1999, the adenovirus type 4 and type 7 oral vaccine went from being an exemplary vaccine success story to disappearing from the market. In the 1970s and 1980s, the vaccine was highly successful in preventing the adenovirus outbreaks that plagued recruits in previous decades. The Department of Defense did not recruit additional manufacturers until 1984, when Wyeth requested additional funding to upgrade its facilities. When the Department of Defense denied Wyeth's request and then failed to secure additional manufacturers, the adenovirus vaccine became unavailable after Wyeth ceased production in 1996 and inventories were depleted in 1999 [15]. Soon after adenovirus vaccination ceased, morbidity and mortality among recruits rose [16]. A 1998 cost-effectiveness study estimated that adenovirus vaccine absence was costing $26.4 million a year [17]. Finally, in 2001 Barr Laboratories agreed to develop and ultimately manufacture adenovirus vaccine.

A TPP can help match vaccine technology with prospective purchasers and profile the characteristics that would attract different purchasers. What technological characteristics would make the vaccine more desirable to a larger range of purchasers? How important is the vaccine to each purchaser? How stable are the purchasers and their interests in the vaccine? Closer communication between those charged with business development and pre-clinical and clinical scientists can help bridge the gap between vaccine characteristics and prospective purchasers.

2.4. Establish a vaccine's target populations early in development

Clearly establishing a vaccine's target population early in vaccine development helps vaccine developers tailor their clinical development, marketing, and sales efforts to maximize a vaccine's chance of success. Nevertheless, policy makers frequently defer vaccine target population selection until seeing extensive clinical data, giving vaccine manufacturers little time to alter their strategy. Often, a vaccine is first approved and recommended for a limited target population, which expands only after additional efficacy and safety data is collected and reviewed. A vaccine that does not fare well in the initial target population may lose momentum and struggle to move to other target populations.

2.4.1. Example: GlaxoSmithKline's LYMERix Lyme vaccine—A vague target population impeded acceptance of SmithKline Beecham's LYMERix, which in December 1998 became the first marketed vaccine to prevent Lyme disease. The FDA approved its use for 15–70 year old individuals who live or work in grassy or wooded areas. Large trials showed the vaccine to be efficacious (76% and 92% protective efficacy after 3 doses) but

did not clearly establish the duration of protection. In 2002, poor sales prompted Glaxo SmithKline to voluntarily withdraw the vaccine from the market. Failure to identify a clearer target population than individuals living or working in grassy or wooded area contributed its demise. Additionally, the initially approved population did not include children 2–15 years old, who (along with adults aged 30–55) had the highest reported rates of Lyme disease. When introducing LYMERix, GlaxoSmithKline had emphasized direct-to-consumer marketing and had not fully engaged key physician groups and public health organizations to establish a consensus over the vaccine's target populations [18–20]. Without clear guidance on which age groups, geographic locations, and risk groups should have received the vaccine, many physician groups, and public health officials were lukewarm about promoting the vaccine and instead favored other measures such as tick control [21].

The target population is an important component of a TPP. Using epidemiological and clinical data, computer models and simulations can predict the impact of selecting different target populations and ones that start small but progressively grow in different patterns and schedules.

2.5. Understand the impact of vaccine technology on the vaccine supply chain

The vaccine supply chain is the series of steps and processes involved in bringing a vaccine from the manufacturer to the patient. Designing a supply chain and a vaccine that complement each other is vital to the vaccine's use and success. A highly efficacious vaccine is relatively worthless without reaching patients in a timely manner.

2.5.1. Example: Merck's RotaTeq and GlaxoSmithKline's Rotarix rotavirus vaccines—Despite addressing a great need, two oral live attenuated rotavirus vaccines (GlaxoSmithKline's Rotarix and Merck's RotaTeq) stumbled out of the gates when they reached the market and were introduced in Latin and South America in 2006–2007 [22,23]. This initial roll-out quickly revealed that the vaccines were too large for the cold chain. RotaTeq (798 cm^3 for a ten-dose box) and Rotarix (259.8 cm^3 for a one-dose box) occupied much greater storage volumes than most other vaccines, displacing other vaccines from already limited supply chain refrigerator space and forcing overburdened health care workers at the end of the supply chain to carry additional thermoses [24]. This unexpected problem forced Merck to develop a smaller version of RotaTeq.

A vaccine TPP could address how a vaccine may fit into various supply chains. Since designing and instituting supply chain changes can take years, projecting the interplay between the supply chain and vaccine characteristics early in a vaccine's development can help develop both in concert to complement each other.

2.6. Anticipate side effects and how their risk may change with time

Since every vaccine (just like nearly every medical intervention) has potential side effects, vaccination decisions depend on adequately low risk-benefit ratios. These ratios may change with time, increasing as population vaccine coverage increases, population disease risk decreases, and consequently tolerance for side effects decreases.

2.6.1. Example: Oral Polio Vaccine (OPV)—The risk-benefit ratio of OPV has evolved over time. Shortly after its introduction in 1958, OPV was remarkably successful in controlling polio. As an oral formulation, OPV prevented gastrointestinal tract carriage of poliovirus and conferred secondary protection to unvaccinated individuals via vaccine virus shedding through stools. When polio incidence was relatively high, OPV's protective benefits far outweighed the risks: the live attenuated virus reverting to a virulent form that causes paralytic polio. However, in locations such as the U.S. where polio incidence

dropped, the relative vaccination risk grew until public health officials switched their immunization recommendations from OPV to inactivated polio vaccine (IPV), which bears no known risk of vaccine-associated polio [25,26]. Compared to OPV, IPV has its problems, costing over five times more, requiring trained health care workers to administer the injection, and failing to prevent gastrointestinal tract virus carriage.

Understanding how vaccine risk-benefit ratios change over time can aid vaccine development and be a critical part of vaccine TPPs. Constructing dynamic risk-benefit models help developers realize what level of side effects would be acceptable for a given vaccine technology, how this threshold may change over time, when new vaccines should be developed to replace existing vaccines, and how these new vaccines should be integrated with the existing vaccines.

2.7. Know the currently unexplained conditions that exist in the vaccine's target population

Since a vaccine's target population is often healthy individuals, it is tempting to blame a vaccine for any otherwise unexplained malady that arises post-vaccination. Focusing on a vaccine as the culprit can divert attention and resources away from searching for other possible explanations for the malady.

2.7.1. Example: measles, mumps, and rubella (MMR) vaccine—Recently fears of autism have motivated many parents in the United Kingdom and United States to refuse measles, mumps and rubella (MMR) vaccination for their children [27]. Many of these concerns stemmed from a 1998 study led by a United Kingdom physician, Andrew Wakefield, that suggested the MMR-autism link and received extensive media coverage [28]. Subsequently, in 2004, 10 of the 13 study authors published a retraction of the study's conclusions [29]. Dr. Wakefield, who did not sign the retraction, is also under investigation for alleged research misconduct [30–33]. To date, additional studies have not supported the autism link [34,35]. The costs of autism fears to society and various vaccine stakeholders have been considerable [36,37].

When constructing a TPP, knowing what afflictions may already exist in the target population can help predict what conditions critics may attribute to the vaccine. Such predictions can lead to patient educational programs and proper studies to allay patients' fears prior to the vaccine's launch.

3. Summary

As history has demonstrated, post-approval obstacles can impede a vaccine's use and potentially lead to its withdrawal. Addressing the following issues early in vaccine development when changes in a vaccine's technology can still be easily made may improve a vaccine's chances of success: engaging relevant stakeholders, exploring pricing effects, matching vaccine technology with supply chain characteristics, selecting an appropriate target population, identifying potential purchasers, performing extensive risk-benefit analyses, and profiling unexplained ailments among the target population. The most successful vaccine launches benefitted from early planning, coordination among important stakeholders, and a well-outlined and well-conceived plan [38]. Although these will not guarantee success, failure to plan will only increase the chances of failure. The TPP can serve as a comprehensive strategic plan, incorporate strategies to overcome potential post-approval obstacles, and galvanize important vaccine stakeholders to work together to benefit all people globally.

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