

# Vaccine R&D success rates and development times

The real time saving in vaccine development is not in the preclinical development itself, but in the accelerated clinical development and reduced regulatory process of dossier preparation and review.

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Two of the most important factors in companies' decisions about whether or not to develop vaccines—the time of development and the success rate in development—are relatively poorly characterized. This article endeavors to remedy that by providing estimates of these factors from data on the progress of vaccine projects between 1983 and 1994. Similar data have also been used to predict more generally the growth rate for the pharmaceutical and biopharmaceutical industries<sup>1,2</sup>. Combined with other considerations, such as return on investment, price, potential market volume, achievable vaccine coverage, and acceptance and distribution<sup>3</sup>, such data can aid rational decision processes in development. The data indicate that although vaccine development—from pre-clinical studies to launch—takes an average of two years less than biopharmaceutical development, only half as many preclinical vaccine candidates make it through the process. The disease prevention-driven approach underlying vaccine development, and the nature of the data that its clinical trials yield, account for much of the differences in the development pattern.

Alarming reports of waning immunity in adults<sup>4</sup>, the emergence of new diseases, and the resurgence of old ones<sup>5-7</sup> have put vaccination back in the public spotlight. This has prompted numerous vaccination initiatives worldwide, including Article 129 of the European Community treaty of Maastricht.

Vaccination is the most elegant and cost-effective way to prevent outbreak of a disease and sequelae resulting from it. The Mercer Report commissioned by the US Department of Health and Human Services (Washington, DC) found that vaccines offer very high economic and health returns on investment<sup>3</sup>. They often contain multiple active ingredients (in contrast to single active ingredients used in drugs or biopharmaceuticals) and

give life-long protection against disease from very few administrations. However, because vaccines are given to healthy people, adverse events associated with vaccinations must be lower than for drugs. Although vaccines comprise a specialized pharmaceutical market, they can achieve substantial sales (for instance, the hepatitis B vaccine).

## The analysis

I have designated seven stages of development through which any vaccine project has to progress to reach the market place: pre-clinical development; clinical phases I, II, and III; preregistration; registration; and launch. There is a limited preclinical phase in which to evaluate potential toxicological, pharmacokinetic, and pharmacodynamic effects<sup>8</sup>. Then follow clinical studies in phase I and phase II<sup>9</sup>, in which investigators look at immunogenicity, generate limited safety data, and study adjuvant effects, dosage, and vaccination schemes. Subsequent clinical phase III trials evaluate efficacy in field studies, household contact studies, or challenge study settings<sup>10</sup>. The next phase is preregistration, during which data is evaluated, analyzed, and compiled for submission to regulatory agencies for review<sup>11,12</sup>. Once regulatory approval has been granted, batches of vaccines are released by the national control authority and market launch is initiated.

Of course, vaccine development does not always follow this scheme exactly (for reasons discussed previously for biopharmaceuticals<sup>1</sup>).

Multicomponent vaccines, especially, may not always fit into this scheme<sup>13,14</sup>.

The analysis here is based on 577 vaccine projects between 1983 and 1994 using source data from the publicly available Pharma Projects

database<sup>15</sup>. Success rate statistics were derived from a total of 266 projects—not all projects, just those for which reports could be traced in the literature, from company reports, or other sources. In addition, I included 14 vaccine projects (7 launched, 3 discontinued, 4 ongoing) from our company; these are not listed in Pharma Projects but have been published elsewhere<sup>16-18</sup>.

In this survey, vaccine candidates are considered to have failed if a project has been terminated or suspended. The rare withdrawals of vaccines from the market in the postmarketing surveillance period have been excluded from the analysis<sup>19</sup>.

It is difficult to estimate the extent to which failed projects are underreported in publicly available databases<sup>20</sup>. However, there is some reassurance in the fact that the inclusion of data on 14 extra vaccine projects from our company did not significantly alter the transition probabilities and development times.

## Progression through the pipeline

The numbers of projects per development stage (Table 1) decreases along the research and development pipeline, as expected.

The first interesting aspect of the phase transition data (Table 2) is the similarity of

**Table 1. Breakdown of vaccine projects per development stage.**

Change in stage	Successful	Suspended	Discontinued
Preclinical to phase I	27	3	111
Phase I to phase II	17	3	32
Phase II to phase III	16	0	15
Phase III to preregistration	5	0	10
Preregistration to registration	2	0	2
Registration to launch	22	0	1

**Table 2. Transition probabilities of vaccines compared to biopharmaceuticals.**

Transition	Vaccine	Biopharmaceutical
Preclinical to phase I	0.57	0.57
Phase I to phase II	0.72	0.88
Phase II to phase III	0.79	0.86
Phase III to registration	0.71	0.93
Registration to launch	0.96	1.00

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the preclinical to phase I transition probabilities for vaccines and biopharmaceuticals and the fact that the probability in both cases is much higher than for "non-bio" pharmaceuticals. For both vaccines and biopharmaceuticals, species specificity means that there is little animal toxicological data that could stop a project from developing past preclinical studies. Equally, pharmacological investigations with vaccines are rarely performed<sup>8</sup> so projects are unlikely to fail on that count. The other main difference is that "lead structures" for vaccines and biopharmaceuticals are much easier to identify at the beginning of the preclinical phase than are drug leads. We can know at the outset that an attenuated organism has a chance of being a vaccine or that a protein will correct a protein-deficiency disease in a way that we cannot know it for small molecule drugs. Thus, proportionally fewer "hopeless" vaccine and biopharmaceutical candidates will enter the preclinical phase.

In later phases transitions, there are differences between vaccines and biopharmaceuticals (see Table 2), differences that are statistically significant despite the sparseness of some of the data. Vaccine projects have a 72% chance of progressing from phase I to phase II, and a 71% chance of going from phase III to registration. For biopharmaceuticals, the likelihoods of progression were statistically significantly higher (Chi-squared test) at 88% and 93%, respectively. Twenty percent more vaccine projects than biopharmaceutical projects are lost at these two phases. All other transition probabilities are within the same range.

The lower probability for vaccines getting from phase I to phase II may be explained by the fact that this first human exposure to the vaccine candidate will reveal grounds for project failure such as hyperattenuation of organisms or viruses, insufficient immunogenicity, or insufficient attenuation<sup>21</sup>.

The probability that vaccines will make the transition from phase II to phase III transition probabilities is slightly lower than that for biopharmaceuticals. One explanation may be the number of variables that are introduced into phase II vaccine trials: The candidate is administered to more patients using different dosing schemes and dosages, various routes of administration, and different adjuvants.

That vaccines should fail with a higher probability to go from phase III to registration than biopharmaceuticals is unsurprising. In vaccine

development, the product has only been tested in healthy volunteers up to this point. Although surrogate markers of efficacy such as serum titers, animal challenge data, or neutralizing antibodies for vaccines are monitored in early development phases, they may be misleading as indicators of the real efficacy of the vaccine. Pharmaceuticals and biopharmaceuticals will have been given to affected patient subsets in phase I or II<sup>20</sup>. Therefore, the decision to put vaccines into phase III is based on generally less decisive data.

### The chances of ultimate success

So what are the chances that a vaccine at a given stage of development will make it to the market? Market entrance probabilities (Table 3) can be calculated by multiplying the various phase transition probabilities. The market entrance probabilities for preclinical vaccine candidates is about half that for preclinical biopharmaceuticals<sup>1</sup>, largely, of course, because of the lower phase I to phase II and phase III to registration transition probabilities. In other words, preclinical biopharmaceuticals are nearly twice as likely to succeed than preclinical vaccine candidates.

The strikingly high success rate for biopharmaceuticals is explained, partially at least, by the fact that many of the biopharmaceuticals developed and marketed between 1983 and 1991 have been substitutes or replacements for natural molecules in humans—less risky markets. The road ahead for biopharmaceuticals may be rockier.

### Development time

How long does it take to develop vaccines and bring them on the market? The average time for all development phases for vaccines appear shorter than for biopharmaceuticals (Table 4) with phase III to preregistration and preregistration to registration taking the shortest time. The difference between the development times of the vaccine and bio-

pharmaceutical groups for the phase III to preregistration and preregistration to registration phase are statistically significant (by the Student t-test).

The overall development (preclinical to launch) time for vaccines is less—by roughly two years—than biopharmaceuticals and "non-bio" drugs; ten years compared with twelve. Two years less in development means two years earlier into the market, a significant advantage in cost-saving, sales generation, and market positioning.

### Conclusions

Vaccine development, like the development of other pharmaceuticals, is still a complex process that takes substantial resources and requires serious and enthusiastic commitment over a period of roughly ten years.

The contexts for vaccine and biopharmaceutical development are very different. The general clinical settings and study endpoints for vaccines are clearer from the start and seem to be better controlled than for biopharmaceuticals. Researchers already know about the disease, the responsible pathogens, and the immune response elicited in humans during infection. Disease staging is not a common feature of vaccine development.

There are also far fewer indications for vaccine than for other pharmaceuticals. New indications for vaccines do not spring forth from elaborate clinical research, and vaccine candidates cannot be rescued from other indications. Thus, vaccine development is highly focused on its clinical indication from the beginning in a way that drug development may not always be. With its target highly defined, vaccine development is already the rational process that pharmaceutical development would like to be.

The total development time is shorter for vaccines than for biopharmaceuticals. One major time saving occurs in the phase III to preregistration transition. Here, the most pertinent difference between vaccines and other pharmaceuticals is the incidence of disease with which investigators have to work. High incidences and high enrollment rates make short clinical trials feasible. For vaccines, incidence is pathogen-related. Therefore, in challenge studies, incidence can be set as desired. And in field studies, investigators can select locations where incidence is sufficiently high to allow rapid conclusion of efficacy trials. Furthermore, as healthy volunteers are included in the study, enrollment in clinical studies is generally not a limiting factor. For new chemical entities, average duration of clinical phase III is roughly 3–5 years<sup>22</sup>. For vaccines (in this survey) it is 1.4 years.

**Table 3. Market entrance probabilities for vaccines and biopharmaceuticals.**

Transition	Vaccines	Biopharmaceuticals <sup>1</sup>
Preclinical to launch	0.22	0.4
Phase I to launch	0.39	0.71
Phase II to launch	0.54	0.80
Phase III to launch	0.68	0.93
Registration to launch	0.96	1.00

**Table 4. Duration of development phases for vaccines and biopharmaceuticals.**

Stage	Vaccines	Biopharmaceuticals
Preclinical to phase I	2.4	2.3
Phase I to phase II	2.0	1.8
Phase II to phase III	1.8	2.2
Phase III to pre-registration	1.4	2
Preregistration to registration	1.1	2
Registration to launch	1.3	1.6
<b>Total</b>	<b>10.0</b>	<b>11.9</b>



The other main source of time saving in vaccine development is in the transition from preregistration to registration. Because there are no large toxicological and pharmacological studies in vaccine development, regulators expect less preclinical data in the final dossier. Fewer variables and "cleaner" endpoints also mean that the compilation of dossiers for regulatory submission take less time for vaccines.

There is a paradox here, however. Time is saved by reducing the size and complexity of the regulatory submissions rather than by reducing toxicological and pharmacological testing of vaccines. The preclinical phase for vaccines is no less onerous than that for pharmaceuticals: Establishing cell banks, studying adjuvants, and evaluating inactivation and detoxification methods are all time consuming. Developing a lot of release methods, conforming to internationally accepted standards, and preparing reference materials for vaccines can also be burdensome and time consuming<sup>23</sup>. With live attenuated organisms, environmental detection methods must be developed, and genetic and environmental stability must be known prior to use.

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