



How to Get a Vaccine Licensed in 10 (Not So) Easy Steps

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Step #1

Appropriate Disease Target

Smallpox –CDC Website





Ideal Disease Target

- Natural disease confers life-long immunity
- Single serotype worldwide
- Mechanism of immune protection known; i.e., neutralizing antibody, cellular mediated immunity (CMI)



Step #2

Predictive Animal Model

Ferret -Influenza





Ideal Animal Model

- Mimics human disease
- Small, non-endangered species
- Can differentiate potent vs. impotent vaccine
- Can predict efficacy in humans



Step #3

Development of Serological Assays
for Correlates of Protection and
Vaccine Potency Assay



Serological Assays

- Need to detect antibody to epitopes which correlate with protection
- Develop early in program and validate before initiation of clinical trials
- Automatable; objective endpoints
- Commercially available



Potency Assay

- Validate assay used for potency of vaccine
 - Correlates to clinical response
 - Defines performance characteristics
- Inappropriate potency assignments to lots of vaccine made early in development will result in inappropriate dose selections for pivotal Phase 3 trials



Correlates of Protection

- Can be shown by use of hyperimmune globulin elicited from test vaccine or natural disease (i.e. HepB, Hib, VZV)
- Animal models helpful
- Necessary when combining vaccines or changing formulations. Otherwise, need to repeat efficacy studies



Step #4

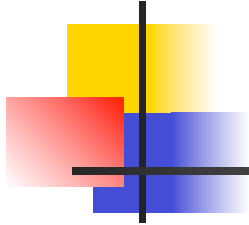
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Step #5

Phase 1 Trials - Safety

Phase 1 Trials:



- “Step-down” Safety: immune adults-immune children-immune infants-susceptible infants
- Use highest dose planned to be used in Phase 2 studies
- Live vaccines: shedding, transmission, reversion and/or re-assortment



Step #6

Phase 2 Trials- Dose and Regimen
Selection



Phase 2 Trials

- Animal models may be helpful in targeting test doses
- Use wide range of doses
- Perform separate studies in each target age group
- Explore various dose regimens (i.e. 2 doses 6 months apart vs. 3 doses 2 months apart)



Step #7

Phase 3 Studies – Efficacy and
Expanded Immunogenicity and
Safety



Efficacy Studies- Phase 3

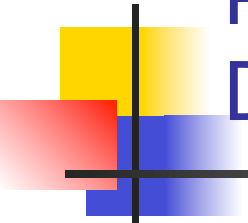
- Use correct dose, dose regimen and final manufacturing process
- Double-blind placebo control; household contact; case-control studies
- One site vs. multiple sites
- Plan for seasonal disease occurrence
- Meet with CBER prior to study start and agree of efficacy endpoints

HPV Infection - Male



HPV Infection-Female



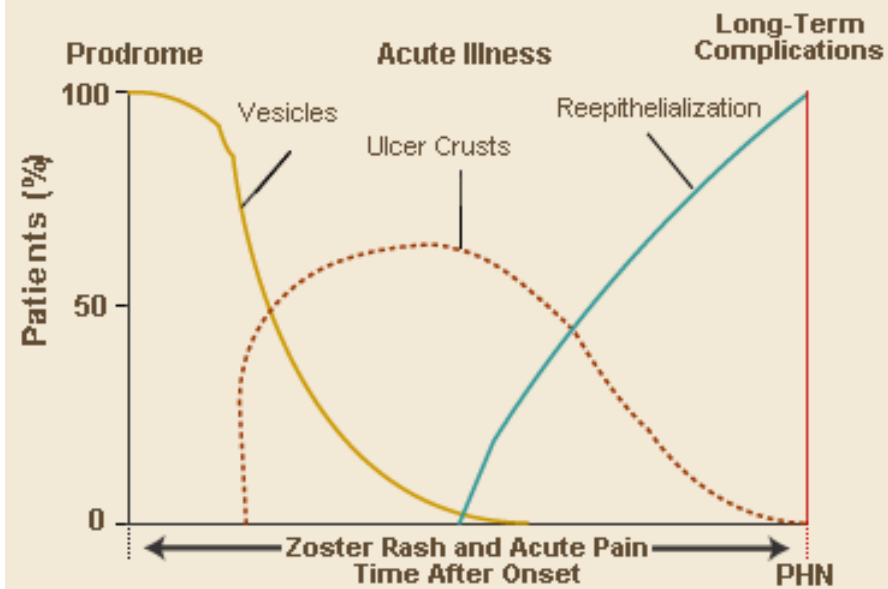


Examples of Efficacy Endpoints- Human Papilloma Virus (HPV) Vaccine*-Case Definition

- Negative HPV-16 at Day 0 & at month 7(vaccine given at Day 0 and Month 2 and 6)
- Subsequently had HPV-16 DNA detected on 2 or more consecutive visits 4 or more months apart
- Cervical biopsy showing cervical intraepithelial neoplasia or cervical cancer AND HPV 16 DNA in the biopsy tissue
- * **Koutsky NEJM 2002;347:1645-51**

HZ-Clinical Course

Herpes Zoster: Clinical Course or Natural History



PHN=postherpetic neuralgia.

Adapted from Hope-Simpson RE. *Geriatrics*. 1967;22:151-159.

Herpes Zoster





Herpes Zoster





Zoster Vaccine Efficacy Study

- Enrolled 38,546 adults \geq 60 years of age
- Randomized to vaccine/placebo
- Active follow-up for median of 3.12 years
- Identification and confirmation of cases
- Primary end point-burden of illness due to herpes zoster

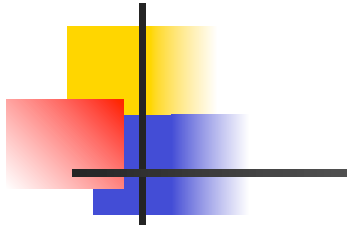


Table 2. Effect of Zoster Vaccine on the Burden of Illness in Herpes Zoster in the Modified Intention-to-Treat Population.*

Group of Subjects	Vaccine Group			Placebo Group			VE _{BOI} (95% CI) [§]
	No. of Confirmed Cases/No. of Subjects	BOI Score [†]	Incidence per 1000 Person-Yr [‡]	No. of Confirmed Cases/No. of Subjects	BOI Score [†]	Incidence per 1000 Person-Yr [‡]	
All subjects	315/19,254	2.21	5.42	642/19,247	5.68	11.12	61.1 (51.1–69.1)
Age							%
60–69 yr	122/10,370	1.50	3.90	334/10,356	4.33	10.79	65.5 (51.5–75.5)
≥70 yr	193/8884	3.47	7.18	308/8891	7.78	11.50	55.4 (39.9–66.9)
Sex							
Male	181/11,390	2.09	5.30	361/11,337	5.81	10.65	64.0 (51.4–73.4)
Female	134/7864	2.34	5.58	281/7910	5.47	11.79	57.3 (39.6–69.8)

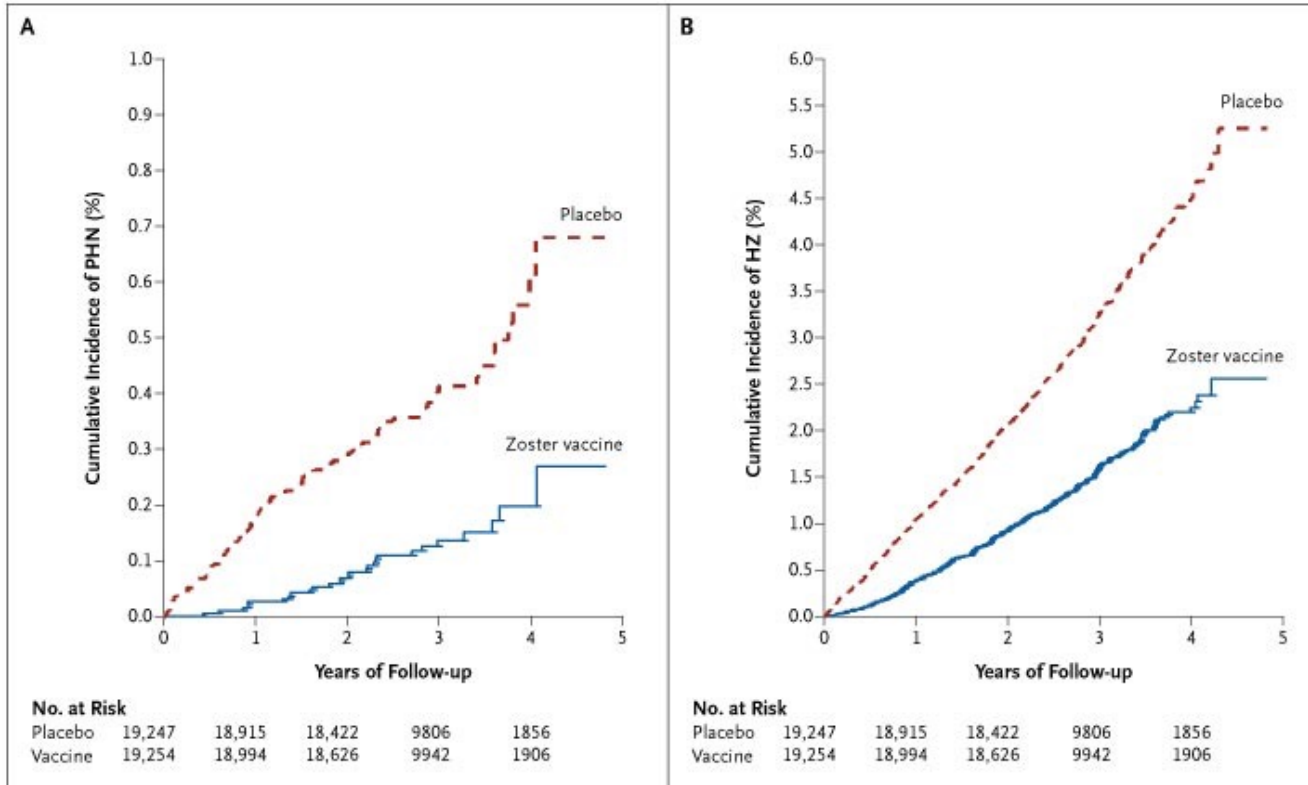
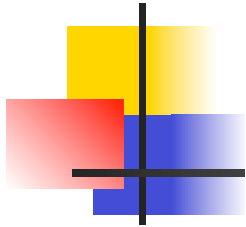
* Efficacy analyses were performed with the use of a follow-up interval that excluded the first 30 days after vaccination and in a modified intention-to-treat population, which excluded subjects who either withdrew from the study or in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. Of three subjects in whom more than one case of herpes zoster developed, only the first case was included. VE_{BOI} denotes vaccine efficacy for the burden of illness due to herpes zoster (BOI), and CI confidence interval.

[†] For the total population and the subgroups stratified according to sex, the BOI score in each treatment group (vaccine or placebo) was the weighted average of the observed BOI stratified according to age, with weights proportional to the total number of subjects within each age group; subjects in whom herpes zoster did not develop were assigned a score of 0 for severity of illness due to herpes zoster on the basis of the Zoster Brief Pain Inventory, a questionnaire developed for the Shingles Prevention Study.

[‡] For the total population and for subgroups stratified according to sex, the incidence of herpes zoster in each treatment group was the weighted average of the observed incidence of herpes zoster stratified according to age group, with weights proportional to the total number of person-years of follow-up in each age group.

[§] VE_{BOI} for all subjects was the protocol-specified primary end point.







Examples of Efficacy Endpoints: Hepatitis A Vaccine*

- IgM to hepatitis A
- ALT 2X ULN during illness (with no other cause)
- One or more of the following clinical signs or symptoms: dermal, scleral or faucial icterus associated with a serum total bilirubin level of at least 2.0mg/dL; fatigue, malaise, abdominal pain, emesis, oral temperature of 38.8°C or higher without any other cause; clay-colored stools, or dark urine
- ***Werberger et al NEJM 1992:327(7):453**



Expanded Immunogenicity and Safety

- Test at least 3 manufacturing consistency lots
- Large sample size (>2000-5000) with extended follow-up planned from onset
- Electronic database of serious and unexpected AEs



Step #8

Pre-Biological License Application
(BLA) Meeting



Step #9

Writing a BLA



The Perfect BLA:

- Plan on 6 months preparation, minimum
- Good indexing and tables
- Reader friendly
- Supply all references
- Annotate every claim in proposed package insert with supporting data



Step #10

Responding to CBER's (Sometimes
Endless) Questions



A License is NOT

THE END



Post-Marketing

- Safety in 30,000 to 60,000 for uncommon AEs
- Inspections of Mfg facility q 2 years
- Persistence of protection
- Need for booster doses
- Changes in manufacturing
- Additional claims