INFLUENZA VACCINE

Manufacturing Process*

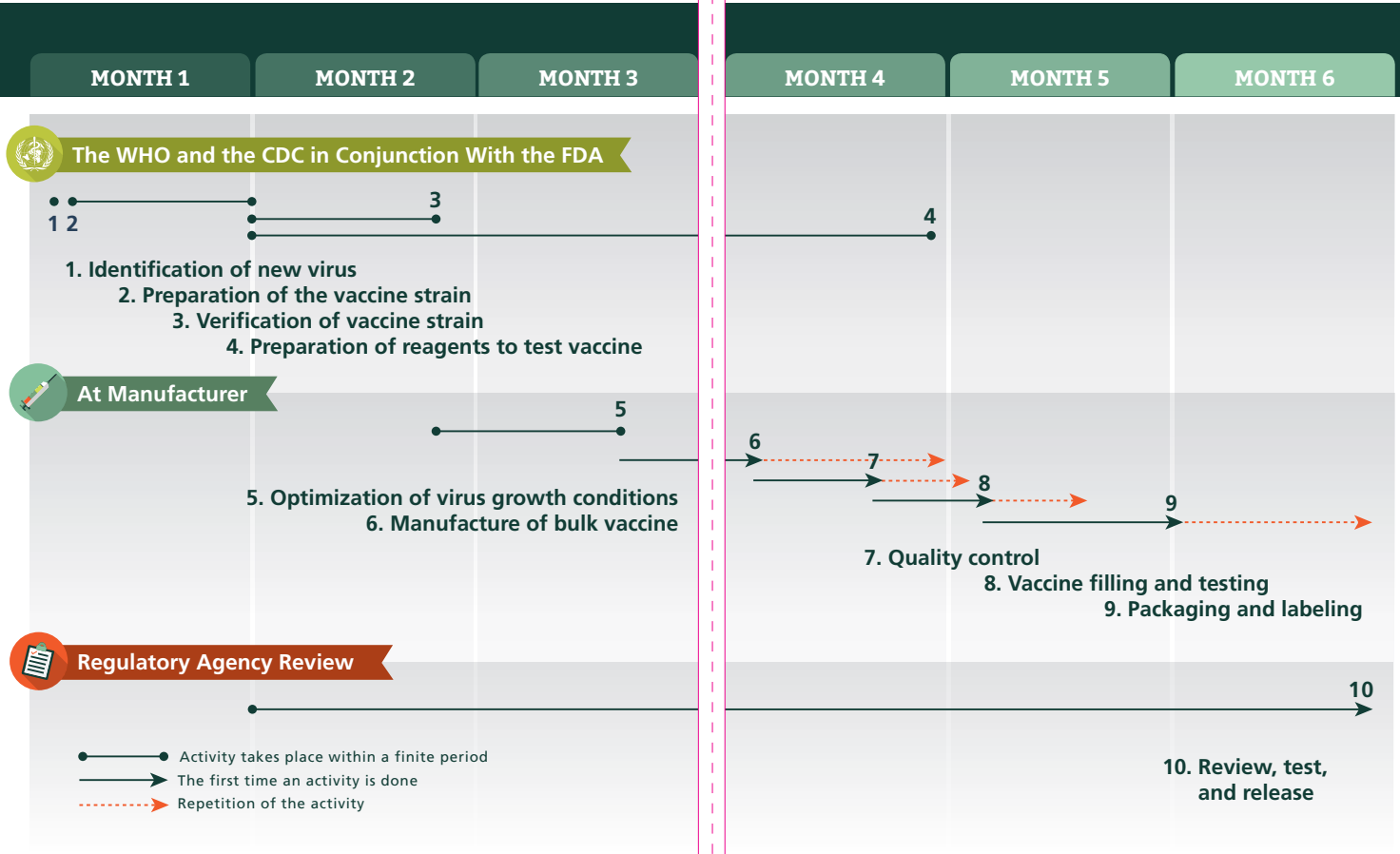
gsk

*Not all influenza vaccines are manufactured in this way. This reflects a simplified representation of a manufacturing process for an egg-based inactivated influenza vaccine.

Influenza Vaccine Manufacturing Process

The process of producing an influenza vaccine requires many sequential steps, each of which takes weeks or months to complete.

Outlined below are steps for egg-based influenza vaccine production for the manufacturer, the WHO, and the CDC in conjunction with the FDA.*



*WHO=World Health Organization; CDC=Centers for Disease Control and Prevention; FDA=Federal Drug Administration.

The size of the batch depends on how many eggs a manufacturer can obtain, inoculate and incubate, and on how much virus each egg yields.

The process is repeated as often as needed to generate the required amount of vaccine.

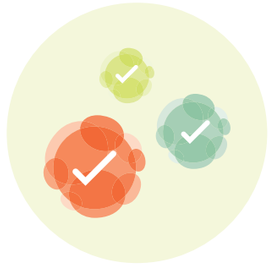
The WHO and the CDC in Conjunction With the FDA

STARTING POINT (but process is ongoing)

Identification

of influenza virus strains for the upcoming influenza season:

- Throughout the year, laboratories around the world routinely collect samples of circulating influenza viruses and submit these to WHO Collaborating Centers for Reference and Research on Influenza.
- The WHO collects this information on circulating and novel influenza strains, and determines which strains to use in the annual vaccine.
- The FDA and the CDC confirm the recommended strains for the US.

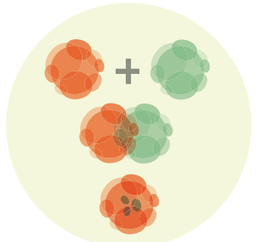


3-4 WEEKS

Preparation

of the 3 or 4 virus strains (called "vaccine virus") that will go into the vaccine:

- The 3 or 4 chosen strains are optimized in the laboratory to ensure that they have the desired properties for large-scale manufacturing.



Typically, the influenza vaccine virus is grown in eggs; the influenza virus grows well in them, and eggs are readily available.

3-4 WEEKS

Verification

of the vaccine virus:

- Each of the 3 or 4 viruses must be tested to make sure it grows well, produces the expected response, and is safe.
- Upon completion of this process, the vaccine strain is distributed to vaccine manufacturers.

3-4 MONTHS simultaneous with Verification process

Reagent Preparation

to enable standardized testing:

- WHO Collaborating Centers produce reagents that are given to all vaccine manufacturers to enable them to measure how much virus they are producing, and to ensure they are all packaging the correct dose of vaccine.

At Vaccine Manufacturer

3-4 WEEKS

Optimization

of growing conditions for the vaccine virus:

- The vaccine manufacturer receives the vaccine viruses from the WHO laboratories, and tests different growth conditions in eggs to find the best conditions.

2-4 MONTHS

Manufacturing

1. **Inoculation** – One strain of the vaccine virus is injected into thousands of eggs.
2. **Incubation** – The eggs are incubated for 2-3 days, during which time the virus multiplies.
3. **Harvesting** – The egg whites, which now contain many millions of virus copies (of Strain #1), are harvested.
4. **Ultracentrifugation** – This separates the virus molecules from the egg white.
5. **Chemical Inactivation** – The partially pure virus is killed with chemicals. This "splits" the virus into pieces, making it inactive. The outer proteins of the virus are then purified and the result is several hundred or thousand liters of purified virus protein that is referred to as antigen, the active ingredient in the vaccine.
6. **Repeating** of the process for each of the 3 or 4 strains selected for the year.
7. **Combining** of the 3 or 4 strains into one vaccine solution.

2 WEEKS but this process can only start once WHO reagent process is completed

Quality Control Testing

- Each batch of vaccine is tested for potency with approved reagents.
- Testing is also done for sterility and purity.

2-4 WEEKS

Filling & Testing

- The batch of vaccine is diluted to give the desired concentration of antigen, then put into vials or syringes.
- Several filled vials/syringes are then tested for sterility, to confirm the protein concentration, and for safety.

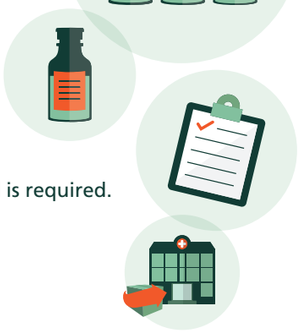
1-3 MONTHS

Packaging & Labeling

3-4 WEEKS

FDA Review & Release

- Before the vaccine can be sold or administered to people, regulatory approval is required.

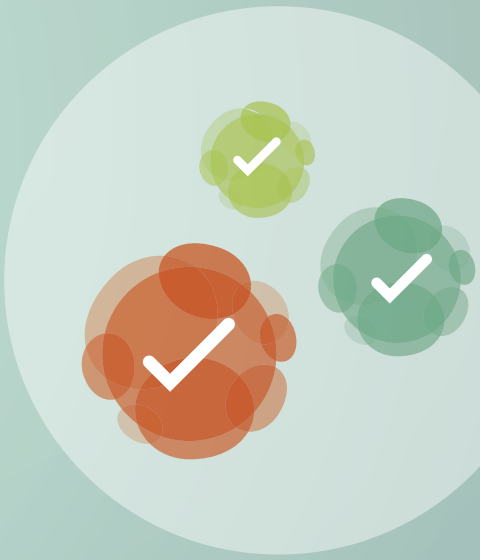


VARIES

Distribution to Healthcare Providers

- Distribution by the manufacturer after FDA release.

The manufacturing process for influenza vaccine is complex and time-consuming. Steps are included in the process to help produce a vaccine that is safe and potent.



References: 1. World Health Organization. Pandemic influenza vaccine manufacturing process and timeline. Available at: http://www.who.int/csr/disease/swineflu/notes/h1n1_vaccine_20090806/en/#. Accessed October 15, 2015. **2.** Centers for Disease Control and Prevention. Selecting the viruses in the seasonal influenza (flu) vaccine. http://www.cdc.gov/flu/about/season/vaccine-selection.htm. Accessed December 9, 2015.