

Influenza Vaccine Production

Roland A. Levandowski, M.D.
Division of Viral Products

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Introduction

- Inactivated Influenza Virus Vaccines
- Commercially Available for More than 50 Years in USA
 - ◆ Parenteral injection
 - ◆ Egg vs Tissue Culture
- Live Virus Vaccines
- In Clinical Development for Commercial Use
 - ◆ Intranasal inoculum

Topic of Discussion

- Similarities and differences in inactivated influenza virus vaccines
 - ◆ Comparing Different Years
 - ◆ Comparing Manufacturers
 - ◆ Comparing Content

Comparing Different Years

Year to Year Changes in Vaccines

- Influenza vaccines most effective if vaccine viruses match wild viruses
- At least one strain changed in almost every year because of antigenic drift and shift
- Vaccine valency relates to circulating strains
 - ◆ Influenza B, Influenza A H1N1, Influenza A H3N2

Strain Change Implications

- Unknown vaccine yield
 - ◆ Vaccine output limited by strain with lowest yield
- Unknown impact on vaccine stability
 - ◆ Vaccine recall 1996
- Unexpected rare adverse events
 - ◆ GBS observed with “swine” flu vaccine

Comparing Manufacturers

Inactivated Vaccine Manufacturers

- Currently 1 manufacturing facility located in USA
 - ◆ 3 as recently as 2000
 - ◆ As many as 5 (1970's)
- 15 + manufacturing facilities on 4 continents
- Increasing vaccine demand in USA
 - ◆ 20 million doses (1989)
 - ◆ 80 million doses (2003)

Vaccines Used in the USA

- Sources of vaccine 1990-2003
 - ◆ Connaught (Aventis Pasteur), Swiftwater, PA, USA
 - ◆ Evans Vaccines, Liverpool, England
 - ◆ Wyeth Vaccines, Marietta, PA, USA (ceased 2002)
 - ◆ Parke-Davis (Parkedale), Rochester, MI (ceased 2000)

Manufacturing Similarities

- Living substrate (eggs)
- Influenza reference viruses for use in vaccine recommended by USPHS (and WHO)
- Purification steps to reduce non-viral (egg) materials and chemicals
- Chemical inactivation
- Sterile but with residual endotoxin
- Preservative

Manufacturing Differences

- Proprietary chicken flocks
- Proprietary seed viruses
- Process differences
 - ◆ Sucrose zonal centrifuge vs. chromatography
 - ◆ Disrupting agent (detergents and lipid solvents e.g. ether)

Disrupting agents

- Cetyl trimethyl ammonium bromide
- Deoxycholate
- Ether *
- Tri-n-butyl phosphate *
- Triton N 101 *
- Triton X 100 *

(* = Used in vaccines in USA)

Comparing Content

Vaccine Content Similarities

- Hemagglutinins standardized to minimum 15 micrograms per dose
- Limits set for endotoxin
 - ◆ 21CFR610.11a
- Limits set for chemical excipients including disrupting agents and inactivating agents

Vaccine Content Differences

- Total Protein Content
- Residual viral proteins
 - ★ (Neuraminidase, nucleoprotein, matrix)
- Endotoxin content
- Formalin vs. beta propriolactone
- Thimerosal content
 - ★ (“Preservative free”)
- Adjuvants
 - ★ (None used in USA)

Summary

- Changes in inactivated influenza vaccines occur yearly to remain current with circulating viruses
- Manufacturing processes vary, but result in products with relatively similar specifications
- Year to year changes in strains and differences between manufacturers result in variations in content but within defined limits