

**International Society for Clinical Biostatistics
30th Annual Conference**

Prague, Czech Republic

August 23-27, 2009

**Multiplicity Issues in Biologics Clinical Trials:
Regulatory Perspectives**

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The views expressed in this presentation are those of the speaker and do not necessarily reflect policies of the U.S. Food and Drug Administration.

Outlines

FDA/CBER/Division of Biostatistics

Multiplicity Issues/Guidance in Clinical Trials

Multiplicity Issues in Vaccine Trials:

- Combination vaccines
- Vaccines with multiple serotypes
- Therapeutic vaccines
- Concomitant vaccines
- Composite endpoints in vaccine trials

Food and Drug Administration (FDA)

- *Center for Biologics Evaluation and Research (CBER)*
 - Office of Vaccines Research and Review
 - Office of Blood Research and Review
 - Office of Cellular, Tissue, and Gene Therapy
- Center for Devices and Radiological Health (CDRH)
- Center for Drug Evaluation and Research (CDER)
- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Veterinary Medicine (CVM)
- National Center for Toxicological Research (NCTR)

CDER Division of Biostatistics

- Vaccine Evaluation Branch supports the Office of Vaccines Research and Review
 - Viral and Bioassay Team
 - Bacterial and Allergenic Team
- Therapeutics Evaluation Branch supports the Office of Cellular, Tissue and Gene Therapies and the Office of Blood Research and Review
 - Blood Therapeutics and Devices Team
 - Diagnostics and Screening Tests Team
 - OCTGT Therapeutics and Devices Team

Statistical Review

Vaccine Products/Disease Areas

- Bioterrorism/Pandemic (Smallpox, Anthrax, Plague, Influenza, Botulism)
- Prophylactic Vaccines: (Hepatitis, Meningococcal, Pneumococcal, HIV, Human Papillomavirus, Measles / Mumps / Rubella / Varicella, Diphtheria / Tetanus / Pertussis, Poliovirus)
- Cancer Vaccines (Prostate, Lymphomas, Melanomas)

Statistical Review

Other Products/Disease Areas

- Tissue/Cell Therapy (Islets transplantation in Type I Diabetes)
- In Vitro Diagnostic Test Kits for blood safety (HIV, Hepatitis, West Nile Virus, Human T-Lymphotropic Virus)
- Blood Products (Red Blood Cells, Platelets, Plasma, Whole Blood, Blood Substitutes, Albumin, Immune Globulin, Antihemophilic Factor, Coagulation Factors, Fibrin Sealants, Blood Grouping reagent)
- Devices used in processing blood products or in delivery of a biologic at point of care

Multiplicity Issues

- Multiple Endpoints in studies
- Composite endpoints
- Primary and secondary endpoint(s)
- Multiple Trials
- Subgroup Analyses

General Guidance

- Type I error rate for each elementary hypothesis must be controlled at $\leq \alpha$ (.05, .01, .001, ...)
- Family of comparisons: Doses and endpoints under testing are all considered in the family (including all intersection hypotheses)
- Control study-level (family-wise) type I error rate (i.e., max type I error rate) at $\leq \alpha$ (.05, .01, .001)
- “Strong control”

Strong control

- Strong control at the study level treats all studies ‘equally’ in regulatory applications
- For each trial, the more hypotheses are tested, the more statistical adjustments and more planning on statistical decision tree needed
- A principle generally followed by the statistical community is to control “experiment-wise” type I error rate, as the clinical trial is an experiment
- Doesn’t control multiplicity on multiple trials

Multiplicity and Type I & Type II Errors

- Multiplicity poses a critical challenge to product licensing
- We simultaneously recognize the genuine scientific need for multiple endpoints in a variety of contexts, and are also very concerned that all clinical trials maintain adequate control of Type 1 error.
- Maintaining strong control of Type I error in the presence of multiplicity can mean inflation of Type II error: false negatives.

Multiplicity Issues in Vaccine Trials:

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Combination Vaccines

- Examples: DTaP, MMRV, DTaP/IPV, DTaP/HBV/IPV, MMRV vs. MMR + Varicella
- Need to be non-inferior for each of the diseases (components) when compared to separate administrations
- Potential interactions/interference between the vaccine components
- Safety

Vaccines with Multiple Serotypes

- Comparison between licensed n-valent vs. new (n+k)-valent
- Examples:
 - Pneumococcal 7-valent vs. 13-valent
 - Influenza trivalent vs. quadrivalent
 - H1N1/H3N2/B vs.
 - H1N1/H3N2/B1/B2
 - H1N1/H3N2/B1
 - H1N1/H3N2/B2

Vaccines with Multiple Serotypes (2)

- When compared to licensed vaccine, non-inferiority test for core serotypes is considered. Then, what would be the endpoint(s) for additional serotypes?
- When adding new serotype(s), how to evaluate risk/benefit?
- Sample size/Power issues

Therapeutic Vaccines

- Examples:
 - HIV
 - Herpes virus
 - Tumor vaccines
- Multiple relevant efficacy endpoints:
 - Overall survival
 - Progression-free survival
 - Morbidity
 - Response rate, duration
 - CD4 counts, viral load, ... → definite endpoint
- Withdrawal is an important factor for the choice of endpoints.

Concomitant vaccines

- Examples:
 - DTaP+Hib+IPV+PCV7
 - Hib+PCV7+MMR
- Evaluate *safety* in particular and immunogenicity in the presence of concomitant vaccines
- Interaction(s): When multiple vaccines are concomitantly administered, some vaccinees may exhibit reduced immune response or increased reactogenicity

Multiple vs. Composite Endpoints

- Test two or more separate endpoints:
 - Combine the results via Fisher's method or multiplicity adjustment
- Create a single composite measure
 - Capture vaccine effect in more than one dimensions
 - Validation issues

	CD4 +	CD4 -
Viral Load +	(1)	(2)
Viral Load -	(3)	(4)

Vaccines for diseases with composite endpoints

- For some diseases (such as zoster and HIV), vaccines are targeted to reduce the incidence and/or the severity of the disease (prolong development, delay full blown)
- Combine preventive and therapeutic aspects of a vaccine
- Define a clinically meaningful change in severity endpoints

Subgroup Analyses

Post-hoc subgroup results may show an increase/decrease in efficacy/safety different from overall results

MI-CP111 Safety Results on Safety population Relative Risk of FluMist to TIV Based on All-Cause Hospitalization

Age (months)	CAIV-T		TIV		Relative Risk of FluMist Compared to TIV (95% CI)
	N	# of Subjects with All-Cause Hospitalization	N	# of Subjects with All-Cause Hospitalization	
6 ~ 59	4179	45 (1.1%)	4173	45(1.1%)	1.00 (0.66, 1.50)
6 ~ 23	1992	32 (1.6%)	1975	24 (1.2%)	1.32 (0.79, 2.22)
6-11	684	15(2.2%)	683	9 (1.3%)	1.66 (0.75, 3.70)
12-23	1308	17 (1.3%)	1292	15 (1.2%)	1.12 (0.57, 2.20)

That is it.

Thanks for the time and listening !