Regulatory Aspects of the Nonclinical Safety Assessment of Adjuvanted Preventive Vaccines

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Disclaimer

- Please contact CBER DVRPA for specific regulatory questions

Objectives

- **Describe nonclinical safety data for inclusion in a US IND**
- **Overview of adjuvants under investigation and in licensed US Vaccines**
- **Provide current OVRR approach to toxicity evaluations of vaccines and adjuvants**

Product Areas Regulated by OVRR

Preventive and therapeutic vaccines for infectious disease indications:

- **Live attenuated preparations of bacteria, viruses or parasites**
- **Inactivated (killed) whole organisms**
- **Living irradiated cells**
- **Crude fractions or purified immunogens, including those derived from recombinant DNA in a host cell**
- **Conjugates formed by covalent linkage of components**
- **Synthetic antigens**
- **Polynucleotides (such as plasmid DNA vaccines)**
- **Living vectored cells expressing specific heterologous immunogens**
- **Cells pulsed with immunogen**
- **Allergenics**

FDA Review is Product-based

- Interactive review process engages product development
- Dependent on characteristics of specific product (CMC)
- Preclinical studies designed to support specific products
- Clinical trial design supported by manufacturing, preclinical data
- Regulations supported by science

Vaccine Regulatory Requirements

- **21 CFR 610 - General Biological Products Standards**
  - **Lot Release, Potency, General Safety, Sterility, Purity, Identity**
- **21 CFR 312 – IND regulations**
  - **312.23 (a)(7) – Chemistry, Manufacturing and Control Information**
  - **312.23(a)(8) – Pharmacology and Toxicology Information**
    - "…adequate information about the pharmacological & toxicological studies… *in vivo* or in *vitro studies* should be conducted on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, & scope of animal and other tests required varies with the duration & nature of the proposed clinical investigations."

Safety is Always Primary (but Safety is Relative)

FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.

IND Regulations [21 CFR 312.22 (a)]

Definition of Safety - "The relative freedom from harmful effects of the recipient when a product is prudently administered, taking into consideration the characteristics of the product in the relationship to the condition of the recipient at the time."

IND Regulations [21 CFR 600.3]

Potential Safety Concerns with Vaccines/Adjuvants

- ***Potential*** **typical Local Reactions**
  - **Pain, redness, swelling; granuloma formation; abscess; necrosis; and regional lymphadenopathy**

- ***Potential*** **typical Systemic Reactions**
  - **Anaphylaxis; pyrogenicity; organ specific toxicity; nausea/diarrhea/malaise; immune-mediated toxicity (e.g., cytokine release, immune suppression, autoimmune disease); teratology; and carcinogenicity**

Adjuvant definitions

- Two main types of adjuvants:
  - enhance antigen delivery
  - immunostimulators

USFDA - **adjuvants** - agents added to, *or used in conjunction with*, vaccine antigens to augment or potentiate (and possibly target) the specific immune response to the antigen

Vaccine Adjuvants

- **Numerous clinical studies with adjuvants* including:**
  - **mineral salts/gels, oil-emulsion and surfactant-based, particulates, microbial (natural and synthetic) derivatives, endogenous human immunomodulators (cytokines), *and* combinations of these**

- **Use in licensed vaccines:**
  - **Limited currently to aluminum-derived adjuvants (in US)**
  - ***Adjuvants alone are not licensed; a specific antigen/adjuvant formulation is licensed***

  - ***Pink and Kieny (2004) Vaccine 22, 2097-2102; Kanzler et al. (2007) Nature Med 13, 552-559**

Vaccine Adjuvants

MPL containing adjuvants:

- ***AS04*** **– in hepatitis B vaccine (Fendrix*)**
  also in HPV vaccine(Cervarix*), genital herpes vaccine[1]
- ***AS02*** **– in malaria vaccine(s)[1,2]**

MF59 adjuvant in influenza vaccine [3] (FLUAD *)

*approval in Europe

[1]Baldridge *et al.* (2004) Expert Opin. Biol. Ther. 4, 1129

[2]Pink and Kieny (2004) Vaccine 22, 2097-2102

[3]Frey, S. *et al.* (2003) Vaccine 21, 4234

Pink and Kieny (2004)

Novel adjuvant-antigen combinations in or close to human testing and discussed in the text[a]

Adjuvant	Brief description	Type of antigen(s) discussed
Oil emulsion and surfactant-based formulations		
MF59	Microfluidized detergent-stabilized oil-in-water emulsion	HIV-env
QS-21	Purified saponin	Many, especially cancer and HIV antigens; MSP-1.p42 (malaria)
AS02	Oil-in-water emulsion + MPL®[1] + QS-21	RTS,S (malaria); tuberculosis
Montanide ISA-51	Stabilized water-in-oil emulsion	Various (cancer, HIV); MSP-1.p19 and p42 (malaria)
Montanide ISA-720	Stabilized water-in-oil emulsion	Various (cancer, HIV); PvRII, CS102, MSP-3, ICC-1132 (malaria)
Particulate immunomodulators		
Virosomes	Unilamellar liposomal vehicles with H1N1 Influenza A/Singapore	Influenza, hepatitis A/B, synthetic peptides, bacterial toxins
PLG	Poly(lactide-*co*-glycolide) particles coated with cationic or anionic detergent	DNA, proteins
ISCOMS	Structured complex of saponins and lipids	HPV, HCV, NY-ESO-1 cancer antigen
DC-Chol	Lipoidal immunostimulator	*H. pylori* urease, HIV-tat
Microbial (natural and synthetic) derivatives		
MPL®	Monophosphoryl lipid A	Microbial and cancer antigens; Leishmania
RC-529	Synthetic MPL® analogue	Hepatitis B
MPL® plus L-tyrosine	MPL® (for TH1 induction) plus insoluble amino acid	Allergens
OM®-174	Lipid A derivative	Malaria CS peptide, cancer antigens
CpG ODN	Synthetic oligonucleotides containing CpG motifs	Hepatitis B
LT	Heat-labile *E. coli* toxin, transcutaneous delivery from a patch	Anthrax, hepatitis B, influenza
Modified LT (LTK63)	Genetically modified, non-toxic LT	Influenza
OmpI	*P. aeruginosa* surface lipoprotein, TH1 stimulator	*Leishmania*, ovalbumin, *M. tuberculosis* gp85
Endogenous human immunomodulators		
hIL-12	Cytokine, TH1 stimulator	HIV-env; *Leishmania*
Dendritic cells	Antigen-loaded DCs can be potent activators of the immune response	HIV, various; load with canarypox, adenovirus, or anti-DC antibody

Regulations Regarding Adjuvants

21 CFR 610 - General Biological Product Issues

21 CFR 610.15 Constituent Materials -

(a) Ingredients, preservatives, diluents, adjuvants

- "All ingredients … shall meet generally accepted standards of purity and quality."
  - Certificate of Analysis provided to IND (or a cross-referenced Master File)
  -
- "An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product."

Nonclinical Testing for Vaccines and Adjuvants

Current Approach to Nonclinical Testing Programs for Vaccines

Goals

- Maximize benefit-to-risk ratio of vaccine
- Toxicology studies in animals may provide:
  - Selection of a safe dose for clinical study
  - Determination of target organs
  - Identification of potential unexpected toxicities

Safety Data in the IND (1)

Provide sufficient CMC information regarding adjuvant *and* adjuvanted vaccine formulation intended for clinical use:

- **Raw materials, purification, identity, potency, pyrogenicity, and sterility or bioburden**
- **Product specific tests (*in vitro,* animal studies)**
- **Lot release/stability data**
  - **antigen content, degree of adsorption or association, particle size and distribution**
  - **stability of adsorption or emulsion, etc.**

Safety Data in the IND (2)

Provide available information on the adjuvanted vaccine formulation intended for clinical use:

- **Rationale for antigen and choice of particular adjuvant(s)**
- **Rationale for choice of dose/ratio of adjuvant to antigen (from pilot studies), etc.**
- **Encouraged to demonstrate immune response to antigen and immune potentiation by adjuvant (comparison of response to antigen with and without adjuvant)**

Safety Data in the IND (3)

Provide results from toxicology testing of novel adjuvant(s)* and adjuvanted vaccine formulation intended for clinical use:

- **Local tolerance and repeat dose toxicity testing**
- **Developmental toxicity testing (in BLA or prior to studies in pregnant women)**

- ***If no Master File exists for adjuvant, toxicology testing of adjuvant alone will be necessary**

Safety Data in the IND (4)

- Toxicology studies *may* not be required if :
- (on a case by case basis, determined by CBER DVRPA, i.e. preIND):
  - a new product sufficiently similar to another, but different product (i.e., a similar viral strain)
  - toxicity study would not provide useful information for safety assessment
  - sufficient prior human experience exists with the product or a similar product

Reference: WHO Guidance on Nonclinical Evaluation of Vaccines

- To globalize and harmonize recommendations and requirements for nonclinical safety evaluation for preventive vaccines across regulatory agencies
- Recognized by CBER
- Recognized by EU
- www.who.int/biologicals/publications/nonclinical_evaluation_vaccines_nov_2003.pdf

Approach to Toxicology Studies: General Remarks

- **Toxicity studies should be conducted in compliance with Good Laboratory Practices (GLP) as specified in 21 CFR 58. Area(s) of noncompliance should be defined and reason included (21 CFR 312).**
- **Test articles used in GLP studies should be from lots manufactured with the same production process, formulation, and release specifications as the lots intended for clinical use. Supporting stability data should be available.**

Approach to Toxicology Studies: Animal Models

- **Considerations for choosing a relevant animal model:**
  - ***US*** **- In general, one species is adequate; non-human primates usually not necessary**
  - **Choose species in which antigen is immunogenic and adjuvant augments immune response**
  - **Ideally, evaluate in animal model that allows challenge (species is sensitive to pathogen)**
  - **Include sufficient number of animals per sex per group**
  - **Evaluate quality of immune response, if possible**

Tox Study Design Considerations (1)

Dose level and frequency of administration:

- **At least one full human dose should be administered, not scaled for body weight or surface area, where feasible.**
- **Sufficient time between vaccinations should allow for the host immune response to develop (usually 2 weeks). Supporting immunology data usually acquired during study.**
- **At least one additional vaccination (n+1), relative to the clinical trial, should be incorporated.**

Tox Study Design Considerations (2)

- Use same route of administration (ROA) as planned in clinical trial.
- Use intended delivery device, if possible.
- Include appropriate control groups, e.g., placebo and recovery groups. Adjuvant-alone group(s) may also be useful
- Include sufficient numbers of animals per sex, group, and time point:
  - minimum of 3-5, small species (e.g., mice) usually warrant additional numbers.

Tox Study Design Considerations (3)

- Parameters to be monitored:
  - In-life procedures:
    - daily clinical observations
    - weekly body weights, feed consumption, and physical examinations
    - assessment of local reactogenicity, limb use impairment after each injection
    - full clinical chemistry, hematology, and immunology assessments after the initial vaccination in a series and at scheduled necropsies.

Tox Study Design Considerations (4)

- Parameters to be monitored (cont'd.):
  - Terminal procedures (1-3 days after final immunization and after 2-4 week recovery):
    - Assess histopathology of injection sites
    - Conduct necropsy (organ descriptions and weights) and comprehensive analysis of gross and microscopic histopathology on:
      - select tissues-pivotal and immune organs
      - or
      - full tissue list for novel adjuvants

Timing of Toxicology Studies

- Prior to initiating Phase 1 clinical trials; agreement prior to or during pre-IND meeting
  - Need to provide adequate information on clinical plan
- Submit protocols for CBER review prior to initiation of animal studies
- Submit toxicity study reports with the new IND or Master File:
  - Full tabulation of data, summary/line listings, well organized tables
  - Certificates of Analysis for test article(s) and supporting stability data
- Additional toxicity studies may be necessary as product/clinical development continues

Summary

- Regulations
- Nonclinical safety assessment:
  - Product - CMC, characterization
  - Pharm/tox testing= risk identification,
  - clinical relevance

- Clinical safety assessment
  - Risk vs. benefit

Contact Information

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CBER Guidance:

- **Web: www.fda.gov/cber/reading.htm**
- **Email: OCTMA@CBER.FDA.GOV**
- **Fax: 1-888-CBER-FAX**
- **Phone: OCTMA: 301-827-1800 or 800-835-4709**

Acknowledgements

M. David Green, Ph.D.
Marion Gruber, Ph.D.
Elizabeth Sutkowski, Ph.D.

Select Publications on Vaccine Adjuvants/Adjuvanted Vaccines

- Goldenthal, K. L., Cavagnaro, J.A., Alving, C.R., and Vogel, F.R.; *Safety Evaluation of Vaccine Adjuvants: National Cooperative Vaccine Development Meeting Working Group*; AIDS Res. Hum. Retroviruses, Vol. 9: S47-51, Suppl. 1, 1993
- Chang, P.Y., Sheets, R., Shapiro, S., Hargus, S., and Gruber, M.; *Vaccine Pre-clinical Toxicology Testing*; http://www.niaid.nih.gov/daids/vaccine/Science/VRTT/00_Main.htm
- Vogel, F.R., Powell, M.F., and Alving, C.R.; A Compendium of Vaccine Adjuvants and Excipients (2nd ed.); http://www.niaid.nih.gov/daids/vaccine/adjuvants.htm
- Workshop on Nonclinical Safety Evaluation of Vaccines (December, 2002) - Meeting transcripts available at: http://www.toxicology.org/ai/meet/cct-vaccines.asp

Select Guidance on Vaccines

- Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive Vaccines for Infectious Disease Indications, 2/2006
- Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, 4/2005
- Draft Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications, 2/2005
- EMEA-Guideline on Adjuvants in Vaccines for Human Use, 1/2005 & Explanatory Note on Immunomodulators, 7/2006
- WHO Guidelines on Nonclinical Evaluation of Vaccines - 2003 http://www.who.int/biologicals/publications/nonclinical_evaluation_vaccines_nov_2003.pdf
- Guidance for Industry: Content and Format of Chemistry, Manufacturing and Control Information and Establishment Description Information for a Vaccine or Related Product, 1999

Tissue list for collection in repeated dose toxicity study

- adrenal glands
- aorta
- bone (femur) and articulation
- bone (sternum) with bone marrow
- bone marrow smears (1)
- brain
- bronchi (mainstem)
- caecum
- colon
- duodenum
- epididymides
- eyes
- heart
- ileum
- injection site(s) (a sample will be taken from the area injected)
- jejunum
- kidneys and ureters
- larynx
- liver
- lungs
- lymph node (mandibular)
- lymph node (mesenteric)
- mammary gland
- oesophagus
- optic nerves
- ovaries and oviducts
- pancreas
- parathyroid glands
- Peyer's patches
- pituitary gland
- prostate
- rectum
- salivary glands (mandibular, parotid, sublingual)
- sciatic nerves
- seminal vesicles
- skeletal muscle
- skin
- spinal cord (cervical, thoracic, lumbar)
- spleen
- stomach
- testes
- thyroid glands
- tongue
- trachea
- ureters
- urinary bladder
- uterus (horns + cervix)
- vagina
- all gross lesions.