Update on FDA Workshop on Immune Globulins for Primary Immune Deficiency Diseases: Antibody Specificity, Potency and Testing

HHS Advisory Committee on Blood Safety and Availability

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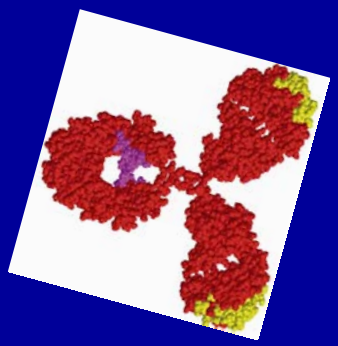
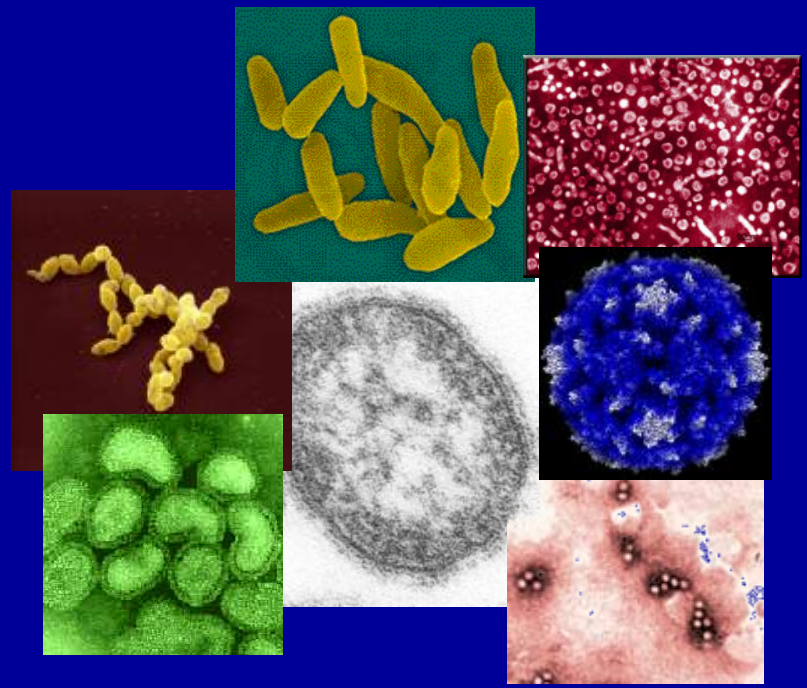
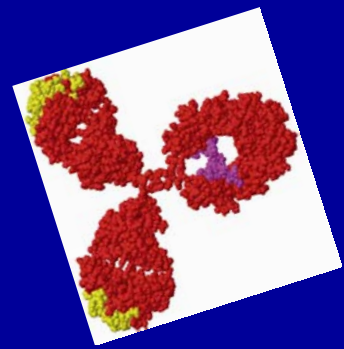
Immune Globulins for Primary Immune Deficiency Diseases

Antibody Specificity, Potency and Testing







April 25-26, 2007
Lister Hill Auditorium
NIH
Bethesda, MD

Workshop Goals

- Assess current potency testing of Immune Globulins
  - Current required tests for antibodies to measles, polio, and diphtheria
- List antibodies needed to protect Primary Immune Deficiency Disease (PIDD) patients from infections
- Identify candidate antibody specificities for potency testing of Immune Globulins for treatment of PIDD
- Address approaches to diminishing measles antibody levels in the Immune Globulin products

Workshop Structure (Day 1)

- Identify the most clinically relevant antibody specificities for PIDD patients
  - Epidemiology and surveillance data
  - Description of European (ESID) and U.S. (USIDNET) patient registries
- Review data on antibody levels in currently licensed products

Which antibody specificities would be useful and relevant to measure with respect to clinical importance and to assure lot-to-lot manufacturing consistency?

Which pathogens are of greatest concern in Immune Globulin treated and untreated PIDD patients?

- Epidemiology of infectious diseases in PIDD presented by clinicians
- Bacterial: *S. pneumococcus* and *H. influenzae* (including “non-typable”) most important bacterial infections
- Viral: EBV, CMV, echoviruses, VZV, adenovirus, coxsackie

Antibody Levels in Current Immune Globulin Products

- Presentations reviewed data on antibody levels in currently licensed products
  - Multiple specificities studied (FDA, industry presentations)
  - Trends over time, across products, and variations with plasma source
  - Emerging disease: WNV antibody titers measurable U.S. product (seasonal and locational variations)

Which antibody specificities would be useful and relevant to measure with respect to clinical importance and to assure lot-to-lot manufacturing consistency?

- *S. pneumoniae* and *H. influenzae*
  - Pilot testing of Immune Globulins proposed
    - Opsonophagocytosis and ELISA assays have been validated for serum
    - Reference labs already exist; WHO information and studies
    - Voluntary study– manufacturers send blinded samples to reference laboratory for testing antibody levels to determine feasibility, antibody levels and function
      - FDA/PPTA effort
    - Trough titer levels of antibody to these bacterial pathogens in PIDD patients receiving Immune Globulin could be measured to determine relationship between in vitro potency and in vivo levels – samples from clinical studies

Immune Globulin and Measles Antibodies (Workshop Day 2)

- Measles antibody levels are a standard lot release measure of potency in U.S. Immune Globulins
  - Historically important specificity
  - Tests available and levels are correlated with protection in normal subjects
- Measured by bioassay – hemagglutination inhibition or neutralization
- Declining antibody levels observed in products over past several years
  - Attributed to decline of titers in donor population
  - Regulatory impact: Lot release specification failure – lot must be rejected (21 CFR 211.165)
  - Supply impact: Lot release failures could impact supply of Immune Globulin products

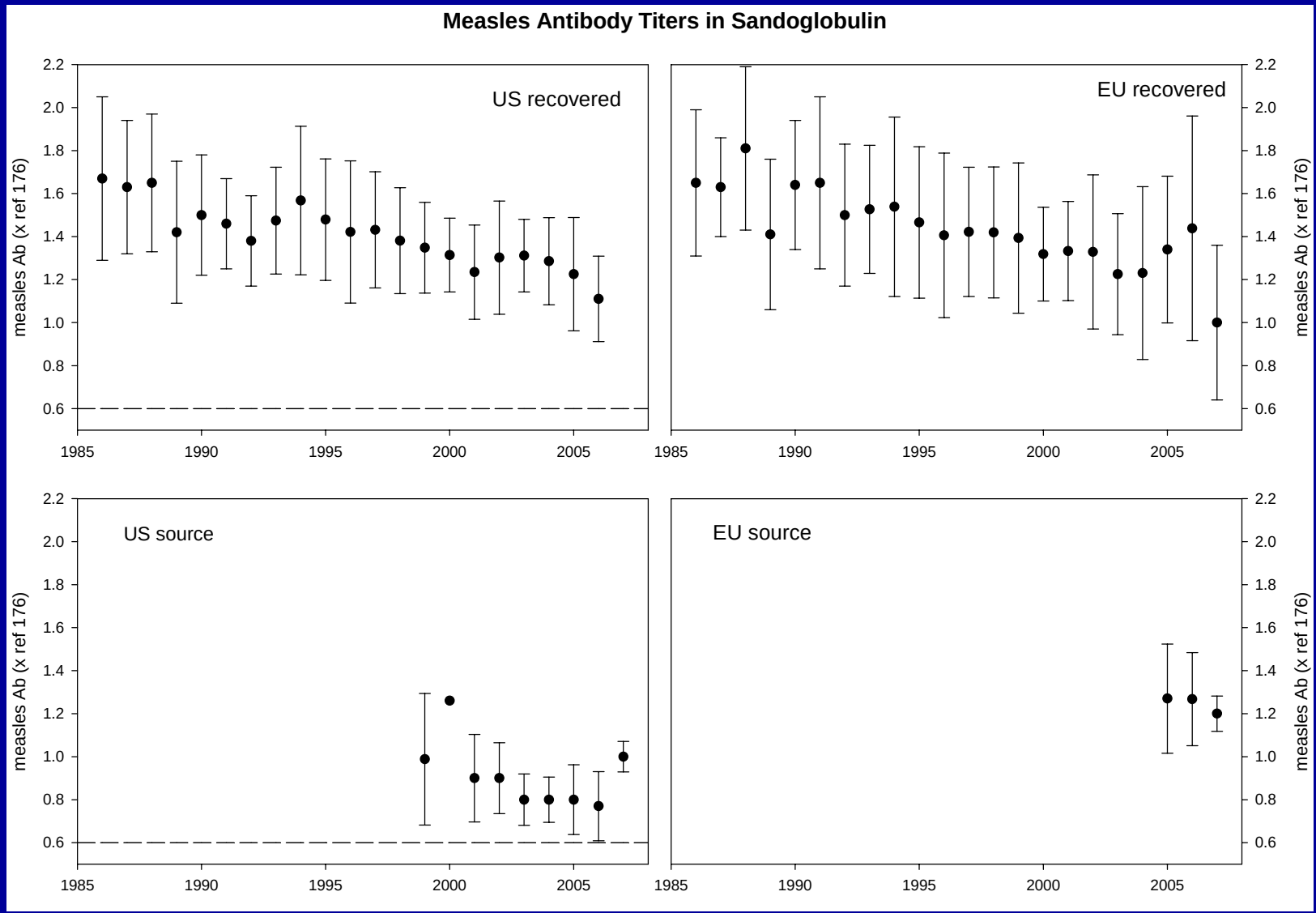
Questions for Panel and Audience

- Is measles infection of current clinical concern for PIDD patients?
- How much measles antibody is needed to attenuate or prevent measles in PIDD?
- What is the potential clinical impact of diminishing anti-measles titers in Immune Globulin products?
- What are possible approaches to address the decline of anti-measles antibodies in Immune Globulins:
    - With respect to clinical efficacy in prevention of measles infection?
    - With respect to utility as a test for lot-to-lot consistency?

Measles Antibodies and PIDD

- Measles outbreaks still occur in the U.S.
  - Relatively small numbers of patients, due to exposures outside U.S.
  - Travelers at risk in countries with low rates of measles vaccination
  - Patients with combined immune deficiencies (cellular + humoral) at most risk of severe disease
- Data at workshop: measles titers decreasing in
  - Donor plasma (Source and recovered)
  - Products, although the calculated trough titers would still be predicted effective
  - PIDD patients receiving Immune Globulin – neutralization data can be generated from clinical studies
- Precise protective level of antibody not certain in PIDD
  - Potential models: cotton rats; T and/or B-cell depleted primates, infected with measles

Trends in Antibody Levels



Peter Lerch, Head, Product Development, CSL Behring, Bern, Switzerland

Workshop presentation April 25, 2007

Possible Approaches to Address Declining Measles Antibody Levels in Immune Globulin Products: Workshop Discussion

- Gather relevant data relating Immune Globulin product titers to patient trough levels and estimated protective levels

- Option: CBER potentially can change recommendation on antibody potency
  - Must be scientifically and clinically justifiable

Immune Globulin Workshop – Next Steps

- Design and implementation of testing protocols to assess levels of binding and functional antibodies in Immune Globulin products to *H. influenza and S. pneumoniae* (Industry/PPTA/FDA)
  - Important/relevant specificities for PIDD patients
  - Evaluation for feasibility as potency tests
- Measuring measles antibody trough levels by neutralization assays in PIDD patients
- CBER/FDA deliberations on solutions to address diminishing measles antibody titers in Immune Globulin products
  - Scientific/clinical/supply concerns

Additional Information

- Workshop transcript – http://www.fda.gov/cber/minutes/workshop-min.htm
- Workshop presentations - http://www.fda.gov/cber/summaries.htm (posted for one year)