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Potency Testing for Immune Globulins: Time for a Change?

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"My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA."

Current Potency Tests for IG Products 21 CFR 640.104

- Purposes
  - Potency testing for "non-specific" immune globulins
    - "The ability of the method to recover specific antibodies shall be demonstrated by titrations for several antibodies…" *
  - Demonstration of lot-to-lot consistency
  - Test of antibody function
    - All tests are in vivo or in vitro bioassays – measure function; antibody integrity
  - Required potency tests with CBER-defined release criteria
    - Measles neutralization
    - Diphtheria "antitoxin"
    - Polio neutralizing antibodies, Type I, II, or III

* Minimum Requirements: Immune Serum Globulin; Dept. Health, Education, and Welfare April 9, 1953

Measles antibody titers serve as a potency test for lot release of all "non-specific" immune globulins in the U.S.

- 1944 – Demonstration of measles prophylaxis by IGIM (Stokes, J. Clin. Invest. 23:531-40, and Ordman J. Clin. Invest. 23:541)
- 1953 Minimum Requirements for Immune Serum Globulin (ISG) "several lots should be effective in prophylaxis of measles" *
- As measles potency tests became available, CBER developed standards (1st standard 1961)

* Minimum Requirements: Immune Serum Globulin; Dept. Health, Education, and Welfare April 9, 1953

Question

- Should measles titers be further lowered (from 0.48 x CBER Standard to 0.30 x CBER Standard), ensuring that future lots will meet specifications:
  - Evidence for declining antibody titers
  - Concern for supply – failure of release testing results in rejection of IGIV/SC lot
  - Concern for Primary Immunodeficiency (PI) patients – will “protective” titers be achieved?

Regulatory Pathway 2007

Manufacturers may voluntarily propose to change the measles antibody specification to 0.48 x CBER standard (adjusted for IgG concentration), as a Prior Approval Supplement, containing:

- Agreement to report measles in a PI patient as a 15-day report to FDA
- Labeling change that reflects the potential need for dosing alterations (timing, total dose) for a PI patient with potential or actual exposure to measles
- Data or a post-marketing commitment to determine measles trough level titers in PI patients receiving a known dose of measles antibodies
    - In context of upcoming, ongoing, or completed trial (with retention samples) for PIDD
    - Alternatively, a separate stand-alone trial is acceptable
    - Measles titers measured by functional assay

2007 regulatory approach for lowering measles specification from 0.60 x to 0.48 x CBER standard

- Protective level against clinical measles = 120 mIU/ml in normal subjects;
  - Sterilizing immunity ~ 1,000 mIU/ml
- Protective level unknown in PI patients
  - Likely to vary depending on type of immune deficiency
  - Proposed 240 mIU/mL serum levels
- FDA-proposed specification based on PK modeling – at 0.48 x CBER standard (adjusted for IgG concentration)
  - Goal to demonstrate that at this specification, IGIV given at 400 mg/kg would provide serum trough levels of at least 240 mIU/ml

Outcomes of trough level studies and PK modeling

- Data from industry studies affirmed likelihood of achieving trough levels greater than 240 mIU/mL with IGIV/IGSC with measles antibody potency at 0.48 x CBER standard
- Ability to achieve 240 mIU/mL trough titers for all patients with measles antibody potency at 0.30 x CBER standard in all cases is questionable

Experience since 2007

- No PI patient has been reported with measles infection
  - Exposures in US are rare
  - One death in an “immunosuppressed” patient related to Disneyland outbreak (measles post mortem diagnosis; no rash).
- Industry predictions of further decline in measles antibody titers
  - Actual decline of titers across lots and products has not been formally assessed for ~9 years
- FDA is not aware of lot rejections due to failure to meet measles antibody titers

Options Questions (1)

- Permit lowering of measles release titers?
  - Should be supported with data to demonstrate downward trends in titers
  - Lowering IGIV/SC measles antibodies diminishes risk of rejection of IGIV/SC lots (supply/economics)
  - Measles titers would remain as a lot release test only to demonstrate antibody function and process consistency
  - Lowering IGIV/SC measles antibodies impacts possible risk to PI patients
    - Role of GamaSTAN or similar products in post-exposure prophylaxis of PI patients

Options Questions (2)

- Could PI population be protected by post-exposure prophylaxis with a immune globulin licensed for measles post-exposure prophylaxis?
  - GamaSTAN (licensed in 1944) has an indication for measles prevention, based on historical data and is directly traceable to original IG's shown to be protective against severe measles infection in normal subjects
  - GamaSTAN dose to ameliorate measles is 0.5 mL/kg i.m., not to exceed 15 mL
  - Post-exposure supplementation of antibodies in PI patients with additional IGIV or GamaSTAN?

Options Questions (3)

- Label “high” measles titer IGIV/IGSC
  - Logistics/practicality
  - Definition of “high”
  - Labeling a titer without a claim
- Precedent concerns

Options Questions (4)

- Maintain current lot release titers by increasing measles antibody titers in donations
  - Immunization
  - Plasma selection
  - Donor selection
  - Imported plasma
- Feasibility

Polio Antibody Lot Release Testing 21 CFR 640.104

- For product consistency and antibody function
  - Polio IG not very effective historically
  - Immunocompromised patients are susceptible to colonization with live vaccine virus and revertant vaccine virus which can cause paralytic disease
- In vitro or in vivo neutralization test
- Lot release criteria differs for each strain; only one strain is required as a lot release test:
  - Type 1 0.28 x Lot 176
  - Type 2 0.25 x Lot 176
  - Type 3 0.20 x Lot 176

WHO Polio Eradication Program

- No wild type (WT) 2 or 3 viruses since 2012
- 70 cases of WT Type 1 paralytic polio in 2015 (Pakistan, Afghanistan)
- Live polio vaccine (OPV) replaced with killed vaccine (IPV) worldwide in 4/2016
- However - Live vaccine virus strains may persist in immunocompromised patients for years
  - FDA cases – SCID child, CVID adult

Laboratory Impact of Polio Eradication Program (1)

Adams and Salisbury, Science May 18, 2016 350(6261): 609.

"…the WHO Strategic Advisory Group of Experts on immunization reaffirmed April 2016 as the date for the globally synchronized withdrawal of type 2 oral poliovirus vaccine. This first step toward the eventual phased removal of all three vaccine types brings urgency to completing the destruction, and securing the containment, of type 2 wild polioviruses in all facilities. The fewer the places that hold either polioviruses or specimens that could contain polioviruses, the more certain we can be that they will not be released inadvertently. This means that the vaccine industry will have to comply with high levels of assurance of containment in their manufacturing processes. "

Laboratory Impact of Polio Eradication Program (2)

"Researchers and institutions holding samples collected from places where there could have been polioviruses must ensure that these are destroyed or secured under appropriate biocontainment levels. Countries will need to submit inventories of all laboratories to the GCC for review, and manufacturers and laboratories planning to retain type 2 polioviruses will need to be inspected for compliance with containment guidelines."

Effect of Polio "Eradication" on IGIV Lot Release Testing

- Impact on potency testing for IGIV's
  - Availability of virus
  - Cost of containment/administrative requirements

Replacement Potency Tests for IGIV?

- Criteria
  - Bioassay is feasible (demonstrates antibody function)
  - Release specification justifiable and reasonable
  - Levels of antibody from lot-to-lot not widely ranging; antibody should be common in donor population
    - Current potency tests for antibodies expected in US population due to widespread vaccination (MMR, diphtheria, polio)
- Potency tests related to infections in PI patients?

Next Steps - Discussion

- Are changes in measles antibody potency release specifications needed?
- Should polio antibody release testing be replaced with another specificity, if so, which one?