Enhancing the Collection, Analysis & Availability of Demographic Subgroup Data

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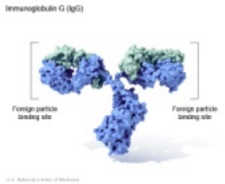
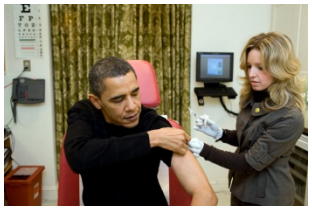
What is a biological product?

CBER Products



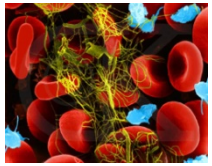
Blood Derivatives



Vaccines

(preventive & therapeutic)

Whole Blood



Allergenic Products

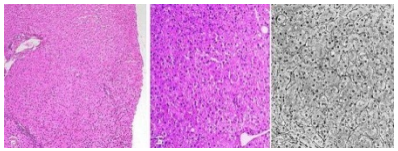
Blood Components

Worldwide Collaborations in Public Health

Emerging Infectious Diseases
Counter-Terrorism

Selected Devices

Cell & Gene Therapies



Human Tissues

Xenotransplantation products

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Part I – Report Findings

- Clinical trial composition for age, sex and race was included in the labeling and/or clinical reviews of the five products and thus the information is publicly available.
- The issue of subset analyses was addressed but in some applications, not all subsets were fully analyzed and the reasons varied

Quality Actions

- Modified Clinical and Statistical IND/BLA **reviewer templates**, to include demographic subgroup participation and analysis
- Incorporated demographic **subgroup analysis in benefit risk/review** discussion
- Incorporated the importance of demographic subgroup data inclusion, analysis, and communication into CBER's **New Reviewer Training Course**
- Education and training courses for experienced reviewers and other staff to better clarify **FDA's data collection and analysis expectations** related to demographic subgroups.

Quality Actions

- Post market:
  - Strengthened systems and infrastructure for making better use of data once products are broadly available on the U.S. market. CBER- **changes made to e-submission and CDISC programs to receive data by subgroups** in marketing/licensing applications
  - **CBER Sentinel processes and AERS** have incorporated demographic subgroup information into those systems to enhance analyses
- CBER requests an outcome analysis by sex, age, and ethnicity in the final clinical report or **annual report**
- Expanding language in **labeling** to reflect ***valid notable*** demographic subgroup differences

Participation Action Items-CBER

Implementing efforts to enhance appropriate use of enrollment criteria in clinical trial protocols

- CBER **pre-submission documents/meetings** with Industry to encourage greater demographic subgroup representation in clinical trials, subgroup analysis and communication of results
- Enhance discussions with sponsors:
  - **Enrollment criteria** to include all subgroups
  - **Analysis/trends of outcomes** by demographic subgroups
  - Language added to **response letters** for pre-submission meetings

Guidance Updates

- With CDER and CDRH continue to review, update, and/or finalize relevant industry guidance
  - ISE final guidance (published 2015)
  - Final Guidance for Industry and FDA Staff: Evaluation of Sex-Specific Data in Medical Device Clinical Studies. (August 2014)
  - Draft Guidance for Industry and FDA Staff: Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices (April 2015)
  - ICH Efficacy/Safety guidelines (ongoing)

Transparency

Lets give them something to talk about

- 907 Steering Committee
- Barb's Blogs / Scientific Publications
- AC Public Meetings
- IOM
- Workshops
- Feb 29th Public Meeting

Meetings/Workshops

- **IOM/OMH** Roundtable on the Promotion of Health Equity and the Elimination of Health Disparities meeting April 9, 2015
- **Workshop** on "Clinical Trials: Assessing Safety and Efficacy for a Diverse Population" -- co-sponsored by FDA & JHU CERSI December 2, 2015
- **Vaccines and Related Biological Products Advisory Committee** November 13, 2015 Open session: discussed considerations for evaluation of the safety and effectiveness of vaccines administered to pregnant women to protect the infant
- **Cellular, Tissue, and Gene Therapies Advisory Committee** February 25, 2014, discussed "oocyte modification and assisted reproduction for the prevention of transmission of mitochondrial disease or treatment of infertility"
- In collaboration with OWH, CBER scientists held a **symposium** on the thrombosis during pregnancy during the **Teratology Society Annual meeting**. September 2015
- **Workshop:** New methods to Predict Immunogenicity of Therapeutic Coagulation Proteins

Transparency
CBER Pilot

To improve the public availability of demographic subgroup data

- **Phase I Process and IT infrastructure**
  - Work process (FY2015)
- **Phase II Public Posting Plan**
  - launched January 2016

Transparency

For *new* approved BLAs posted on CBER's Approval Page

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts

Zemaira
STN: 125078
Proper Name: Alpha1-Proteinase Inhibitor (Human)
Tradename: Zemaira
Manufacturer: Aventis Behring LLC, License #1281
Indication:

Chronic augmentation and maintenance therapy in individuals with alpha1-proteinase inhibitor deficiency and evidence of emphysema

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Product Information

Package Insert - Zemaira (PDF - 101KB)[1]
-Patient Information

-

Demographic Subgroup Information- [Zemaira]

Refer to Section 1.1 of the clinical review memo for information about participation in the clinical trials and any analysis of demographic subgroup outcomes that is notable

Supporting Documents

July 8, 2003 Approval Letter - Zemaira[2]
STN 125078/0, indicated for use as chronic augmentation and maintenance therapy in individuals with alpha1-proteinase inhibitor deficiency and evidence of emphysema.

Summary Basis for Regulatory Action - Zemaira (PDF - 1.9MB)[3]

Related Information

FDA Online Label Repository[4]
Search this database for drug labeling and other information. The content has not been altered or verified by the FDA and may not be the labeling on currently distributed products or identical to the labeling that is approved.

New!

Demographic Subgroup Information – [Product B]

Refer to Section 1.1 of the clinical review memo for information about participation in the clinical trials and any analysis of demographic subgroup outcomes that is notable

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Transparency

Pregnancy and Lactation Labeling Final Rule

- **CDER/CBER** Published Dec 2014 – in effect June 2015
  - Applies to biological products subject to the Physician Labeling Rule. vaccines, allergenics and cellular and gene therapies.
  - In assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication,
  - **New:** **Females and Males of Reproductive Potential** subsection (8.3),includes information about the need for pregnancy testing, contraception recommendations, and information about infertility as it relates to the drug
  - The PLLR also requires the label to be updated when information becomes outdated.

Research - Pregnancy

Non-clinical issues of thrombosis in pregnancy

Protecting and treating mother and neonates from vertical transmission of HBV, HCV, and CMV during pregnancy

Pregnancy outcomes after exposure to vaccination including risk of spontaneous abortion after influenza vaccine

Influenza Vaccines and Pregnancy Outcomes

PK/PD of CBER regulated antibody therapies used during pregnancy to benefit the mother and the baby

safety and efficacy of IGIV when used to combat infectious diseases during pregnancy to better understand transplacental transfer of the antibody during pregnancy

animal model of pregnancy;

when used at the end of pregnancy HBIG may benefit the newborn & help prevent vertical transmission of hepatitis B.

Research - Age/Sex Differences

blood donors' travel &exposure behaviors by sex and age: different age groups donate differently; sample = accurate population data.

RISK OF VENOUS THROMBOEMBOLISM AFTER GARDASIL VACCINATION

Examine different age groups & their immune response to influenza vaccine w/ & w/out adjuvant

Clotting Factor Product Use And Same-Day Risk For Thrombotic Adverse Events, As Recorded In Large Health Care Database

Evaluating a biomarker in - neonates –to distinguish who experience thrombotic with neonates with no events

Research - Ethnicity Differences

The genetic determinants of immunogenicity to Factor VIII used in the treatment of hemophilia A

Examining different ethnic groups and their risk factors with developing inhibitors to factor VIII

X-linked bleeding disorders in carriers (women who carry mutated genes) may also need proper treatment of bleeding of hemophilia

Research-Outcomes in the Elderly

Retrospective cohort study of Medicare beneficiaries to assess the relative effectiveness of high dose inactivated influenza vaccine among the elderly.

Pilot case control study to evaluate the effectiveness and duration of protection of the Herpes Zoster Vaccine in persons >65+ yrs using data from CMMS and CDC

First population-based study of transfusion-related acute lung injury showed that elderly persons receiving blood transfusions in inpatient facilities are at significantly greater risk of developing the disorder

Comparative effectiveness of high-dose versus standard dose influenza vaccines in US residents aged 65 years and older

CBER conducted comparative effectiveness study to compare High-dose and Standard-dose influenza vaccination in medicare population 65 years and older.

The study suggested that HD is more effective in preventing influenza infection and influenza related hospitalization in elderly

CBER conducted effectiveness study to investigate the effectiveness of Herpes Zoster vaccination in medicare population 65 years and older

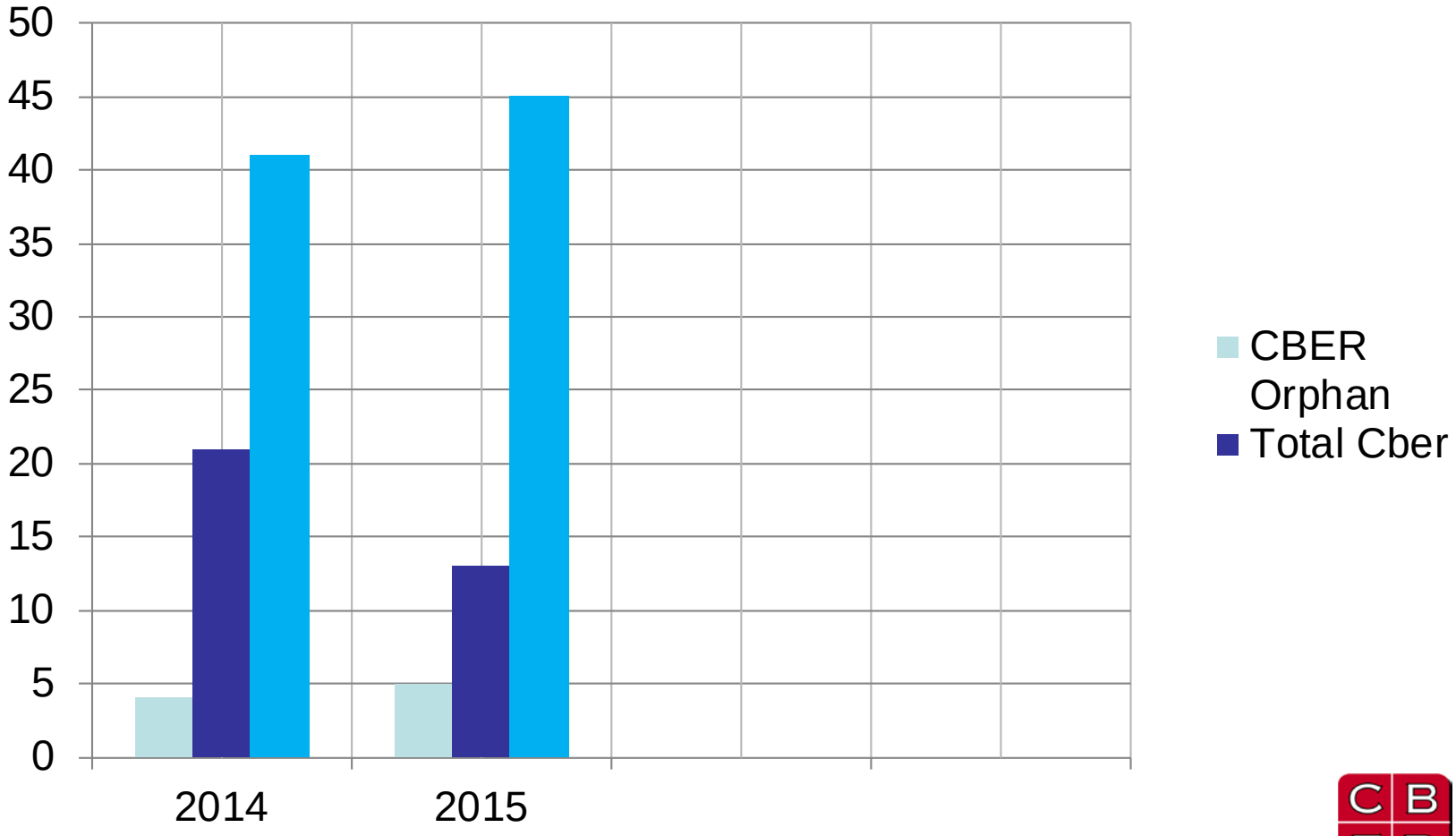
Observations

- Demographic information is routinely included in submissions
- Many sponsors have presented the results by demographics; if they leave it out, we do the calculations and include them in the review (descriptive)
- We look at these factors post hoc in completed phase 3 trials & we consider potential safety issues based on demographics in planning future clinical trials
- Have considered demographic issues in labeling, in the few products that we have labeled
- Vaccines are regularly analyzed by age, and often stratified by sex/gender
  - Elderly may have a lower response to a vaccine and safety profiles could vary by age
- HPV vaccines: studies done by gender/sex

Examples

- **Ruconest** (C1 -esterase inhibitor) showed regional and gender differences but they were hard to interpret. This was clearly spelled out in the label
- The **Factor VIII** products are primarily for males, but….
- **Prostate cancer vaccine** is indicated for older men
- We have asked sponsors to include efficacy and safety analyses by age, sex, race, and ethnicity in their final study reports. (e.g.) **Glassia** (Alpha-1 Proteinase Inhibitor)
- We have seen different *trends* in analyses of deaths by sex with **Prothrombin Complex Concentrates**
- We have seen differences in the magnitude of the placebo effect with **C1-esterase inhibitor products** between men and women (example: recombinant C1-INH)

Challenges



Ongoing Challenges

- **Self identification for sex**
  - confused with Gender identity
- **Self identification for ethnicity**
  - there is a lot of missing data on ethnicity (>half)
  - Sentinel search on “ethnicity” generated 80 different responses
- **Very few products have reached phase 3 or any trial with substantial numbers of subjects**
- **CBER products for small populations/rare diseases Indications for diseases with limited subgroup affected (e.g. Hemophilia)**
- For >95% effectiveness, **the high rate of effectiveness precludes the necessity of additional subgroup analysis (e.g. Vaccines)**

CBER POSTERS

Transplacental Transfer of Hepatitis B Neutralizing Antibodies during Pregnancy in an Animal Model: Implications for Newborn and Maternal Health;
Xu Y, Ma L, Zhong Z, Norton MG, Mahmood I, Zhong L, Zhang P, Struble E
CBER/OCTGT/DCEPT

Up close and personal: The genetic determinants of immunogenicity to Factor VIII used in the treatment of hemophilia A
Zuben Sauna CBER/OBRR/DHRR/LH

Efficacy of a Candidate Universal Influenza Vaccine in Mice of Different Ages
Mayra García[1,2], Julia A. Misplon[1], Chia-Yun Lo[1], Graeme E. Price[1], Suzanne L. Epstein **CBER/OCTGT/DCGTand CDRH**

A pharmacogenetic approach to immunogenicity: Implications for overcoming attrition owing to development of anti-drug antibodies during clinical trials using a Factor VIIa analog as a model
Zuben Sauna CBER/OBRR/DHRR/LH

Biomarkers of immune protection of genetically modified Live attenuated Leishmania donovani parasites in young and aged mice
Parna Bhattacharya
CBER/OBRR/DETTD

Development of a mouse model to mimic the responses of female and pregnant human subjects to avian influenza infections and to evaluate the protective efficacy of pandemic H5N1 vaccines;
Hang Xie
CBER/OVRR/DVP/LPRVD

Modulatory Effects of Progesterone on Maternal Immunity and Their Implications in Pregnancy-associated Susceptibility to Avian Influenza Infections in a Mouse Model addressing sex differences in response to avian influenza infections **Hang Xie**
CBER/OVRR/DVP/LPRVD

Thank you !