U.S. FOOD & DRUG ADMINISTRATION

CBER Response to:

Review of CBER's Current and Planned Post-marketing Safety Practices

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FDA Science Board Subcommittee members

- Lynn Goldman MD, MPH (subcommittee chair) :
- Russ Altman MD, PhD
- Chris Gibbons MD, MPH (Population health, IT, analytics)
- Tim Goodnough, MD (Transfusion, Internal Medicine)
- Saad Omer, MBBS, MPH, PhD (Epidemiology, Vaccines)
- Patrick Ryan, PhD (Population databases)

CBER VISION FOR POST-MARKET SAFETY MONITORING

- All patients' biologic product exposures and health outcomes are immediately and continuously accessible in automated database(s) allowing optimal detection and analysis of potential problems in biologics safety

- FDA will use many sources of data

- FDA will integrate automated signal generation from all sources with signal validation

FUNCTIONS OF THE OFFICE OF BIOSTATISTICS AND EPIDEMIOLOGY

Division of Biostatistics

- Review of clinical study and bioassay data
- Conducts statistical analyses
- Methods Development

Division of Epidemiology

- Review adverse event reports, pharmacovigilance plans, study protocols
- Conducts surveillance and epidemiological studies

FUNCTIONS OF THE OFFICE OF BIOSTATISTICS AND EPIDEMIOLOGY

Analytics and Benefit-Risk Assessment Team

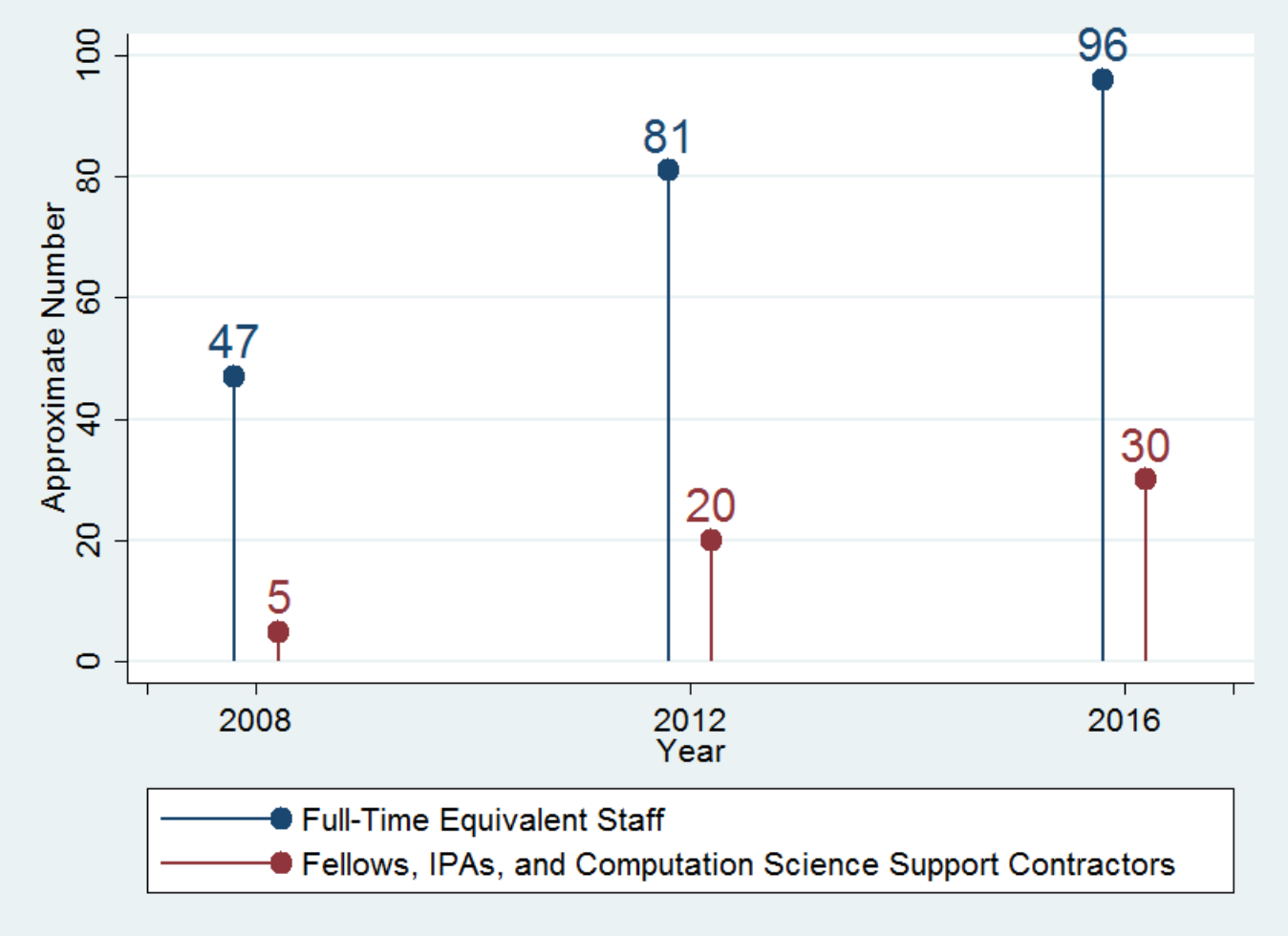
- Conducts quantitative benefit risk assessments & modeling
- Develops new methods for analyzing post-market observational data

Business Management Team

- Special support for contracting, visiting academic faculty and research fellows

CBER INCREASED POST-MARKET SAFETY MONITORING 2007-2016

OBE Substantial growth since 2007 FDAAA



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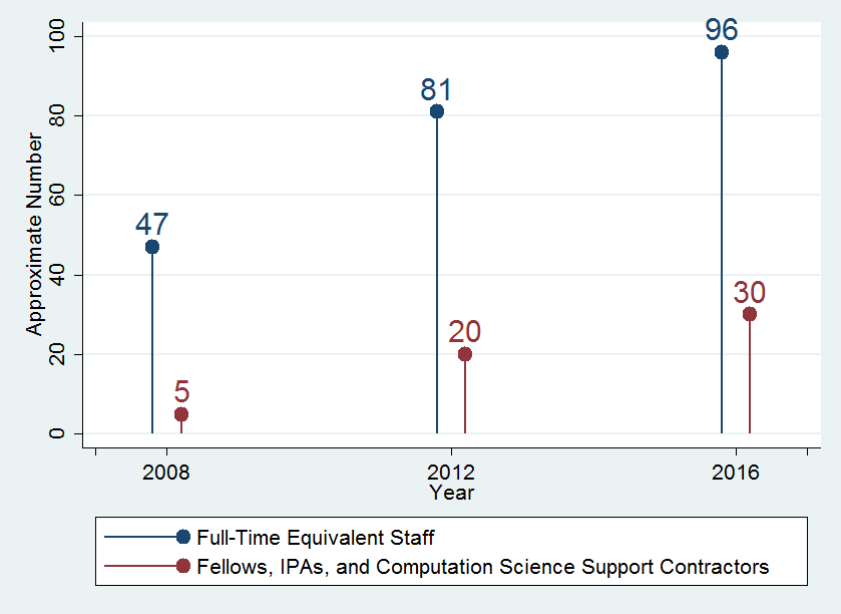


Increased staffing across the board, plus

- Analytical Epidemiology Branch

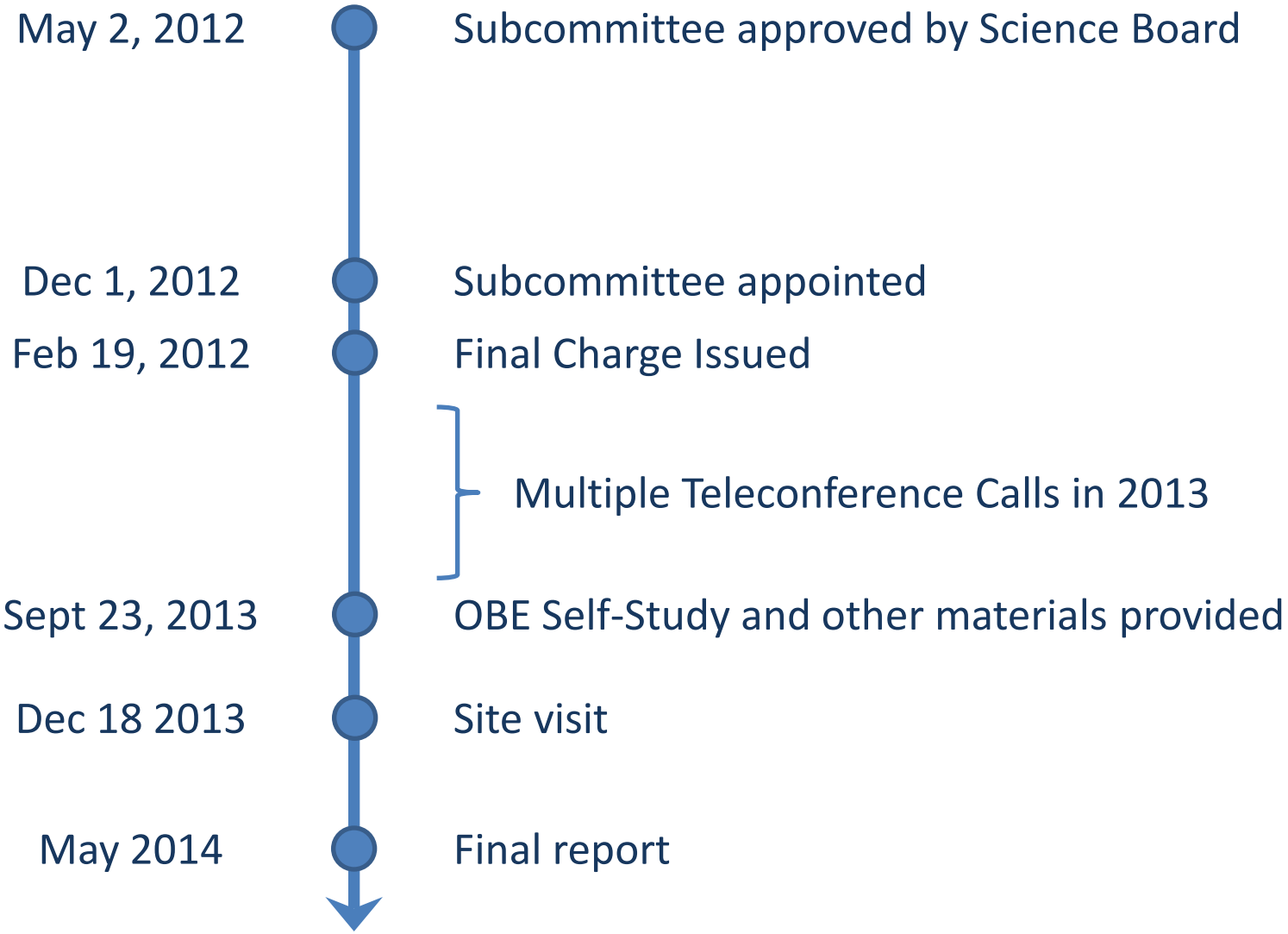
SUBCOMMITTEE'S CHARGE

- **Conduct** a review of CBER's current and planned post-marketing safety practices **for vaccines and blood products**. Review objectives include:
  - Processes and analysis tools FDA/CBER uses for identifying safety signals for CBER regulated products in FDA spontaneous reporting systems, especially the Vaccine Adverse Event Reporting System (VAERS) and the Adverse Event Reporting System (AERS)
  - Approaches FDA/CBER is taking to improve the use of population-based healthcare databases for both safety surveillance and hypothesis testing studies, including the FDA/CBER's mini-sentinel projects, PRISM and BloodScan; collaborative activities with other government agencies including CMS and CDC; and special studies with private health care providers

SUBCOMMITTEE'S CHARGE (Continued)

- Efforts to use genomic and other "omic" data from the post-marketing period to improve the safety of CBER regulated products, especially vaccines
- Efforts to develop and evaluate novel methodological approaches in the post-marketing safety areas outlined above

Review PROCESS/TIMELINE



ISSUES EXAMINED

- Processes and analysis tools FDA/CBER uses for identifying safety signals for CBER regulated vaccines, blood, and blood-derived products in FDA spontaneous reporting systems, especially the Vaccine Adverse Event Reporting System (VAERS) and the Adverse Event Reporting System (AERS);
- Approaches FDA/CBER is taking to use population-based healthcare databases for both safety surveillance and hypothesis testing studies of vaccines, blood, and blood-derived products including the FDA/CBER's Mini-Sentinel projects, PRISM and BloodScan; collaborative activities with other government agencies including CMS and CDC; and special studies with private health care providers;

ISSUES EXAMINED (Continued)

- Efforts to use genomic data from the post-marketing period to improve the safety of CBER regulated vaccines; and
- Efforts to develop and evaluate novel methodological approaches in the post-marketing safety areas outlined above.

SELF STUDY AND MATERIALS REQUESTED/REVIEWED

Items generated by CBER:

- Research strategy
- Listing of CBER-funded research projects related to post market surveillance of blood and vaccine products
- Biosketches of CBER researchers in this area
- Organization chart indicating the location of CBER researchers in this area
- Listing of CBER-funded extramural grants and contracts related to research in this area
- Budgetary resources for research in this area, including FTE, extramural and intramural funds
- Non-budgetary resources for research in this area, e.g., laboratories, libraries, computing resources, support contracts, pre-doctoral and postdoctoral fellows, etc.
- Case studies for both vaccine and blood products

COMMITTEE HAD A NUMBER OF RECOMMENDATIONS

- The CBER OBE Self Study provided an excellent basis for our review and we agreed with most of their conclusions
- **The site visit:**
  - well worthwhile
  - very much improved our understanding of the workings of OBE and how they develop the scientific underpinnings for that work
- **Recommendations were in several areas:**
  - general,
  - science and resource management,
  - population surveillance,
  - spontaneous reporting and
  - genomics

Committee Recommendations: General

- CBER needs to more effectively communicate its activities in OBE
- It needs an anticipatory process to adapt its approaches to changes in the healthcare delivery system
- OBE needs to consider how to improve its capture of adverse effects on subpopulation groups like minorities and women

OBE Response 1

Improving communication and outreach

- CBER One-day Workshop planned on PRISM: December 7th, 2016
- Held first annual OBE Science Day and participated in CBER Scientific Impact Series, CBER Science Symposium, and other CBER meetings
- Presentation of Sentinel, CMS, and other study outcomes at FDA-CBER product Advisory Committee Meetings
- Numerous presentations at scientific meetings and publications in peer-reviewed journals

OBE Response 2

Anticipatory Process

- Methods and Infrastructure Development Projects in Sentinel:
  - Analysis of EMR data from Health Corporation of America
  - Improving methods for sampling medical charts for review
  - More timely queries of Sentinel data / Pandemic preparedness
  - Analyzing data by geographic location to support decision-making for emerging infectious diseases
  - Data mining using TreeScan for AE signal detection in Sentinel
- Informatics to improve the review of adverse event reports
  - Deploying text mining and network analysis tools to improve review of adverse event reports
  - PCORTF collaboration with CDC to develop NLP web service for structuring and standardizing unstructured clinical information

OBE Response 3

Activities to study subpopulations

- FDA published an action plan to "Enhance the Collection and Availability of Demographic Subgroup Data" in August 2014
  - Priorities are to improve the quality of data collection, the participation of individuals from relevant subgroups, and the transparency of subgroup data reporting
- Medwatch and VAERS updated to include race and ethnicity
- Race/ethnicity data are not captured well in post-market medical databases (~30%)
- Postmarket analyses of AEs using Sentinel, CMS and others usually evaluate sex-specific differences

Committee Recommendations: SCIENCE AND RESOURCE MANAGEMENT

- This issue was flagged in the self study
- Budgets for FTE and other resources need to be more clearly articulated, stable and predictable
- Staff vacancies need to be filled more quickly. We are concerned about the recent departure of a number of medical officers and recommend that exit interviews be conducted to understand factors related to attrition
- OBE needs to more vigorously engage the scientific community in its work
- OBE scientists need to have a stronger presence publishing and presenting their work at scientific conferences

OBE Response

Budget

- OBE receives base funding for Sentinel and PM safety projects
- CBER new budgeting process provides forward funding for most of the OBE budget
- 'End of Year' funding used

OBE Staffing

- Continuous challenges with FDA HR – but situation is improving
- Several departures in past year – DE Director, Deputy and AEB Branch Chief
- Recent Leadership Recruitment:
  - New DE Director, Scott Proestel
  - Deputy Office Director, Telba Irony
  - AEB Branch Chief, Deepa Arya
  - PVB Branch Chief, Meghna Alimchandi

Committee Recommendations: POPULATION SURVEILLANCE

- CBER should consider establishing Data Safety Monitoring Board – like processes as a way of obtaining more robust external scientific review. Science workshops would also provide enhanced external input
- We support the focus on surveillance of pregnancy related outcomes
- We recommend expanding and strengthening international collaborations particularly for rare but clinically important outcomes

OBE Response 1

Number of ongoing PRISM studies of vaccine safety during pregnancy

Improving scientific review

- Established FDA and CBER governance systems for all Sentinel activities
- Includes scientific and management oversight
- Holding public workshops and present findings at advisory committees

OBE Response 2

Expanding and strengthening international collaborations

- OBE has numerous international collaborations
- Monthly call with European Medicines Agency to discuss Pharmacovigilance drug and biologic product specific issues
- CBER funds WHO Co-Op agreement to pilot work in pharmacovigilance using worldwide hospital-based surveillance network
- CBER participation in ADVANCE – a European Commission-Innovative Medicines Initiative (IMI) project to establish population-based surveillance system
- WHO Uppsala Monitoring Center sharing of FAERS data and OBE staff have participated in annual PV training
- OBE staff regularly participate in annual WHO Global Vaccine Safety Initiative meetings

Committee Recommendations: SPONTANEOUS REPORTING

- We would recommend that CBER expand the requirements for manufacturers to include events occurring outside the US and to be more proactive in exchanging safety information with other national regulatory authorities
- Blood product adverse event reporting needs to be extended to serious events other than those resulting in mortality
- We support CBER's exploration of social media approaches

OBE Response

- FAERS does include AE reports from outside of US
- Safety Reporting Rule (SRR) will require reporting of serious AEs
- FDA has sponsored contracts for exploring use of social media to support PM surveillance and safety activities. OBE staff participate in these efforts

Committee Recommendations: GENOMICS

- We support CBER's effort to recruit scientists with expertise in genomics and informatics related to genomics data
- We support CBER collaborating across FDA centers and with academics to more quickly increase its pool of expertise
- Again, there is a need to expand the range of scientific input being made available to CBER and specifically in this area to make use of external peer reviewers in the development and evaluation of projects to assure that the portfolio of projects is more at the state of the art
- CBER, and FDA generally, need a stronger computational infrastructure and scientific staffing to support the analysis of genomics data

OBE Response 1

- As of January 2015, OBE manages the High-Performance Integrated Virtual Environment (HIVE) computing resource – a cloud-based environment for storage and analysis of data
- HIVE provides NGS capability and analysis of data from a variety of sources to support regulatory decision-making
- Support for scientific computing including an FDA annual Scientific Computing Day

OBE Response 2

- OBE has completed one vaccine-related genomic project and another is ongoing

IN CONCLUSION

- Overall, review of OBE Postmarket Safety Program was very constructive and positive
- OBE is grateful to the FDA Science Board Subcommittee for:
  - Taking their time to conduct the review
  - Their enthusiasm and dedication
  - Providing useful insights and advice on the important safety work that OBE and DE do every day


CBER
FDA
WHITE OAK CLASSIC


FINISH
STOP
STOP
Gut Risk?
Risk Analysis Branch

Thank you!