Biovigilance in the USA: Regulatory Perspective

Steve Anderson, Ph.D., M.P.P.
Office of Biostatistics & Epidemiology
Center for Biologics Evaluation and Research
US Food & Drug Administration

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HHS Biovigilance Gap Report

www.hhs.gov/ash/bloodsafety/biovigilance/index.html

- "Biovigilance: Efforts to Bridge a Critical Gap in Patient Safety and Donor Health“ - 2009
- Gaps identified:
  - Patchwork system of adverse event (AE) reporting
  - Likely under-reporting of transfusion AEs
  - Need more/better donor and recipient denominator data, case definitions, training
  - No national surveillance of donor serious AEs other than fatalities
  - Need timely analysis of reported data

Reasons for US Biovigilance deficiencies

- Absence of national blood system
- Very strong investigator-initiated and federally-funded epidemiologic research
- Transfusion Services and Blood Establishments under tight financial restraints
- Barriers to data-sharing
- Lack of investment in areas such as ‘near real time’ data analysis/interpretation
- Legal and Regulatory liability

Biovigilance: Regulatory Perspectives and Needs

- Near real-time signal detection and resolution
- Increased power for surveillance
- Ability to conduct specific, rapid follow-up to identify and act on unsafe products/practicies
- Denominator data
- Harmonization of data/case definitions/reporting
- Universal reporting from regulated manufacturers, least-burdensome as possible

Major Biovigilance Concepts in Presentation

Biovigilance focus is on safety of Donors and Recipients

Big Data – playing an increasingly important role

New Technologies - Big Data, Machine learning, new therapies, etc.

Automation – potential to advance data analysis and input, assisted review medical charts, etc.

Elements of FDA Hemovigilance

1. Passive Surveillance Systems:

- Review of Fatality reports in donors and recipients
- FDA Adverse Event Reporting system (FAERS)

2. Active Surveillance Systems:

a. Serological testing and monitoring

- Transfusion Transmitted Infections Monitoring System (TTIMS)

b. Vigilance using large Medical databases

- FDA / CBER Sentinel Initiative
- Center for Medicare & Medicaid Services

c. CDC- NHSN National Healthcare Safety Network

1. Passive Surveillance: FDA Blood Safety Required Reporting

- Product deficiencies
  - Biologic product Deviation reports (BPDR)
  - Medical device reports
- Fatalites – donors and recipients
  - Notify FDA-CBER as soon as possible, submit written report 7 days
  - Reviewed by CBER team
- Severe Adverse Events – *Pending*

- Data collection form for required reporting of FDA-approved pharmaceuticals
- Supports voluntary report to FDA for Blood Donors and Recipients
- CBER receives >10,000 AE reports for blood and tissues every serious, unexpected report reviewed by physician

1. Passive Surveillance (cont'd)

- Strengths:
  - Timely information on AEs compared to other data sources
  - Can capture rare AEs
  - Nationally representative

- Limitations:
  - Lack denominator data / lack rate data – difficult to identify trends
  - Significant level of incomplete report details
  - General underreporting of AEs
  - Biases in reporting – e.g. prompted reporting, etc

Passive reporting: Application of new Technologies to aid review

FDA and IBM Watson Contract

Project objective – investigate use of IBM Watson to assess FAERS reports using the WHO-UMC Causality Criteria

Approach

- 1,000 FAERS reports scored by FDA staff
- 5,000 FAERS/VAERS reports scored by IBM
- Machine learning training /evaluation with subset of FAERS reports

Benefits

- Automation/semi-automation could reduce physician review time and effort

1. FDA Passive Surveillance (cont'd)

FDA and IBM Watson: Conclusions and Next Steps

- Results show promise of Natural Language Processing and Machine Learning for use in Pharmacovigilance
- Probable/Likely reports scored higher (~90%) than reports that were less certain (e.g., possible, etc.) scoring correctly <70% of the time
- Further work needed

2. FDA Active Surveillance

a. Serological testing and monitoring

Transfusion Transmitted Infections Monitoring System (TTIMS)

b. Vigilance using large Medical databases

- FDA / CBER Sentinel System
- Center for Medicare & Medicaid Services

2a. Active Surveillance: Transfusion-Transmissible Infections Monitoring System (TTIMS)

Objective: To develop a database representing **>60% of the US blood supply** to monitor transfusion-transmissible infections

- Monitor incidence, prevalence and behavioral risk factors of **HIV, HBV, HCV infections** in blood donors
- Partners: American Red Cross and Blood Systems Inc., several blood centers, NIH, HHS, CDC.
- Includes behavioral risk factor questionnaire of risk factor characteristics of HIV, HBV and/or HCV-NAT yield-positive donations

2a. Active Surveillance: Transfusion-Transmissible Infections Monitoring System (TTIMS)

- Are there changes in rates of infection? impact of blood safety strategies? i.e, US change in MSM policy – before and after late 2016?
- 2-Years of data – Preliminary data being analyzed
- Expect completion of 2-Yr data collection and analyses in early 2019

2b. Active Surveillance: Vigilance with large Medical databases - 'Big Data'

FDA / CBER Sentinel Initiative

1. FDA Sentinel (Contract: Harvard Pilgrim HealthCare Inst.)

2. Biologics Effectiveness and Safety (BEST) Initiative

   September 2017

   - Contract #1: Data, Tools, and Infrastructure for Surveillance of Biologics
   - Contract #2: Innovative Methods to Automate and Improve Active Hemovigilance

2. Active Surveillance

FDA / CBER Sentinel

1. Harvard Pilgrim Health Care Institute

- Covers >225 million persons – claims (billing) data
- Data Sources: 17 Data Partners (insurers, payers)
- BloodSCAN program - Blood Surveillance Continuously Active Network
- Active surveillance system – provides denominator data
- Distributed data system – data held by partner and protects patient privacy
- Sentinel Common Data Model and Tools

1. FDA Sentinel Program: Harvard Pilgrim

Eight years of prior CBER Sentinel Active surveillance has been based on Harvard-Pilgrim

Strengths:

- Allowed FDA to meet Congressional mandate of FDAAA 2007 (>100 million patient records to evaluate safety)
- HCPCS, CPT, ICD-9/ICD-10 codes
- Several transfusion/blood derivative-related outcome studies reported by FDA

Limitations:

- Transfusion /Blood AEs extremely not easy to study in the system
- Timeliness
- Expense

FDA / CBER Sentinel Harvard Studies

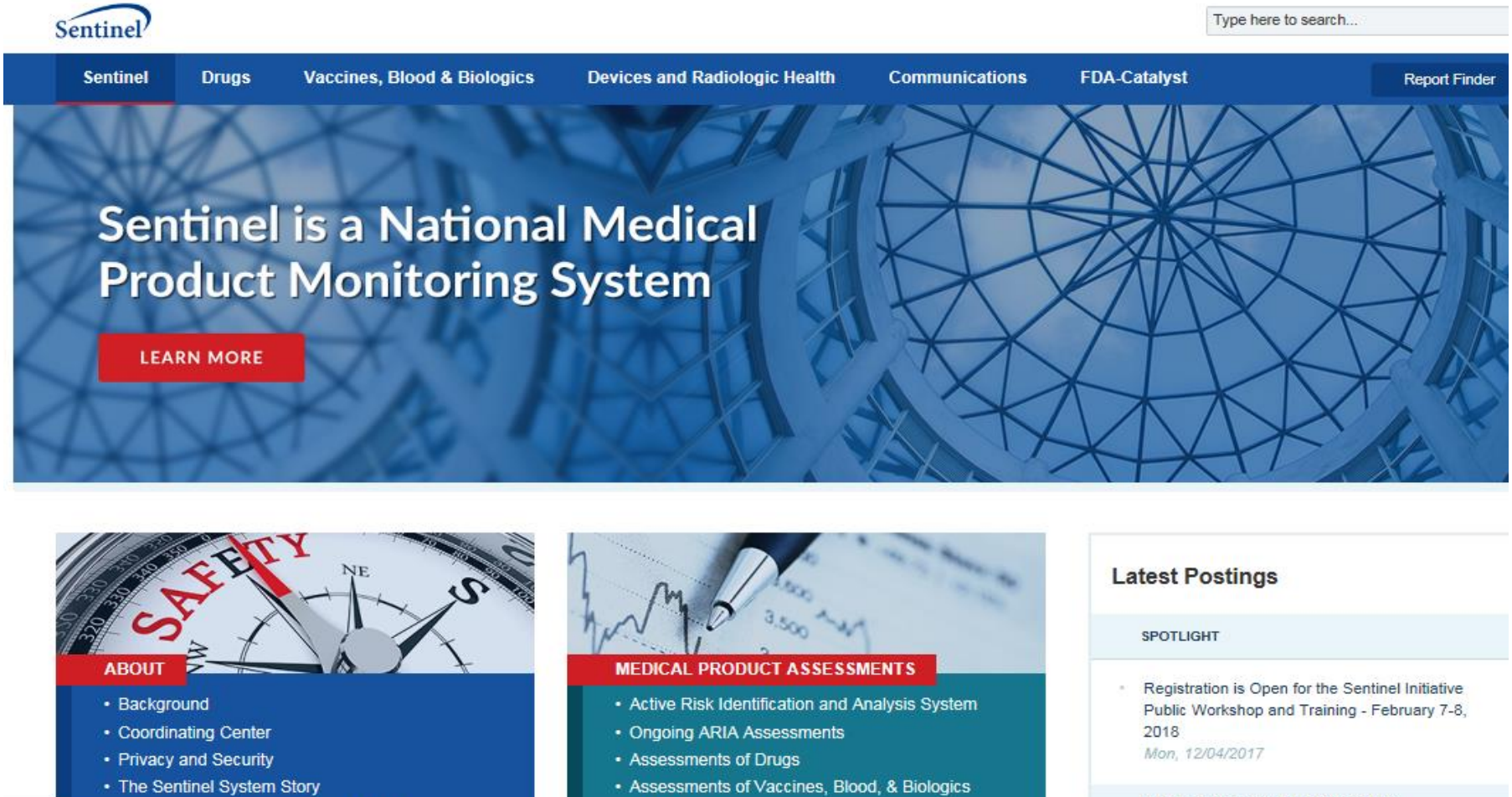
Several Blood product safety studies conducted:

1. Immune globulins - thromboembolic events (3 published studies)
2. Transfusion risks of TRALI (completed)
3. Platelet transfusion adverse events (underway)

Queries:

1. Transfusion characterization during pregnancy (Zika risk)
2. Utilization of Factor VIII products in the US

More information on CBER and FDA Sentinel Projects found at: www.sentinelinitiative.org



2. BEST: Biologics Effectiveness and Safety Initiative

Launched as a pilot in September 2017

Two one-year BEST contracts ($2.5 million ea.) awarded to:

IQVIA / OHDSI (Observational Health Data Sciences and Informatics)

- Contract 1: *Surveillance system for **Blood** using EHRs Products: Data, Tools, and Query system*

- Contract 2: *Develop Innovative methods to Automate AE Reporting for **Blood** using EHRs, Artificial Intelligence, NLP, etc.*

Active Surveillance (cont'd)

FDA / CBER Sentinel BEST Initiative

BEST and IQVIA*/OHDSI

- Covers ~20 million persons with EHR data
- Covers 160 million persons with claims data
- Data Sources:

  EHR Data Partners (at POC)

  Claims Data Warehouses/Processors
- OMOP Common Data Model and OHDSI Tools

* formerly QuintilesIMS

Why BEST?

Goals

- First generation Sentinel system worked poorly for evaluating blood/transfusion AEs – needed another option
- Provide new data electronic health record (EHR) sources
- EHR data: Reduced access time for medical charts
- EHR = >2 days vs Claims (paper charts) = 7- 9 mos
- Address unique challenges of Blood and Blood Products
- Employ cutting edge technologies – semi-automated chart review, Machine Learning, Natural Language Processing, etc.
- Reduce inefficiencies and costs (e.g., chart review, quicker data access, etc.)
- Deliver "*Better, Faster, Cheaper*" capabilities and capacity

BEST Contract # I. Data, Tools, and Infrastructure for Surveillance of Biologics

Develops system for FDA to conduct:

- Routine surveillance of product safety
- Epidemiological studies of potential safety signals
- Studies of product effectiveness
- Monitoring spread of emerging infectious diseases and risks to donors
- Queries to quickly evaluate simple regulatory questions such as number of transfusions by product type, incidence of an AE, or combination thereof, etc.

BEST: Contract 1 Accomplishments first 6 months

Foundational Work for Blood Product Query System

- Incorporated ISBT-128 Coding System into OMOP CDM (~14,000 codes)
- Built library of multiple coding systems for EHR databases: blood components/products, tissues and advanced therapies

- Queried ~4000 codes (equivalent to 160 simple queries)
- 2 Epidemiological studies

- Conducted 3 training sessions for FDA CBER staff

BEST Contract #2: Innovative Methods for Automated Reporting for Blood Products

Goal: Use new, innovative technology to advance blood safety

To use case definition elements /key words/concepts to mine AE data from EHRs; populate an FDA AE report form and automatically submit to FDA via MedWatch or other means

Approach:

- Improve the quantity and quality of blood product exposure and safety surveillance beyond the capability of current code-based systems
- Use technology such as Machine Learning, Natural Language Processing, etc. to mine AE case codes (ISBT-128) and information from EHRs
- Informative data mined from fields with free text such as nurse or physician notes, etc

BEST NLP Development Work in Progress

- NLP Templates being built based on each element of ISBT WP/AABB surveillance case definitions
- **Medical judgement needed regarding how each of the elements may be described in EHR text ('term set")

- Build NLP computable phenotype (patient cohort) via iterative analysis and chart validation
- Query larger EHR datasets

- Currently evaluating Sepsis (AABB) and TACO (ISBT WP original and revised definitions)

BEST Automated Case Reporting Development Work in Progress

- Currently evaluating Sepsis (AABB) and TACO (ISBT WP original and revised definitions)
- Identify transfusion exposure and outcome (Exposure + NLP phenotype = FLAG)
- Final Individual Case Study Reports (ICSR) will be constructed for electronic submission to the FDA MEDWatch/FAERS adverse event reporting system

Active Surveillance: Center for Medicare & Medicaid Services (CMS)

- Large medical database system
- Covers 50 million persons >65 yrs old in US, disabled persons
- Largest government health insurance program
- Covers >95% of elderly persons in US
- Inpatient (hospital), and Outpatient care
- Claims (billing) data
- CBER and FDA have used these data since 2003

Active Surveillance: Center for Medicare & Medicaid Services (CMS)

Numerous FDA blood safety studies published:

- TRALI and potential risk factors
- TACO and potential risk factors
- Immune globulins and Thromboembolic events (TEE)
- Clotting Factors and TEE
- Babesiosis occurrence
- Febrile Non-hemolytic reactions in Elderly
- Postransfuion Purpura
- Many others

CDC Voluntary Hemovigilance Reporting: NHSN

- **Goal:** Establish comprehensive system for multiple end-users and multiple uses

- CDC NHSN System – National Healthcare Safety Network
- Healthcare facilities to track transfusion AEs for a dozen events such as TACO, TRALI, TAD, allergic rxns, etc.
- Voluntary, functionally anonymous, mostly surveillance design
- >250 US hospitals participating

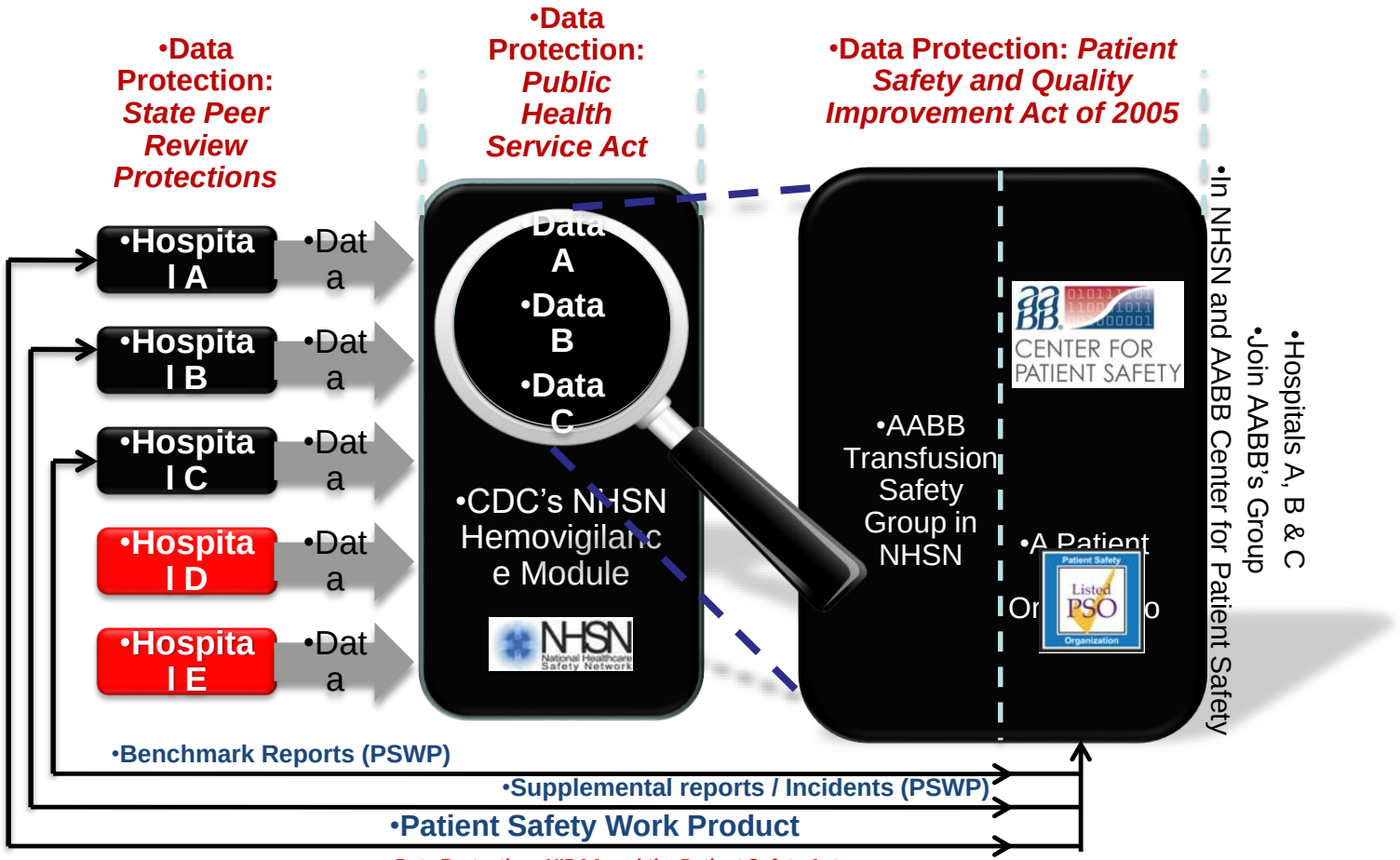
AABB Center for Patient Safety

- AABB established the Center for Patient Safety (CPS), a Patient Safety Organization, so that hospitals reporting to NHSN may share their data and maintain confidentiality and protections.
- Why a PSO?
  - Allows the privileged and confidential reporting of patient safety information for the aggregation and analysis of patient safety events without fear of legal liability or professional sanctions.
- AABB CPS is the **ONLY** transfusion safety PSO!

CENTER FOR PATIENT SAFETY

•www.aabb.org

•AABB Center for Patient Safety
•Data Flow & Protection



•Data Protection: *HIPAA and the Patient Safety Act*

•Note: Reports, benchmarking, analysis, etc. cannot be returned to participating facility without the HIPAA Business Agreement and AABB's Participation & Confidentiality Agreement in place.

CENTER FOR PATIENT SAFETY

Current CPS Participation

- 115 participating hospitals (24 of which are on-boarding)
  - < 300 beds: 33
  - 300 to < 400 beds:13
  - 400 to < 500 beds: 12
  - 500 to < 600 beds: 7
  - 600 to <900 beds: 10
  - >900 beds:7
- 10 Childrens Hospitals

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•www.aabb.org

Biobigilance and Advanced Therapeutics: Gene Therapies

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FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

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For Immediate Release August 30, 2017

Release

YEAR IN REVIEW CANCER, IMMUNE SCIENCE, 2017 TOP 10

Approval of gene therapies for two blood cancers led to an 'explosion of interest' in 2017

CAR-T cell therapy treats patients for whom other therapies haven't worked

USA TODAY

NEWS SPORTS LIFE MONEY TECH TRAVEL OPINION 25° CROSSWORDS WASHINGTON DETROIT AUTO SHOW VID

10 medical advances that raised our hopes in 2017

Kim Painter, Special for USA TODAY Published 3:16 p.m. ET Dec. 14, 2017 | Updated 3:19 p.m. ET Dec. 14, 2017

Advanced Therapies and Pharmacovigilance

FDA Approved three gene therapy products in 2017

- Two CAR-T Cell Products – Kymriah, Yescarta
  - Cancer Immunotherapies
- Rare Childhood Blindness - Luxturna

Risk Management for Advanced Therapies

Benefit-Risk Assessment – B-R balance can be favorable with risk mitigations

1. **REMS Program instituted** for the two CAR-T Products: to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities

   Kymriah REMS
   - https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=368

   Yescarta REMS
   - https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=375

2. **Post Market Requirement (PMR)**
   - Observational trial 1,000 patients long-term 15 year follow-up – endpoints: malignancy, AEs

Biovigilance: Blood Products and New Advanced Therapeutics

- New therapies may require new strategies to monitor product safety and effectiveness (e.g., coding, etc.)
- Engage passive and active surveillance to ensure safety
- FAERS
- Active surveillance with Sentinel, BEST and CMS systems
- Long-term follow-up of patients needed but may be challenging since current medical databases not linked among insurers

Recent Safety Activities: Stem Cells

FDA U.S. FOOD & DRUG ADMINISTRATION

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FDA News Release

FDA warns US Stem Cell Clinic of significant deviations

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For Immediate Release August 28, 2017

Release

The U.S. Food and Drug Administration today posted a warning letter issued to US Stem Cell Clinic of Sunrise, Florida, and its Chief Scientific Officer Kristin Comella for marketing stem cell products without FDA approval and for significant deviations from current good manufacturing practice requirements, including some that could impact the sterility of their products, putting patients at risk.

"Stem cell clinics that mislead vulnerable patients into believing they are being given safe, effective treatments that are in full compliance with the law are dangerously exploiting consumers and putting their health at risk," said FDA Commissioner Scott Gottlieb, M.D. "As the FDA takes new steps to advance an efficient, modern approach to the regulation of cell based regenerative medicine, at the same time we will be stepping up our enforcement actions against clinics that abuse the trust of

Summary

- Biovigilance is ongoing in the US and employs
  - Passive surveillance
  - Active surveillance
- More/better coordination among partners needed and is improving
- US PHS agencies leveraging new technologies to improve biovigilance capabilities
- FDA will share technology and tools to advance biovigilance in the international setting

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TTIMS - CBER OBE, CBER OBRR, NHLBI, OASH, ARC, BSI, NYBC, OneBlood, Creative Testing Solutions

Thank you