

# Postmarketing Safety Surveillance in CBER

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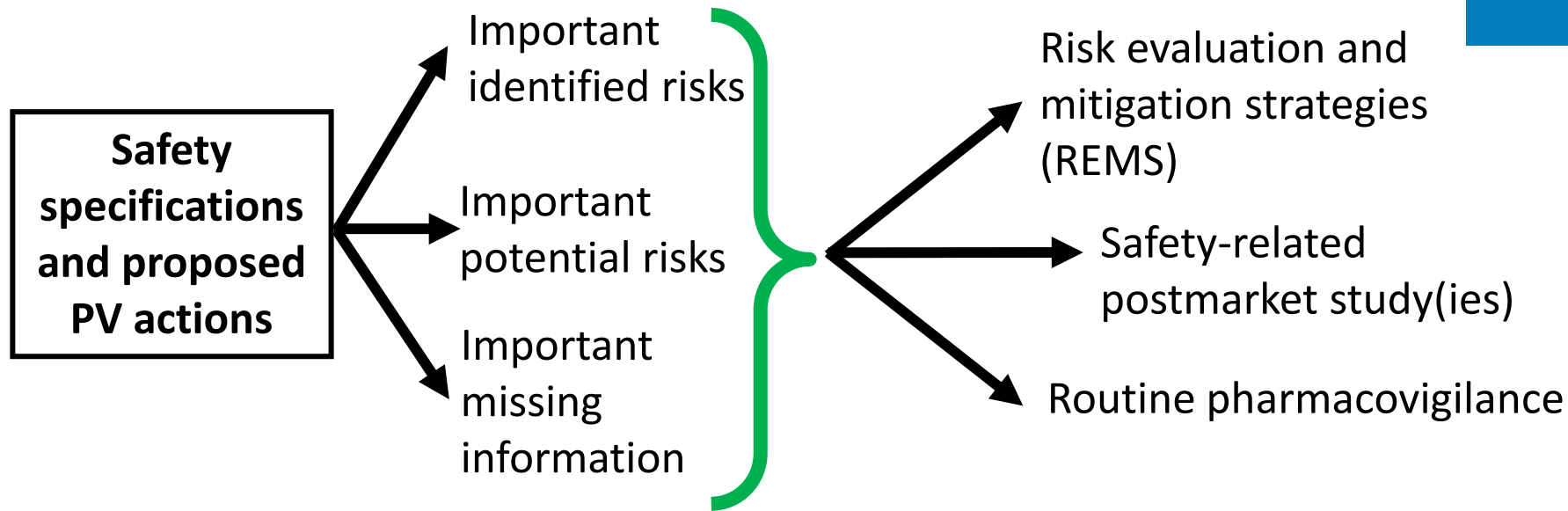
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# Learning Objectives

- Describe a pharmacovigilance plan
- Describe routine pharmacovigilance
- Describe safety-related postmarket studies
- List statutory factors for Risk Evaluation and Mitigation Strategies (REMS)
- Understand the process for signal detection and evaluation

# Pharmacovigilance plan (PVP)

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FDA Guidance for Industry: E2E Pharmacovigilance Planning (April 2005) available at <https://www.fda.gov/media/71238/download>

FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005) available at <https://www.fda.gov/files/drugs/published/Good-Pharmacovigilance-Practices-and-Pharmacoepidemiologic-Assessment-March-2005.pdf>



# Routine pharmacovigilance

# Routine Pharmacovigilance



- Continuous postmarket safety monitoring
- *Spontaneous* adverse event (AE) reports (*passive surveillance*)
- Reporting regulations:
  - Voluntary AE reporting for healthcare providers and the public
  - Mandatory AE reporting for manufacturers under **21 CFR 600.80**
    - Expedited (15-day) reports; Non-expedited (periodic) reports
    - Periodic safety reports
- Systems involved: pharmacovigilance databases
  - FDA Adverse Event Reporting System (FAERS); sponsor databases; global pharmacovigilance

# Analysis of passive surveillance data: Qualitative Methods



- Sequential review of incoming Individual Case Safety Reports (ICSRs)
  - Look for patterns to detect “signal” of AE
  - Unexpected clinical or demographic clustering
  - Biological plausibility/consistency with known effects
  - Absence of alternative explanations (concomitant medications, underlying conditions)
  - “Positive re-challenge” reports
- Case series

# Analysis of passive surveillance data: Quantitative Methods



- Data Mining: screening for disproportional reporting
- Reporting Rates
  - Number of reports/ time
  - Number of reports/ number of doses distributed
  - Reporting rates vs. background rates

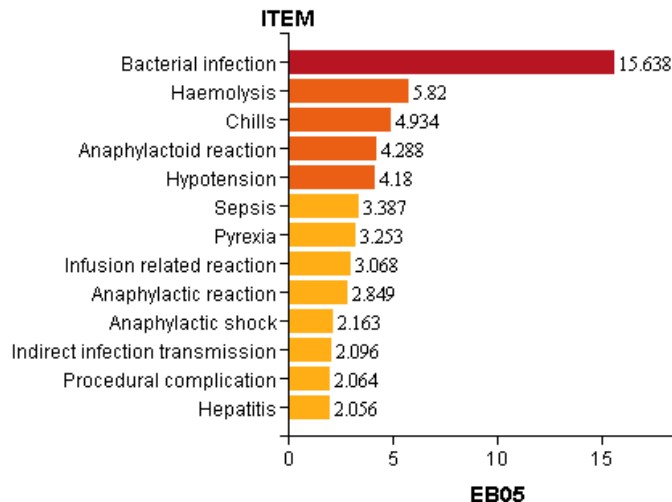


## Data Mining

- Assess the proportion of reports with a specific product–AE pair
- An elevated score does not mean there is a causal association between a product and event, although such an association might exist
- If data mining score is elevated, the product-AE pair is further evaluated

- Unexpected and/or unlabeled?
- Confounding by indication?
- Case series analysis

or epidemiologic study



# Passive Surveillance Systems



FDA accepts AE reports regardless of the plausibility of the product causing the event or the clinical seriousness of the event

## Strengths

- Rapidly detects potential safety issues
- Potential detection of rare AEs
- Open-ended for hypothesis generation
- Geographic diversity
- Capability to monitor product lots

## Limitations

- Missing and/or inaccurate data
- Reported diagnoses are not verified
- Under-reporting
- Reporting bias (stimulated reporting)
- Absence of control group
- Inability to assess causation
- Not likely to detect long latency events

# Examples of safety signals

## July - September 2016 Report | Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS)

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Product Name: Trade (Active Ingredient) or Product Class	Potential Signal of a Serious Risk / New Safety Information	Additional Information (as of April 16, 2020)
Imlygic (talimogene laherparepvec) suspension for injection	Disseminated herpetic infection	<div>Updated</div> <p>FDA decided that no further action is necessary at this time based on available information.</p>

[Voluntary Lot Withdrawals of Immune Globulin Intravenous \(IGIV\) and Immune Globulin Subcutaneous \(IGSC\) for Increased Reports of Allergic/Hypersensitivity Reactions | FDA](#)

**FDA Safety Communication:**  
New boxed warning for thrombosis related to human immune globulin products.

[Home / FDA Safety Communications: New boxed warning for thrombosis related to human immune globulin products](#)

JUNE 11, 2013

# Challenge Question #1



## **Routine pharmacovigilance for biological products includes:**

- A. Adverse event reporting in accordance with 21 CFR 600.80
- B. Submission of expedited 15-day reports for serious and unexpected (unlabeled) adverse events
- C. Submission of non-expedited reports for serious and expected, and non-serious adverse events
- D. Submission of periodic safety reports at quarterly intervals for 3 years postapproval and at annual intervals thereafter
- E. All of the above



# Safety-related postmarket studies

# Safety-related postmarket studies



A study being conducted specifically to evaluate safety or further investigate a safety issue(s) associated with a product.

**NOTE:** A study must have a primary safety endpoint to be considered a safety-related study. Examples of safety-related studies include an observational epidemiology study, a pregnancy registry, or survey or study using population-based data sources.

# Safety-related postmarket studies



- Sponsor conducted studies
  - Postmarketing requirement (PMR) studies
  - Postmarketing commitment (PMC) studies
  - Voluntary studies
- FDA active surveillance studies
  - CBER Biologics Effectiveness and Safety (BEST) Initiative

# Regulatory considerations for safety PMR



- Postmarketing studies and clinical trials may be **required**:
  - To assess a known serious risk related to the use of the drug
  - To assess signals of serious risk related to the use of the drug
  - To identify an unexpected serious risk when available data indicate the potential for a serious risk
- **Before** a PMR, FDA must find that AE reporting under section 505(k)(1) of the FD&C Act and the active postmarketing risk identification and analysis system as available under section 505(k)(3) of the FD&C Act will not be sufficient to meet above purposes
- Similarly, **before** requiring a PMR clinical *trial*, FDA must find that a PMR study(ies) will not be sufficient to achieve these same purposes.

[Postmarketing Studies and Clinical Trials—Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry](#)



# Examples of safety-related postmarket studies



## POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

1. A post-marketing, prospective, multi-center, observational study to assess the long-term safety of tisagenlecleucel and the risk of all secondary malignancies occurring after treatment with tisagenlecleucel. The study will include at least 1000 pediatric and young adult patients with relapsed / refractory B cell acute lymphoblastic leukemia; the enrolled patients will be followed for 15 years after the product administration.

We acknowledge the timetable you submitted on August 28, 2017, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: September 8, 2017

Study Completion Date: December 31, 2037

Final Report Submission: December 31, 2038

1. A prospective observational study in children and adults with congenital afibrinogenemia and hypofibrinogenemia treated with FIBRYGA for at least 10 major bleeding events to further characterize the risk of thromboembolic events following FIBRYGA treatment.

We acknowledge the timetable you submitted on December 4, 2020, which states that you will conduct this study, according to the following schedule:

Final Protocol Submission: January 15, 2021

Study Completion Date: December 31, 2027

Final Report Submission: June 30, 2028

# Challenge Question #2

## **Safety-related postmarket study may include:**

- A. A postmarketing requirement study under FDAAA
- B. An agreed-upon postmarketing commitment study
- C. A voluntary sponsor study
- D. An active surveillance study using population-based data sources
- E. All of the above

# Risk evaluation and mitigation strategies (REMS)

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- Food and Drug Administration Amendments Act of 2007 (FDAAA) created section 505-1 of the FD&C Act, which establishes FDA's REMS authority
- FDA determines whether a REMS is necessary to ensure that the benefits of a drug outweigh its risks
  - At the time of initial approval
  - Post-approval when FDA becomes aware of new safety information (NSI)
- REMS is a required risk management plan that can include one or more elements

# FDA may require elements to assure safe use (ETASU) as part of a REMS



- Health care providers who prescribe the drug have particular training or experience, or are specially certified;
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified;
- The drug be dispensed to patients only in certain health care settings, such as hospitals;
- The drug be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results;
- Each patient using the drug be subject to monitoring; or
- Each patient using the drug be enrolled in a registry

# Statutory Factors in Determining When a REMS Is Necessary



- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- The expected benefit of the drug with respect to the disease or condition;
- The seriousness of the disease or condition that is to be treated with the drug;
- Whether the drug is a new molecular entity;
- The expected or actual duration of treatment with the drug; and
- The estimated size of the population likely to use the drug.

FDA Guidance for Industry: REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary (2019).  
Available at:

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdas-application-statutory-factors-determining-when-rems-necessary>

# Examples of CBER REMS programs

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for CARVYKTI to ensure the benefits of the drug outweigh the risks of cytokine release syndrome (CRS) and neurological toxicities.

Your proposed REMS must include the following:

**Elements to assure safe use:** Pursuant to section 505-1(f)(1), we have determined that CARVYKTI can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks for CRS and neurological toxicities. Your REMS includes the following elements to mitigate these risks:

- Health care settings that dispense CARVYKTI are specially certified;
- CARVYKTI is dispensed to patients only in certain health care settings.

*CBER has approved REMS programs for the chimeric antigen receptor (CAR) T-cell therapy product class (Kymriah, Yescarta and Tecartus, Breynanzi, Abecma, Carvykti)*

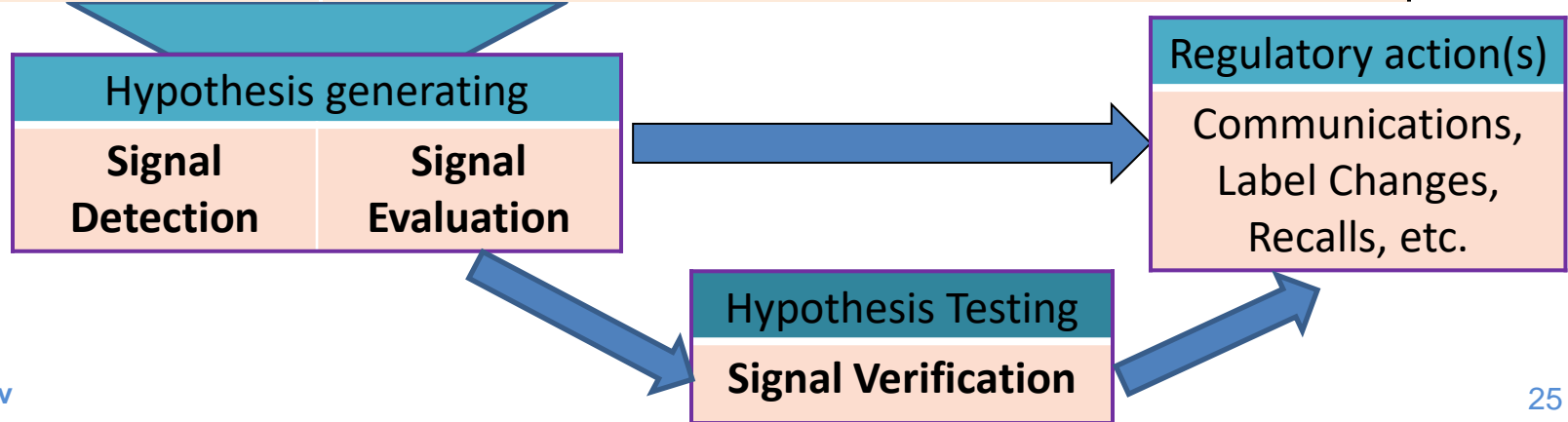


# Signal Detection, Evaluation, and Verification



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Sources of Safety Data	
Pre-licensure	Post-licensure
Clinical trials	Spontaneous AE reporting Large electronic healthcare database (CBER BEST, CMS) Observational studies/clinical trials REMS Assessment Reports Other (Literature, foreign regulatory agencies)



# Risk Management Actions



- Changes to Package Insert (voluntary or required safety label change)
- Section 921 Posting
- Public Health Notification
- “Dear Doctor Letters”
- Inspections
- Product Withdrawal/Recall
- REMS
- Postmarket requirement/commitment study (PMR/PMC)
- Active surveillance study using population-based data sources
- Professional meeting presentation/abstract; peer-reviewed publication

# Challenge Question #3

**FDA has the authority to require safety-related postmarketing studies or clinical trials (PMRs); require sponsors to make safety related label changes; require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS). True or False.**

- A. TRUE
- B. FALSE



# Summary and Conclusions

# Surveillance Process Summary



- Signal detection in pre-licensure data
  - Clinical safety database
  - Sponsor's PVP as part of review of Biologics License Applications (BLA)
- Informs plans for postmarket studies and/or REMS
  - Early consideration of FDAAA (Title IX, Section 901)
    - Post-market Requirement (PMR) and/or Risk Evaluation and Mitigation Strategy (REMS)
  - Active surveillance postmarket studies to address product safety issues

# Summary and Conclusions



- FDA is conducting continuous safety monitoring of all licensed products
- Postmarketing surveillance includes many approaches including passive and active surveillance
- FDA may require postmarketing studies by manufacturers
- FDA may require safety label changes
- FDA may require risk evaluation and mitigation strategies (REMS)
- New databases have expanded population-based surveillance capabilities
- **Our goal is to ensure safe and effective products**

**Thank you!**