U.S. FOOD & DRUG ADMINISTRATION

Postmarket Drug Safety Surveillance: Cardiovascular Toxicities

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December 1, 2017

Outline

- Definition and Utility of Pharmacovigilance
- FDA Adverse Event Reporting System (FAERS) and Data Mining
- Case Series Development and Evaluation
- Postmarket Safety Analysis: Everolimus-Associated Cardiac Failure
- Postmarket Safety Analysis: Cardiovascular Toxicities Associated with Immune Checkpoint Inhibitors

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.

* The Importance of Pharmacovigilance, World Health Organization 2002

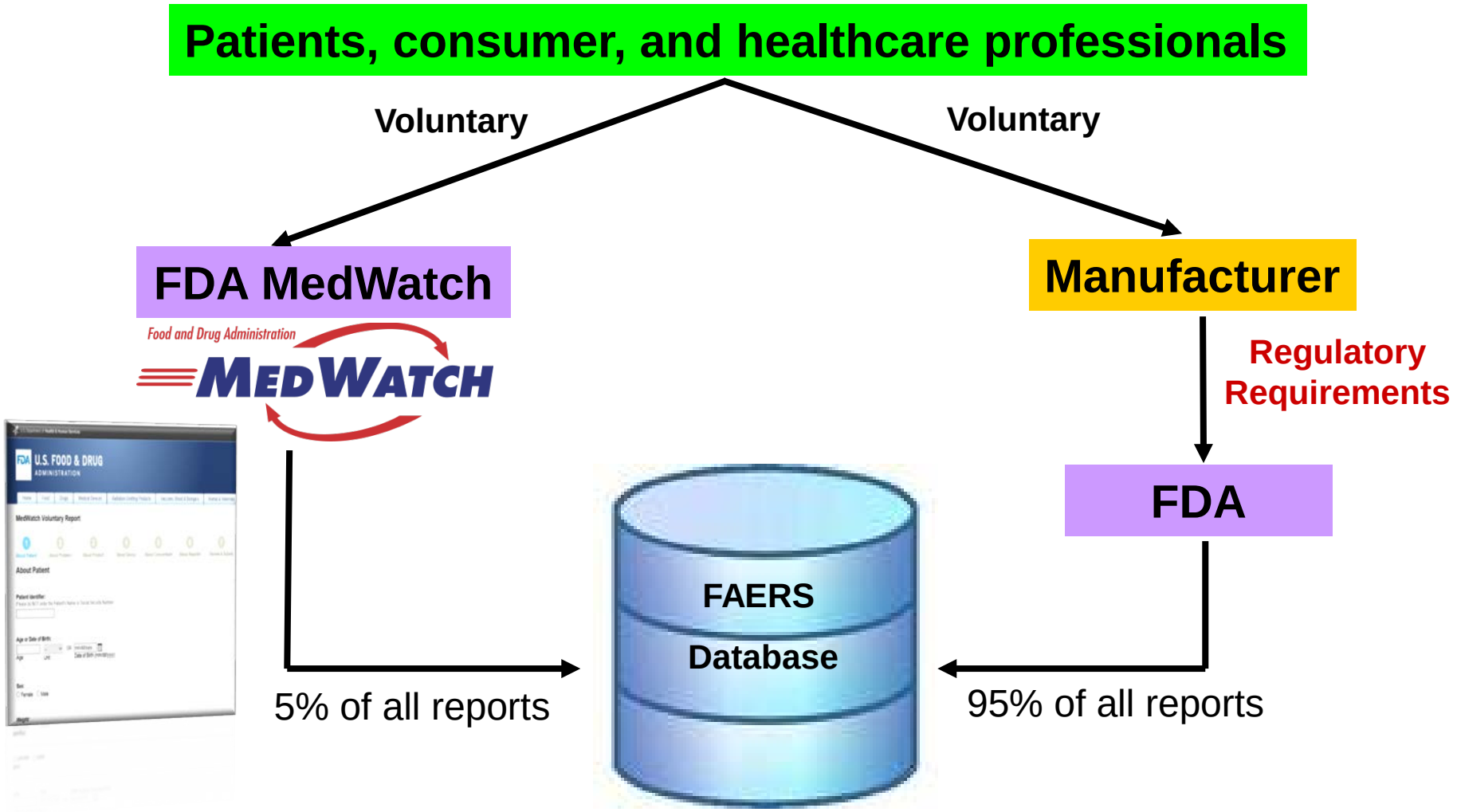
Pharmacovigilance

Limitations of Premarket Clinical Trials	Benefits of Postmarket Monitoring - *Ability to study the following:*
• Relatively small size of patient population • Narrow population - often not providing sufficient data on special groups • Narrow indications studied • Short duration	• Low frequency reactions (not identified in clinical trials) • High-risk groups • Long-term effects • Drug-drug/food interactions • ↑ Severity and/or reporting frequency of known reactions

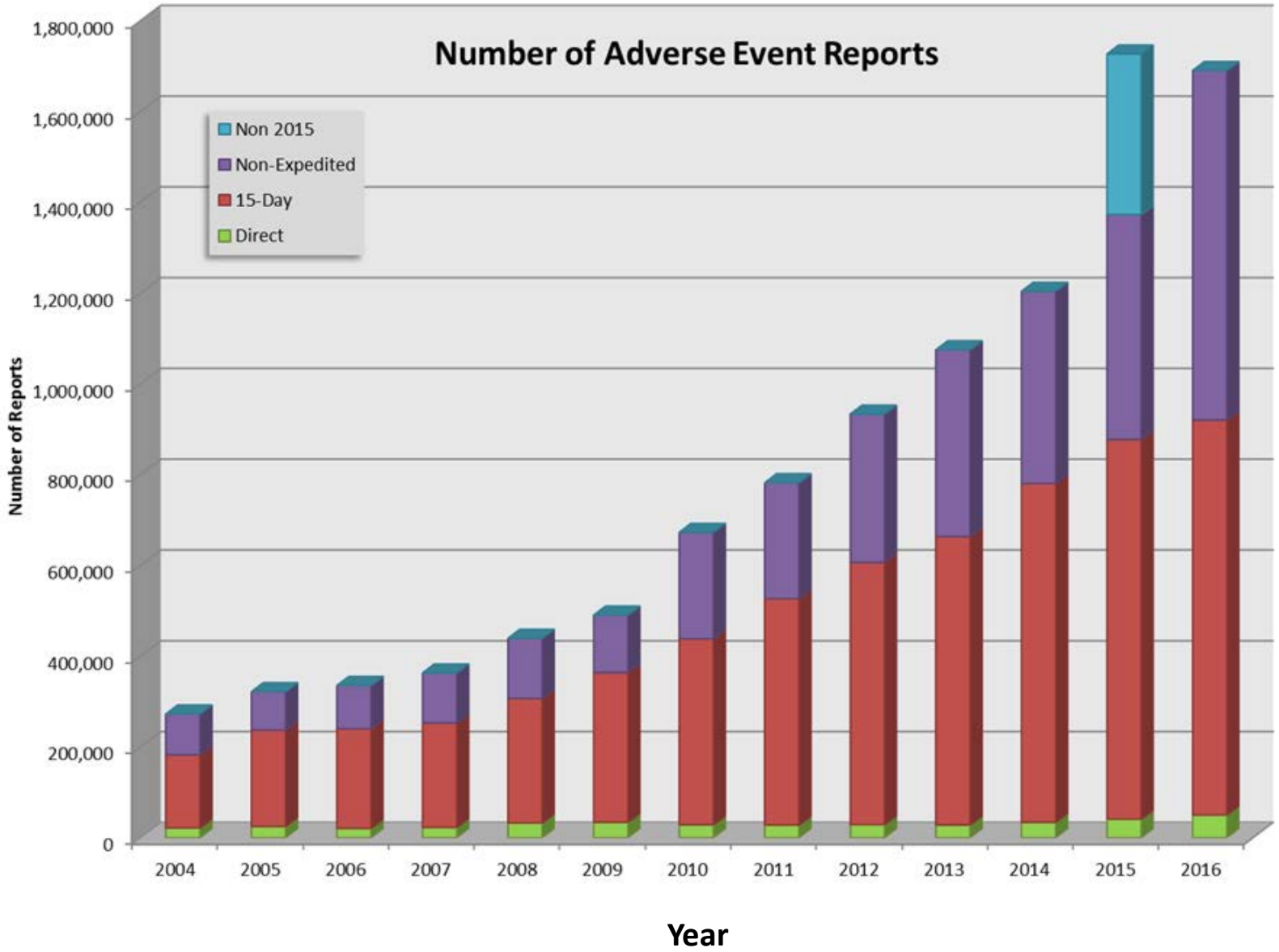
FDA Adverse Event Reporting System

- A computerized database of spontaneous reports
- Contains human drug and therapeutic biologic reports
- ~13 million reports since 1968
- Over 1.69 million new reports in 2016

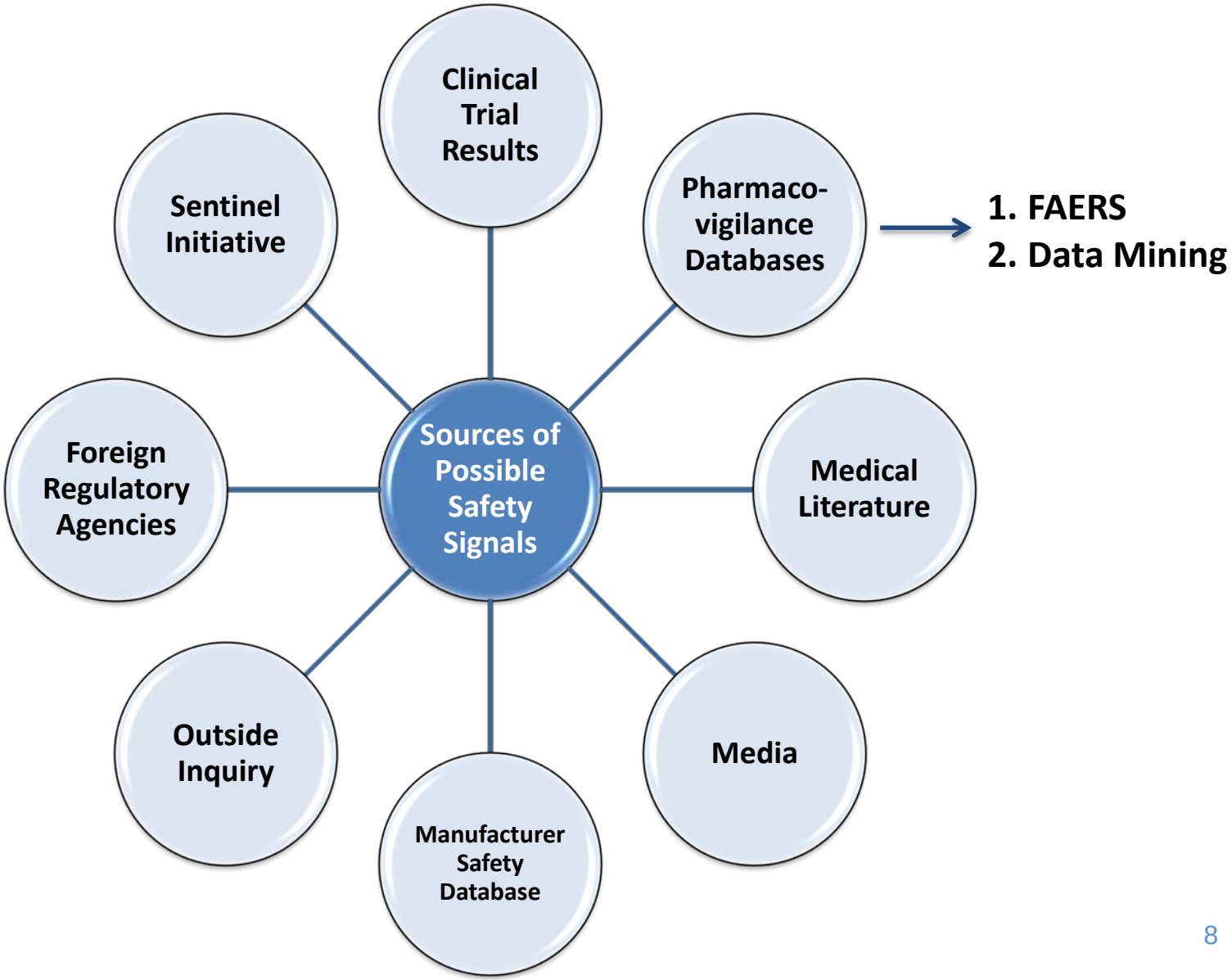
FDA Sources of Postmarket Reports



Adverse Event Reports Entered into FAERS



Sources of Possible Safety Signals

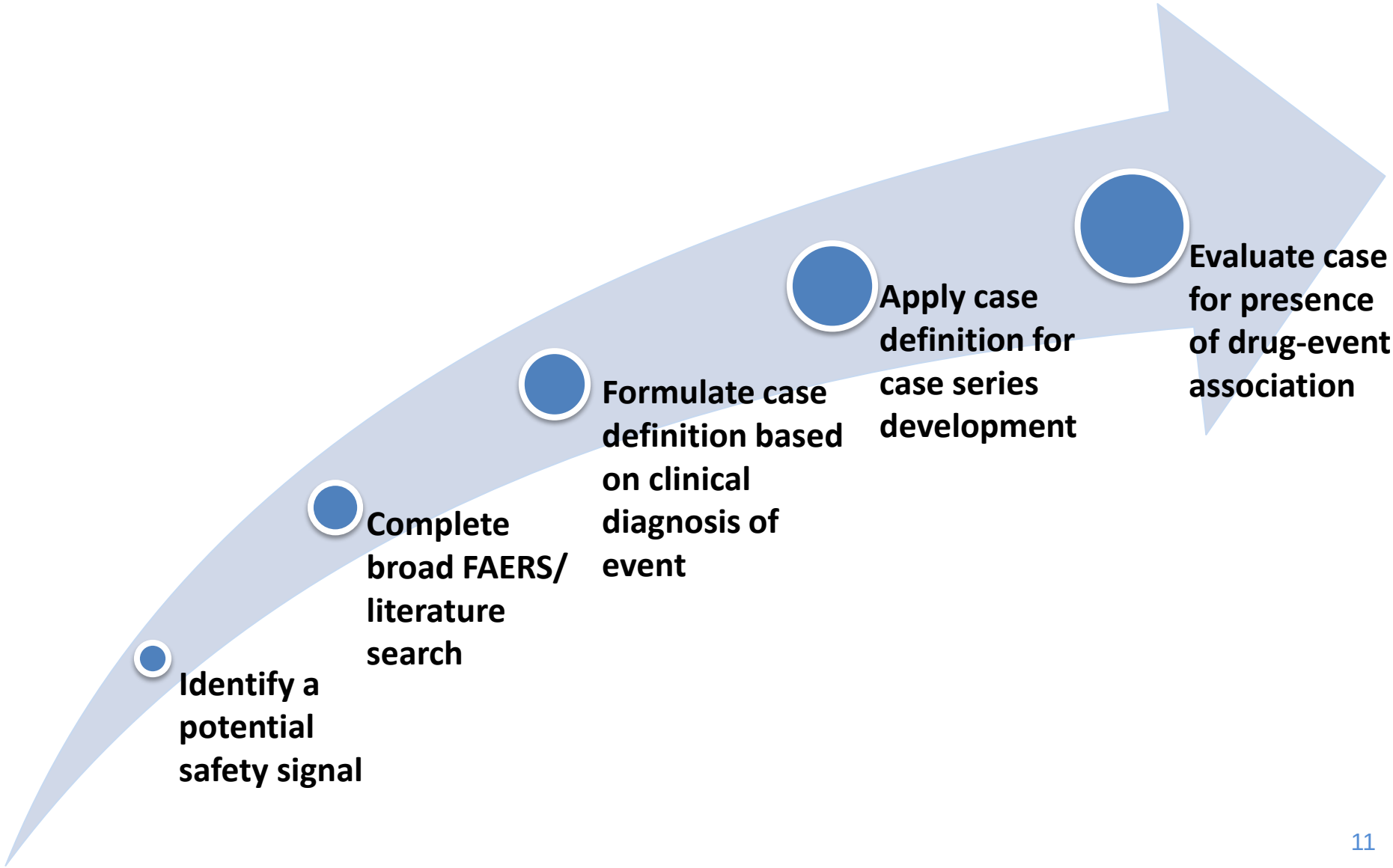


Use of Data Mining

- Mathematical tool identifies higher-than-expected frequency of product-event combinations
- Tool for hypothesis generation
- Supplements FAERS data review
- Does not replace expert clinical case review

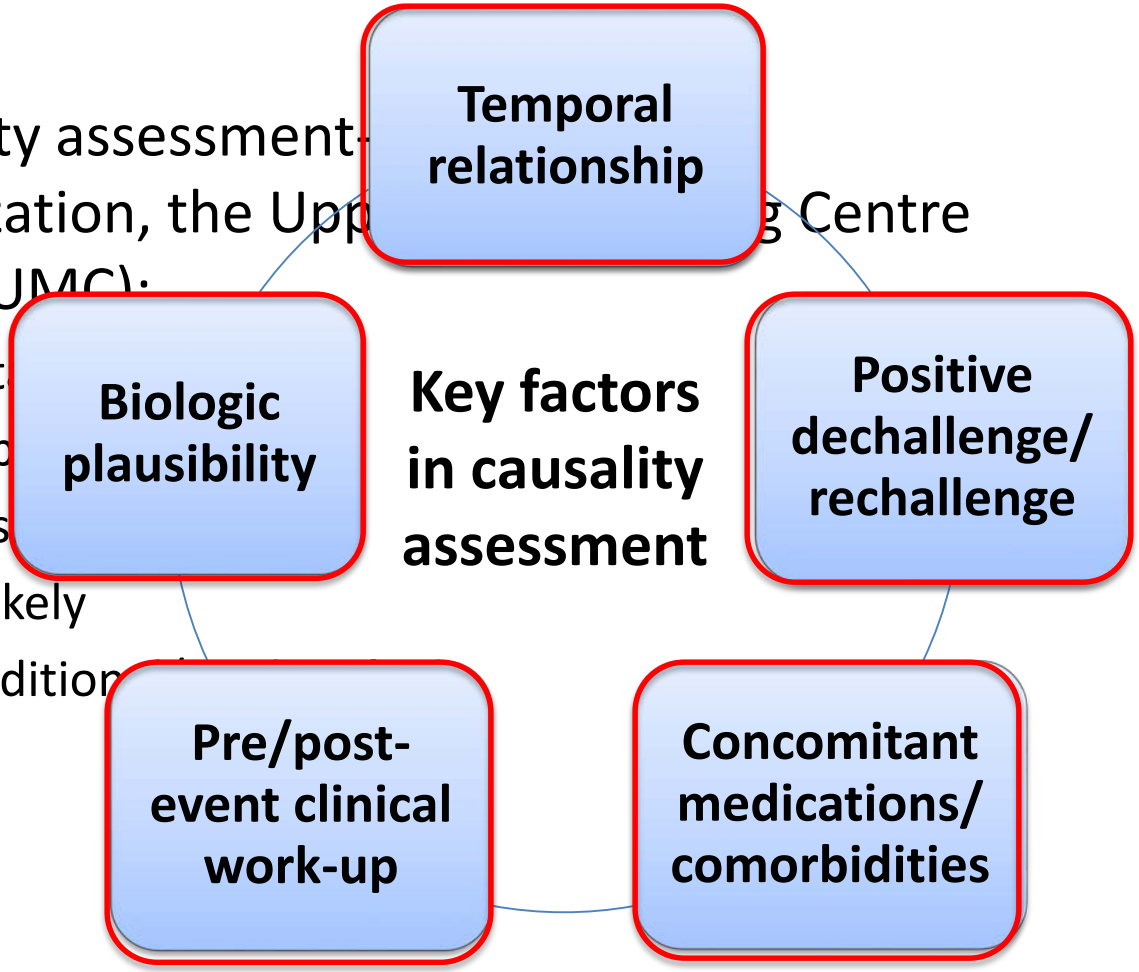
Case Series Development and Evaluation

Developing a Case Series

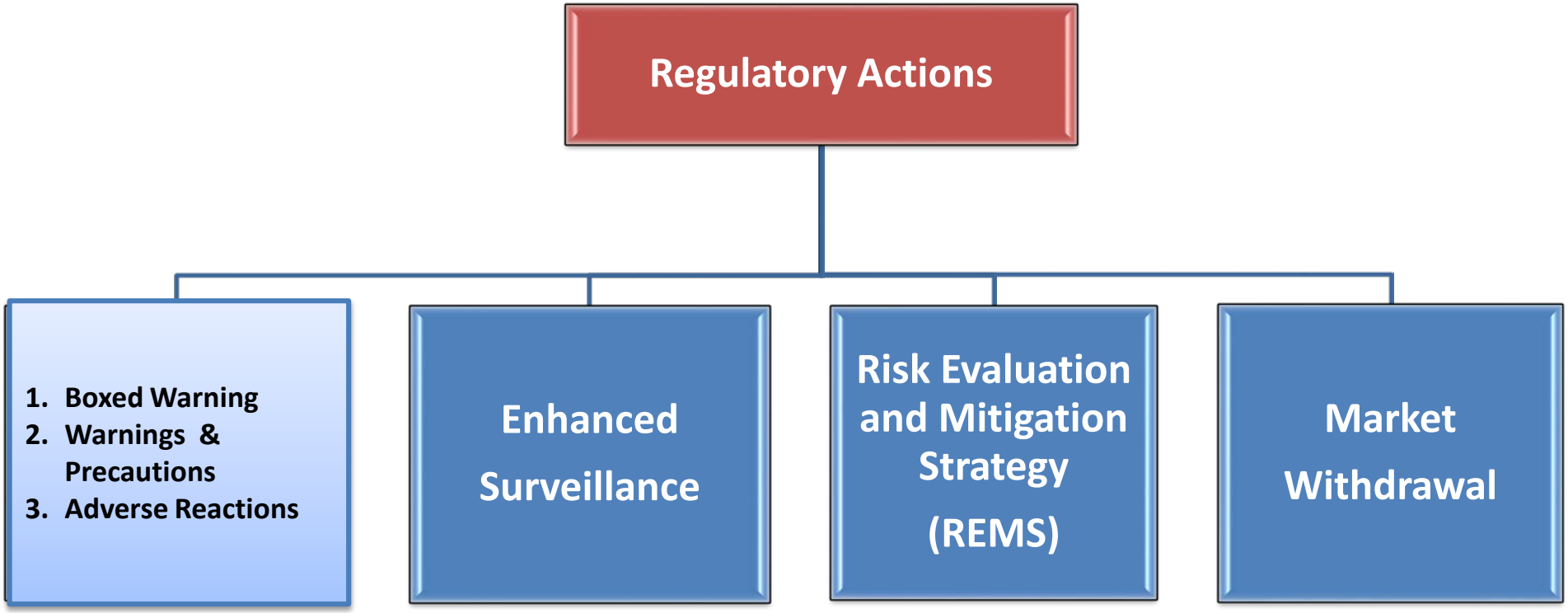


Principles of Case Evaluation

- Causality assessment
  Organization, the Upp g Centre
  (WHO-UMC):
  - Cert
  - Prob
  - Poss
  - Unlikely
  - Condition



Possible Review Outcomes

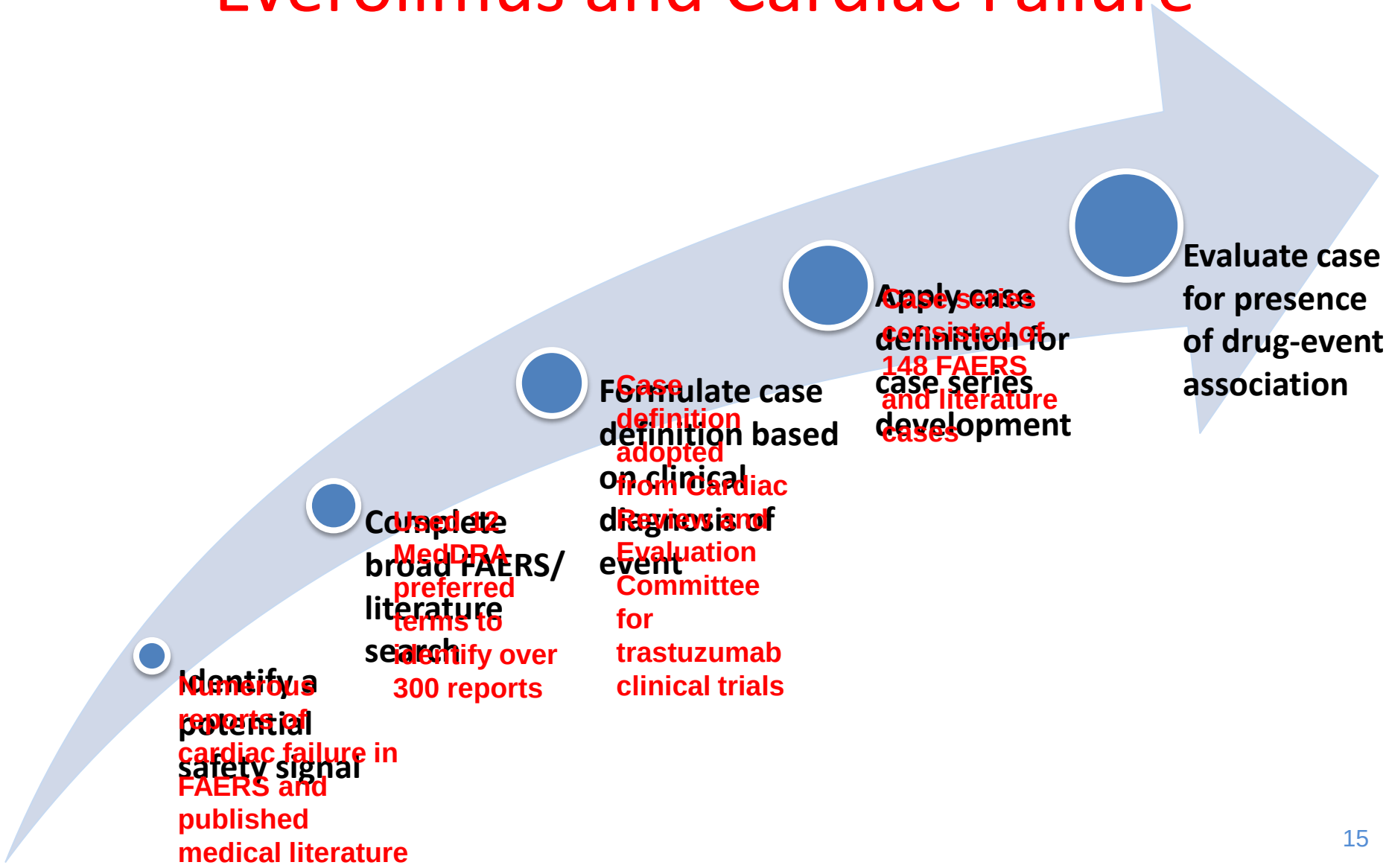


Methods of communication may include:

1. Drug Safety Communication
2. Publication in a peer-reviewed journal
   - Lee R et al. Ibrutinib-associated Pneumocystis jirovecii pneumonia. *Am J Hematol*. 2017;92:e646-648.
   - Nayernama A et al. Postmarketing safety review of everolimus and cardiac failure or left ventricular dysfunction [abstract]. *J Clin Oncol*. 2016;34:suppl. e18226.

Safety Signal Review: Everolimus and Cardiac Failure

Postmarket Safety Signal:
Everolimus and Cardiac Failure



Key Findings in Determining Drug-Event Association

Category	Characteristic	Number of cases
Top 3 Indications	Renal cell carcinoma Breast cancer Pancreatic neuroendocrine tumor	65 47 19
Risk factors (RF) for cardiac failure	Concomitant/prior meds labeled for cardiac failure and LV dysfunction <u>Cardiac RF</u> 1 RF 2 RF 3 RF >4 RF No RF None reported	63 46 33 4 7 31 26
Time to Onset	Median days to onset (range) Time to onset <u>≤</u> 90 days	86 (3-1143) 75
Rechallenge information	Positive rechallenge	2
Severity	Fatal outcome reported Heart failure as cause of death Reported Grade 3/4 decrease in LVEF	43 21 30

Regulatory Action: Labeling Revision

- Discussed findings with Office of New Drugs (OND) designated Review Division

- Decision made to include under **Adverse Reactions – Postmarketing Experience** in the product information

- Peer reviewed medical journal: J Clin Oncol 34, 2016 (supple;a bstr e18226)

Cardiovascular Toxicities Associated with Immune Checkpoint Inhibitors in the Postmarket Setting

Cardiovascular Toxicity in Immune Checkpoint Inhibitor Product Information

Checkpoint Target	Product	Labeling
CTLA-4	Ipilimumab	Warnings and Precautions: Other immune-mediated adverse reactions • Pericarditis, fatal myocarditis Adverse Reactions: Clinical trials experience • Pericarditis (including fatal outcome), myocarditis (including fatal outcome)
PD-1	Nivolumab	Dosage and Administration: Dose modifications • Grade 3 myocarditis – permanently discontinue Warnings and Precautions: Other immune-mediated adverse reactions • Myocarditis Adverse Reactions: Clinical trials experience • Cardiac disorders: ventricular arrhythmia
	Pembrolizumab	Warnings and Precautions: Other immune-mediated adverse reactions • Myocarditis Adverse Reactions: Clinical trials experience • Cardiac failure (0.4%) • Myocarditis (0.5%) Medication Guide • Shortness of breath, irregular heartbeat, feeling tired, or chest pain (myocarditis)

Cardiovascular Toxicity in Immune Checkpoint Inhibitor Product Information

Checkpoint target	Product	Labeling
PD-L1	Avelumab	Dosage and Administration: Dose modifications • Other immune-mediated adverse reactions: Myocarditis – either withhold or discontinue based on severity immune-mediated adverse reactions Warnings and Precautions: Other immune-mediated adverse reactions • Immune-mediated myocarditis including fatal cases
	Durvalumab	Warnings and Precautions: Other immune-mediated adverse reactions • Myocarditis Patient Counseling Information • Myocarditis
	Atezolizumab	Adverse Reactions: Clinical trials experience • Myocardial infarction

Notable Postmarket Literature Publications of Myocarditis

FDA

Johnson et al. *NEJM.* 2016.

- Fatal fulminant myocarditis in 2 patients treated with combination ipilimumab and nivolumab

- <u>Supportive evidence for a drug-event association:</u>
  - Temporal association
  - Laboratory information provided (i.e. CK-MB, troponin)
  - Viral studies
  - Lymphocytic infiltration within the myocardium and skeletal muscle
  - PD-L1 was expressed on injured myocytes and on infiltrating lymphocytes

Heinzerling et al. *Journal for Immunotherapy of Cancer*. 2016.

- Case series of 8 patients cardiotoxicity following immune checkpoint treatment
- 4 of 8 cases were myocarditis
- **2 fatal cases**

- <u>Supportive evidence for a drug-event association:</u>
  - Temporal relationship
  - Reduced ejection fraction from baseline
  - Cardiac biopsy determined lymphocyte-induced infiltration
  - Endomyocardial biopsy
  - Viral studies

Atezolizumab and Myocarditis

- Atezolizumab product information does not include risk of myocarditis

- Identified reports of myocarditis in FAERS and the medical literature
- Sufficient data to initiate review

- Genentech issued Dear Health Care Provider Letter
  - Includes analysis of company safety data in the postmarket setting
  - Prescriber action recommendation

Postmarket Literature Reports of Other Cardiovascular Toxicities

- Acute pulmonary edema
- Cardiac arrest
- Cardiac failure (acute, congestive) → Pembrolizumab product information
- Cardiac tamponade
- Cardiopulmonary failure
- Cardiorespiratory arrest
- Hypertension
- Left bundle branch block
- Left ventricular dysfunction
- Myocardial infarction → Atezolizumab product infor
- Myocardial fibrosis
- Paroxysmal atrial fibrillation
- Pericardial effusion
- Pericarditis
- Pulmonary edema
- Subacute Takotsubo-like cardiomyopathy
- Transient supraventricular tachycardia
- Ventricular arrhythmia → Nivolumab product information

Potential safety signals that require further analysis

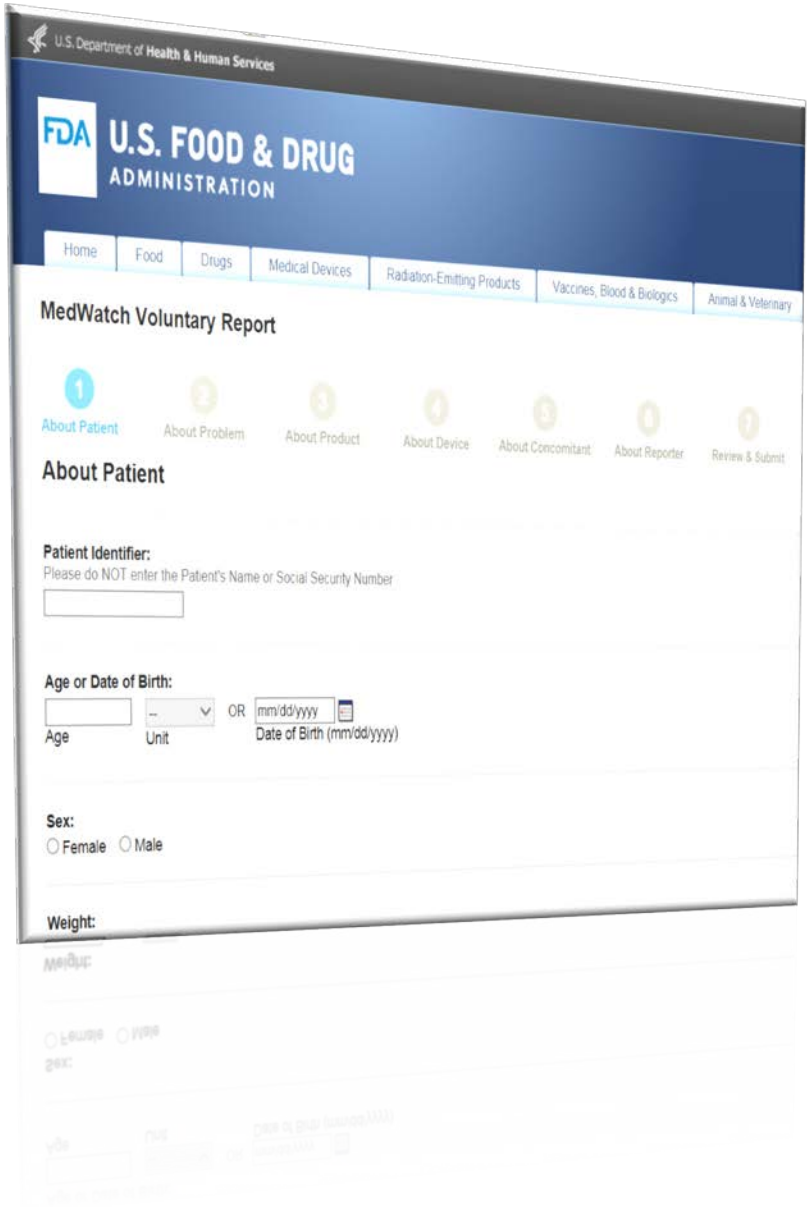
Challenges of Evaluating Postmarket Reports of Other Cardiovascular Toxicities

- Differentiating other cardiovascular adverse events from the spectrum of myocarditis
- Reported cardiovascular adverse events have a high background rate in the general population
- Potential contributory role of comorbidities or concomitant medications
- Variable quality of reporting

Future Directions

- Continued pharmacovigilance monitoring of immune-mediated and non-immune mediated cardiovascular toxicities with immune checkpoint inhibitors
- Collaborative work with subject matter experts: cardiologists, oncologists, Board Certified Oncology Pharmacists (BCOP) in DPV
- Determine optimal language in the product information to convey risk to health care practitioners
- Consider the impact of postmarket data on guiding clinical practice on the monitoring and management of cardiovascular toxicities with immune checkpoint inhibitors

Reporting to MedWatch



- How to Report:
  - Online (www.fda.gov/medwatch)
  - Download the form
    - Mail
    - Fax 1–800–332–0178
- For questions about the form:

  1–800–332–1088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Back-Up Slide

Panel Discussion Questions

1. What is the best strategy to identify and characterize other cardiovascular toxicities with immune checkpoint inhibitors in the postmarket setting?

2. How do we differentiate cardiovascular toxicities that result from immune checkpoint inhibitor-induced myocarditis versus a non-immune-mediated mechanism?

3. What is the clinical threshold for including specific language for cardiac monitoring in the product information of immune checkpoint inhibitors?