Enabling Patient Safety Through Risk Management: The Role of Epidemiology

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2014 ICPE Pre-Conference Educational Session: Topics in Pharmacoepidemiology

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

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Outline

- Fundamentals of Risk Management
- Epidemiology for Risk Management
  - Risk Assessment
  - Risk Minimization
  - “Big Epidemiology”
- Concluding Comments

Risk Management

Benefit-Risk Balance

- All medicines have benefits and risks, which must be characterized and managed
- Risk Management Planning is essential to ensure that benefits outweigh risks
  - This is a proactive, iterative process
  - It occurs for the entire product life-cycle
  - Routine risk management is built into all products
  - Non-routine assessments and interventions are sometimes needed
- Protection of patient safety is the highest priority at all times

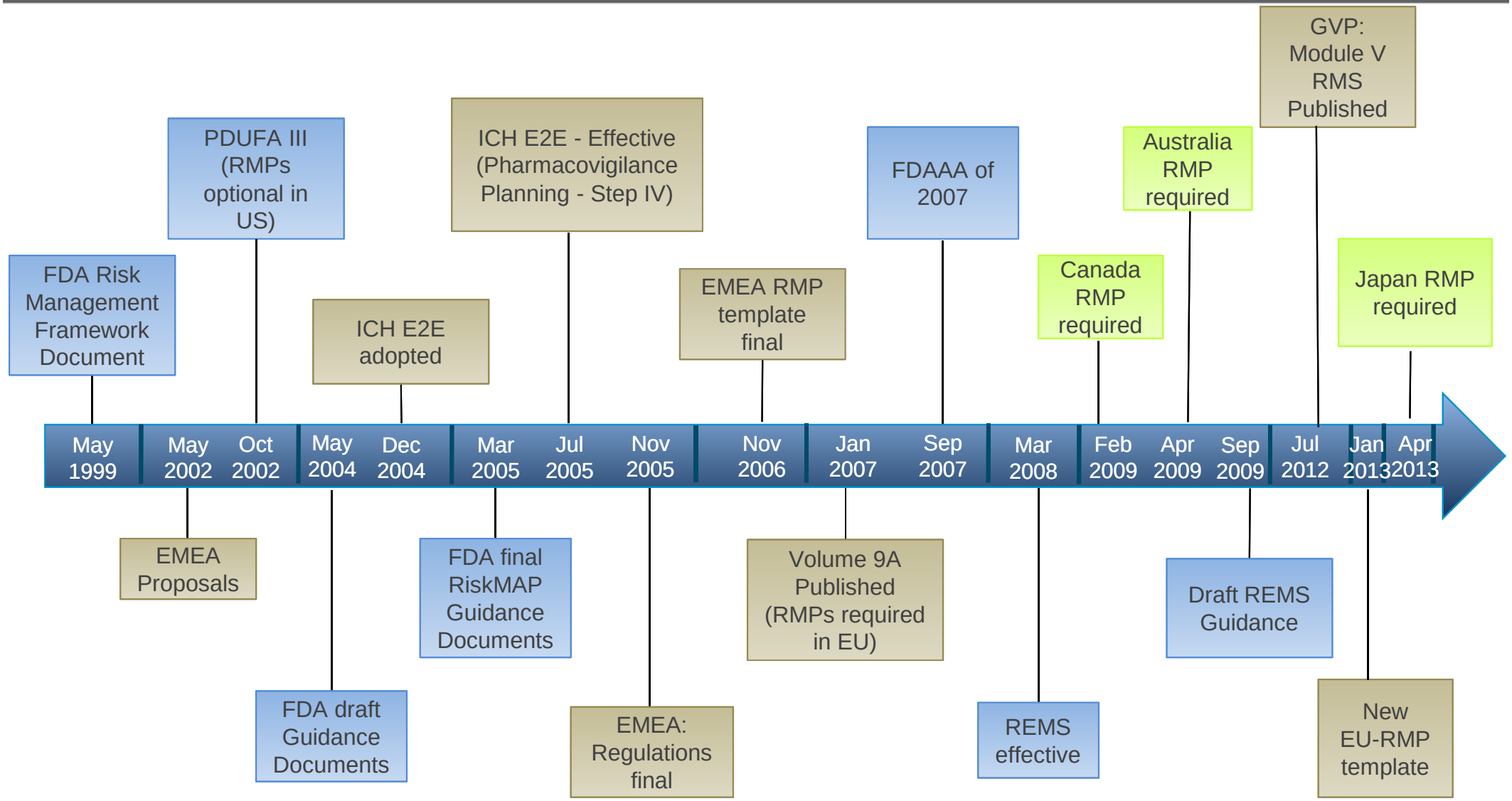
Need Strong Science

- Strong scientifically-based drug regulatory frameworks and capabilities enhance
  - Innovation
  - Patient safety
- Need pragmatic, reliable and flexible approaches
- Partnering to improve methods that inform evidence-based decision-making
  - Consistent and valid observational drug safety research
  - Rapid safety assessment using electronic healthcare data

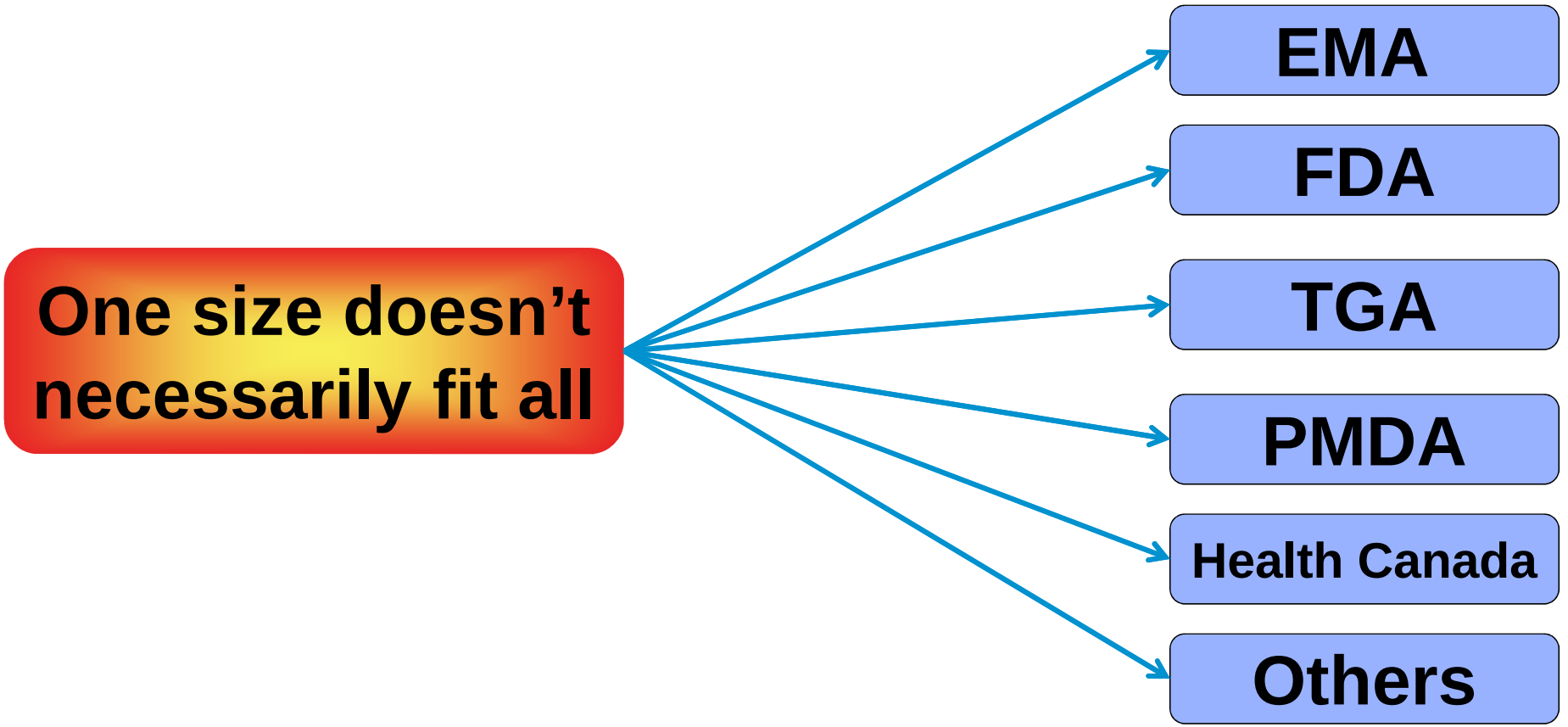
Risk Management

- RISK MANAGEMENT is defined as the comprehensive and proactive application of scientifically-based methodologies to *identify, assess, communicate, and minimize risk* throughout a drug life cycle to establish and maintain a favorable benefit risk profile in patients

Evolution of Risk Management Regulation



Global Risk Management Strategies



Reference and Local RMPs (1)

- Reference RMP
  - EU RMP required with all new EU Marketing Applications
  - Usually the first formal RMP created
  - Importance of various risk(s) is discussed
  - For the minority of products that require risk minimization, specific goals for reducing risk outcomes are identified
  - In many companies, the RMP in effect at EU authorization of the product is considered the global “Reference” RMP
- Local RMP
  - Information, as applicable in the Reference RMP should be presented in an equivalent place in the local RMP, as determined by local regulations, guidelines, and/or templates.

Reference and Local RMPs (2)

- Labeling is the cornerstone of risk management and the foundation for managing the risk of products
  - Investigator Brochure
  - Regulator approved prescribing information, e.g., Package Insert, Summary of Product Characteristics
  - Risks considered in the context of benefits
- Routine assessment and reporting requirements allow contextual evaluation of the evolving data
  - In a small number of products, may need to introduce risk minimization or mitigation tools to minimize or mitigate risks and preserve benefits, i.e., maintain favorable benefit-risk profile

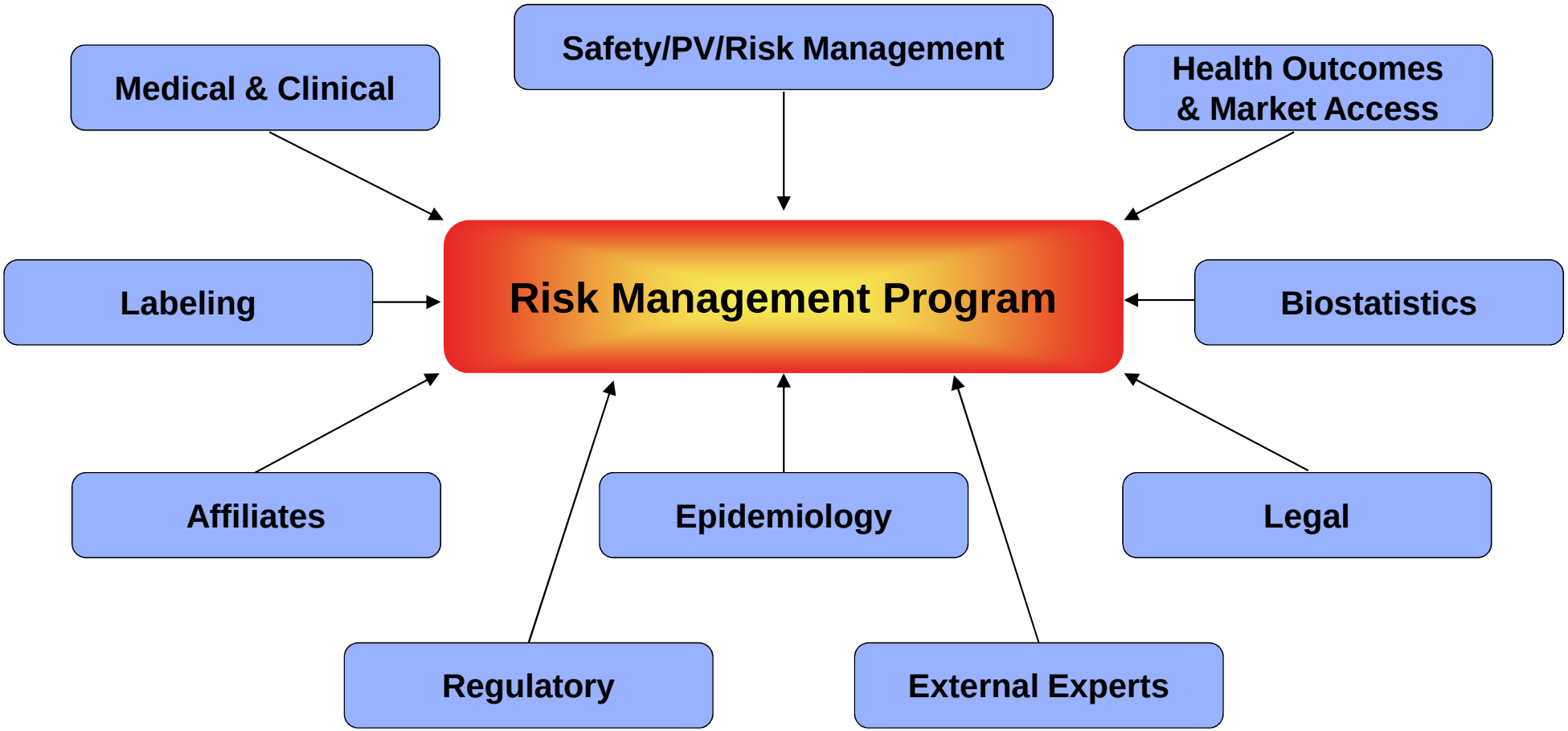
Reference and Local RMPs (3)

- Risk management planning is a global activity
  - Disease epidemiology may vary geographically and there may be additional or fewer safety concerns, depending on the target population, indication, burden of disease, or other factors
  - Risk minimization activities may need to be tailored to the healthcare delivery system
  - Benefits of a medicinal product may also vary between regions
  - Thus, the best available and least burdensome tools may not be the same in every jurisdiction

Reference and Local RMPs (4)

- Examples of differences:
  - Patient education
    - MedGuides are available in the US
    - Patient Information Leaflets and Patient Safety Cards are used in the EU
  - Prescriber education
    - May be provided by MAH with or without metrics
    - May require government certification
  - Controlled distribution
    - Free transborder commerce may not permit

Collaboration to Develop and Implement the Risk Management Strategy



Focus of Risk Management Planning

- Target:
  - Important identified risk(s)
  - Important potential risks(s)
  - Important missing information
- “Important” or “Potential”
  - Possible impact on benefit-risk balance
  - May need assessments beyond routine
  - May need interventions beyond routine

Routine vs. Additional Pharmacovigilance and Risk Minimization Activities Comparison

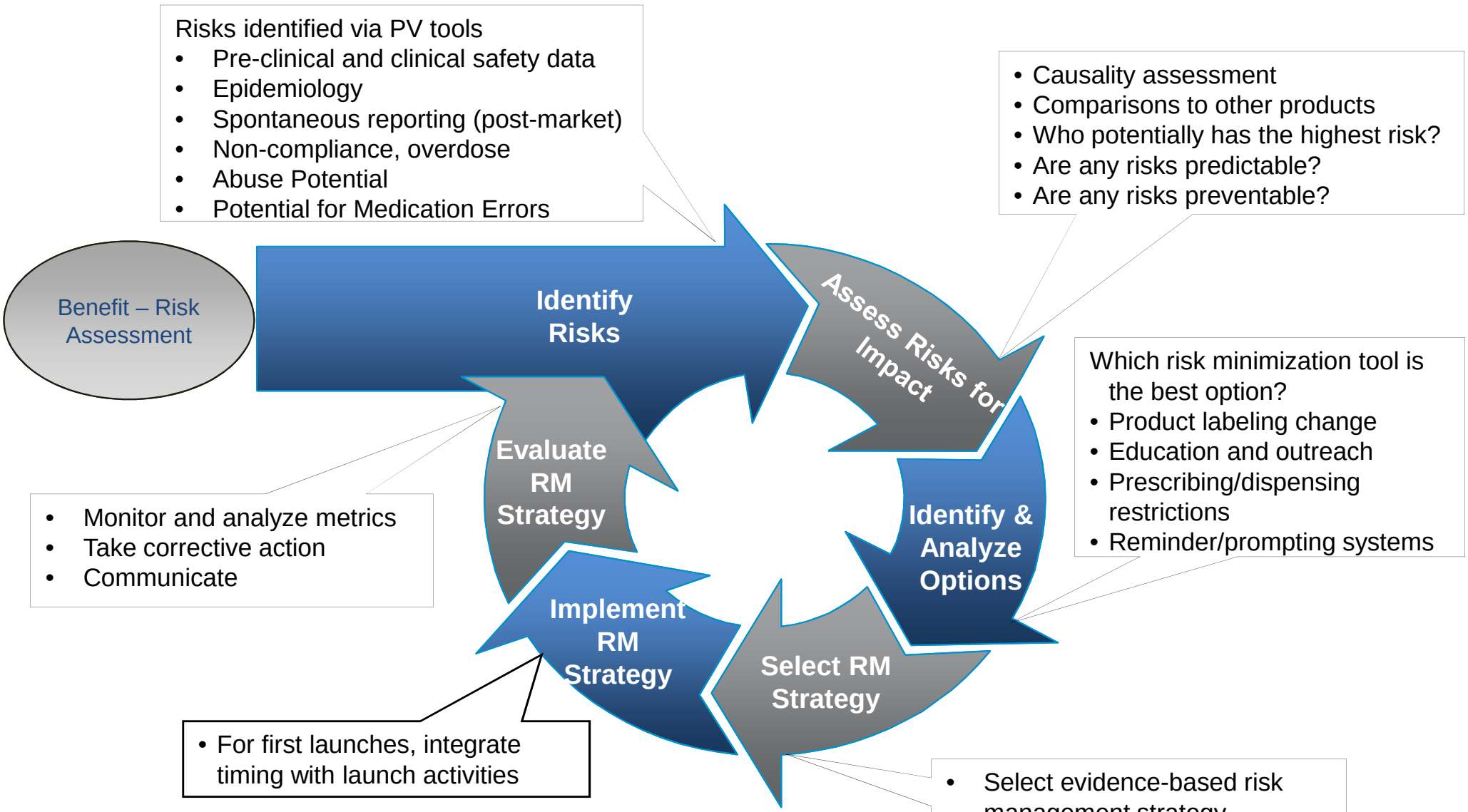
Pharmacovigilance

- Routine pharmacovigilance to identify and characterize safety concerns:
  - Real-time Review of individual case safety report (ICSR), expedited safety reporting (ESR/SUSAR)
  - Periodic aggregate safety data review, signal detection/data mining
  - Aggregate safety reports (ASR, PSUR, PADER)
- Enhanced PV:
  - Supplemental CRFs in clinical trials (CSP for selected event categories)
  - Targeted questionnaires for selected postmarketing spontaneous adverse event reports
- Additional pharmacovigilance to further characterize the safety concerns
  - Epidemiology studies to define incidence and/or outcome of AEs
  - Post-marketing non-interventional observational safety studies
  - Drug utilization studies

Risk minimization

- Routine risk minimization activities/ measures
  - Protocol entry criteria to exclude high risk population, dose modification guideline, concomitant medication guideline, safety monitoring plan, stopping rules, study steering committee review, data monitoring committee review
  - Warning/precaution in reference document-Investigators Brochure and guidance to investigators
  - Informed consent
  - Clear safety information presentation in product label and patient information
  - Package strategy
- Additional risk minimization action activities
  - Educational material
  - Training programs for prescribers /pharmacists/patients
  - Restricted access

The Risk Management Lifecycle is an Iterative Process



Example: US Incremental Enhancement

Isotretinoin risk minimization program element	1988-2000	2001-2005	2006-current
	Voluntary	Voluntary	**Mandatory**
Warning on label, education, red stickers	✓	✓	✓
Avoid pregnancy icon, consent form	✓	✓	✓
Pregnancy test, 2 forms birth control		✓	✓
2 pregnancy tests, 30-day supply (no refill)		✓	✓
MedGuide to patient via pharmacist		✓	✓
Qualification stickers by registered prescribers		✓	✓
Monthly pregnancy tests			✓
Registration of patients, prescribers, pharmacists, wholesalers			✓
Patient qualification questionnaire			✓
Identify contraceptives each month			✓

Situation In the US (1)

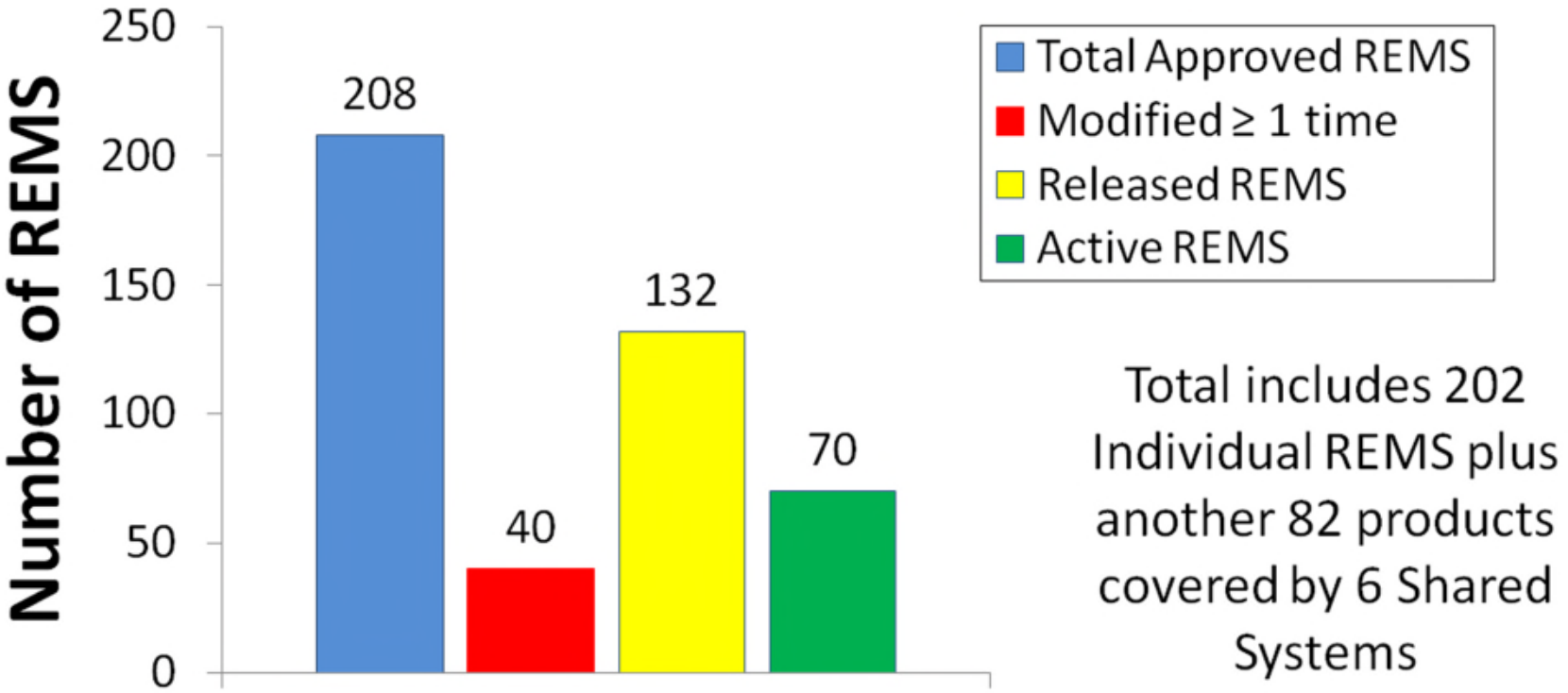
- FDA has a long history of risk management, before today's vernacular
  - 1932, Food, Drug & Cosmetics Act: Pre-market review of safety
  - 1962, FDA Amendments Act: Approval based on both safety and efficacy
  - 1990, Clozapine "no blood, no drug"
  - 1998, Thalidomide S.T.E.P.S.
- The US Package Insert is the primary Risk Management Plan for the US

Situation In the US (2)

- FDA can require a Risk Evaluation and Mitigation Strategy (REMS)
  - At time of initial marketing application (NDA)
  - With a line extension
  - When “new” safety information is received for an approved product
- FDA must consider specific points specified in legislation before requiring a REMS
  - Very few products meet the criteria for a REMS
  - Summary required for public disclosure

Situation In the US (3)

- FDA regulates many thousands of products
  - "Over-the-counter" REMS not needed
  - Prescription products: 70 active REMS



Total includes 202 Individual REMS plus another 82 products covered by 6 Shared Systems

Situation In the EU (1)

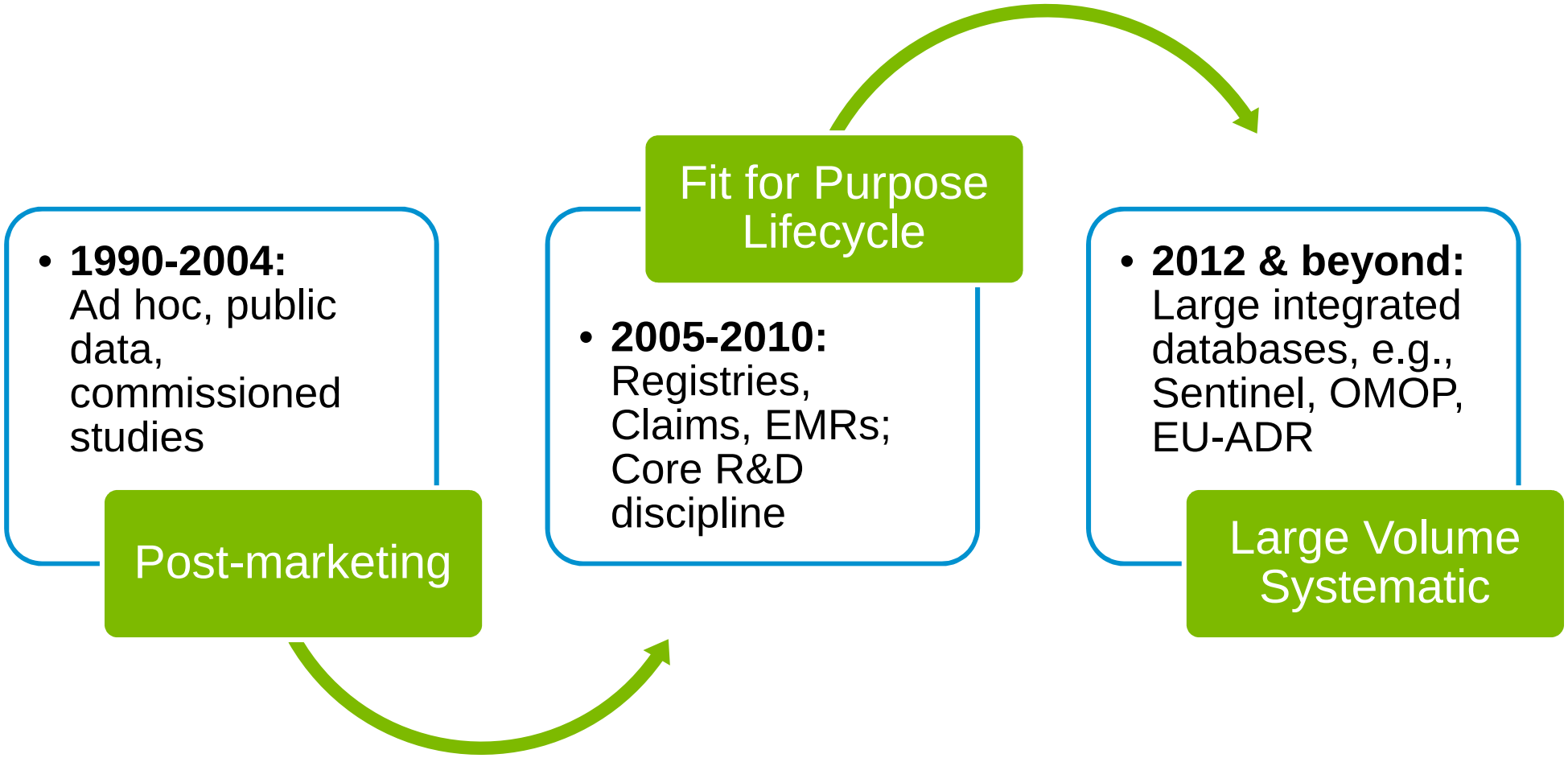
- An EU RMP is required for all new marketing applications as of January 2013
  - Most RMPs will specify only routine measures, not a Risk Minimization Plan
  - New format requires integration of benefit and risk
  - Concise summary of all relevant information
  - Prospective, dynamic, risk proportionate
  - Special allowances for generic products

Situation In the EU (2)

- EU RMP is a stand-alone regulatory document
  - Separate summary in lay language
- Clear responsibilities
  - Pharmacovigilance Risk Assessment Committee (PRAC) must approve and periodically assess
  - Authority remains with European Commission
  - EU Qualified Person for Pharmacovigilance (QPPV) must sign-off RMP for company
  - “Proportionate and dissuasive” civil and monetary penalties for non-compliance

Epidemiology for Risk Management

Epidemiology
From ‘Nice to Have’ to ‘Must Have’ in Risk Management



Epidemiology
Part of Pharmacovigilance Regulations Worldwide

Epidemiology Required

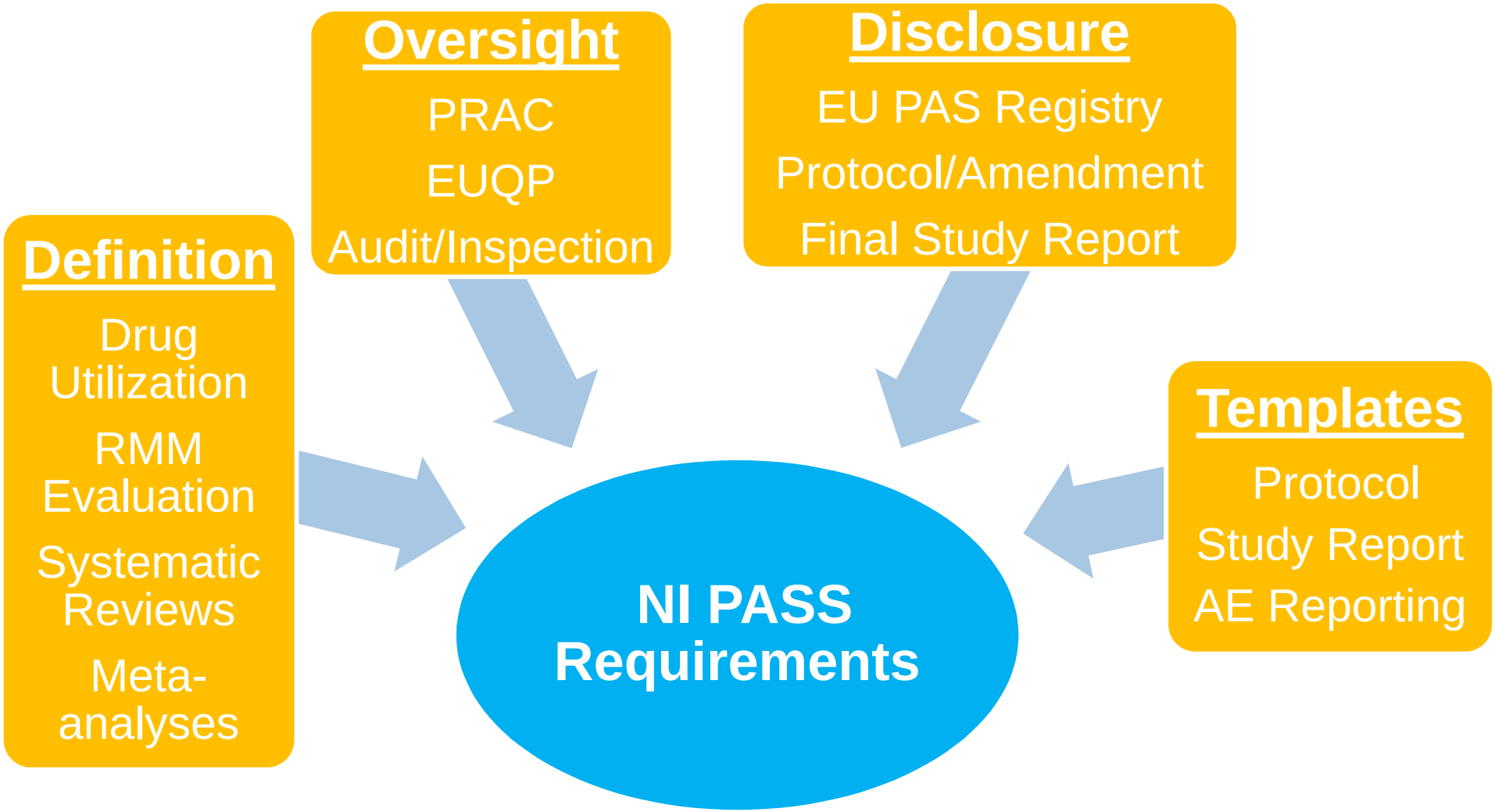
- Risk Management Plans
- Post-approval safety studies
- Active surveillance
- Evaluation of risk minimization measures
- Observational pediatric safety surveillance

Epidemiology Emerging

- Risk Management Plans
- Recent guidance on post-approval safety surveillance in China

2012 EU PV Legislation

PASS Definition & Requirements Expanded

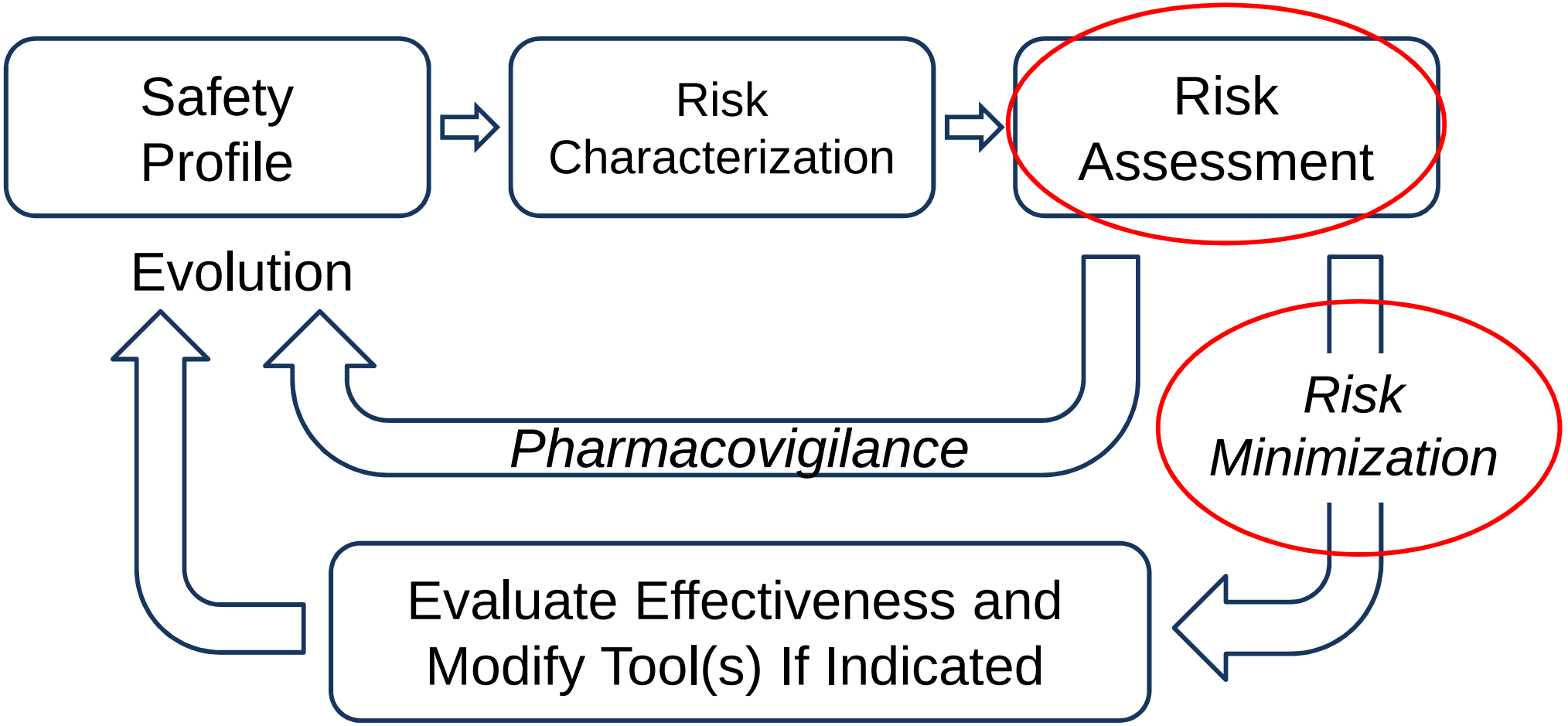


NI: Non-Interventional
PASS: Post-authorization Safety Study

Epidemiology
Advantages for Drug Safety

- 'Real World' or 'Naturalistic'
  - Permits assessment of outcomes as actually used
- Limited inclusion and exclusion criteria, e.g., approved label
- Heterogeneous patient populations
- Patients enrolled by disease/condition or exposure
  - Describe disease progression and therapy use patterns
  - Contemporaneous comparison groups
  - Evaluate long latency outcomes, e.g., cancer
  - Special or vulnerable populations
    - Elderly using multiple concomitant mediations
    - Pregnant women

Epidemiology Contributes to Two Key Risk Management Activities



Epidemiology
Data Sources for Risk Management

- Study designs use primary or secondary data collection or a combination
- Field of epidemiology has been using ‘Real World Data’ aka automated insurance claims, electronic medical records, registry linkage data, and national population surveys for several decades
  - Collected for administrative/reimbursement purposes by insurance provider, as clinical data by general practitioner, or as part of universal healthcare coverage
- Greater access and diversity of ‘Real World Data’ offer many advantages for pre and post approval safety assessment
- Studies using existing data sources are not always feasible
  - A primary data collection study may be the only option



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Epidemiology for Risk Management During Development

Characterize Patient Risk Profile

Evaluate Product Risks

Approval

Standing Cohorts

- EMRs
- Claims
- Registries

Active Surveillance
Monitor and detect signals in defined patient cohorts using innovative analytic methods

Post Approval Safety Studies
Compare medication risks in the real world, as prescribed and taken during routine clinical practice

Risk Minimization
Evaluate the effectiveness of risk minimization measures (e.g., product label/education)

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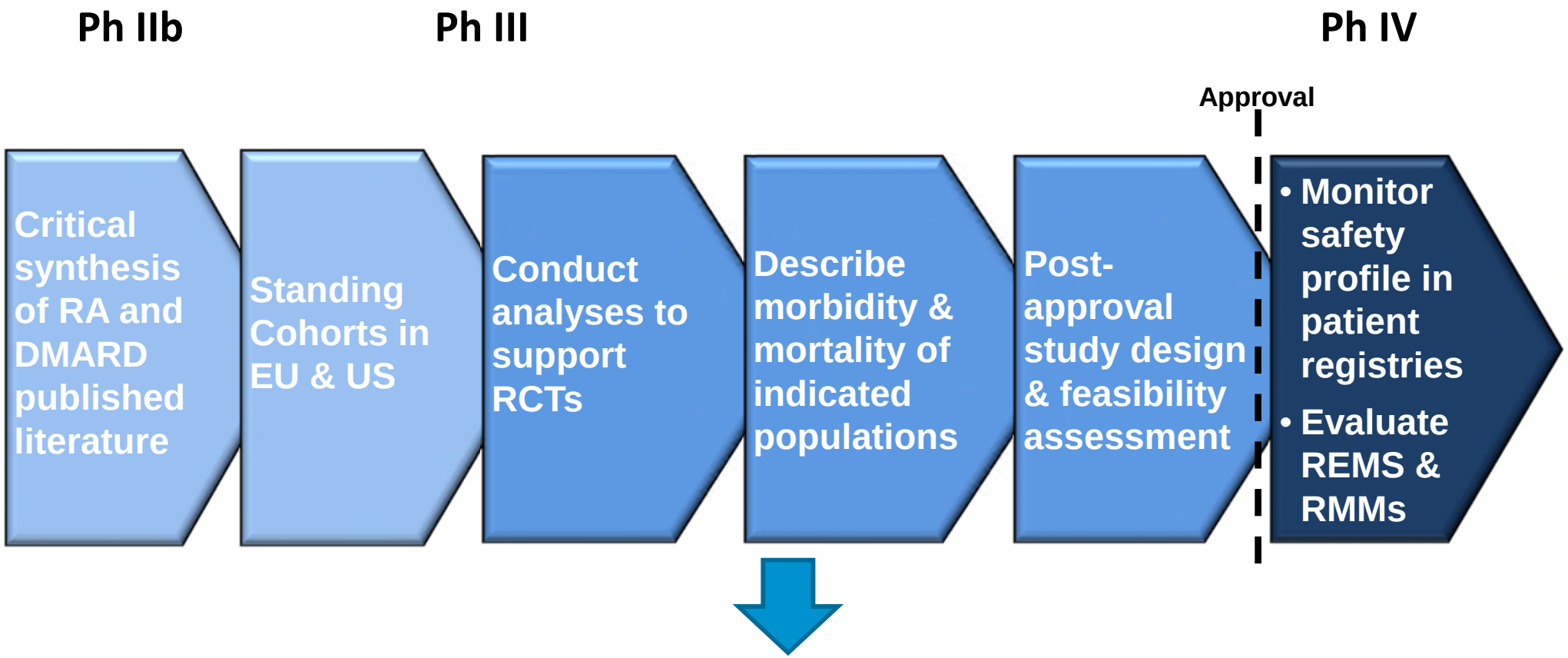
Risk Assessment
Case Studies

Lifecycle Risk Management: Use of Epidemiology in the Tofacitinib Rheumatoid Arthritis Program



Briefing Documents, FDA Advisory Committee, CHMP Oral Explanation

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XELJANZ™ [tofacitinib citrate]

Real World Database Studies

Macugen® (Pegaptanib Sodium Injection)

- A vascular endothelial growth factor (VEGF165) antagonist
- Approved (US in 2004, EU in 2005) for treatment of neovascular age-related macular degeneration (AMD), a primary cause of vision loss in elderly in developed countries
- First approved therapy for neovascular AMD regardless of lesion location, subtype, size or baseline visual acuity
- Administered through intravitreal (IVT) injection every 6 weeks (8-9 times/year)

Real World Database Studies
Macugen® Safety Concern: Endophthalmitis

- In Macugen clinical program, endophthalmitis incidence comparable with other IVT injection clinical studies
- Real-world incidence of endophthalmitis unknown
- Designed one pre-approval and two post-approval epidemiologic safety studies:
  - Both before and after Macugen approval: What is risk of endophthalmitis following IVT injection in AMD patients?
  - What is risk of endophthalmitis among AMD patients after Macugen exposed, under routine care, i.e., in the real world?

Real World Database Studies

Phase I Medicare Study (Pre-Approval Standing Cohort)

Objective

- Estimate incidence of IVT injection-related endophthalmitis among AMD patients in the US Medicare population prior to Macugen launch

Design

- A cohort study of all Medicare beneficiaries who received an IVT injection for AMD in 2000-2003

Key Findings

- The use of IVT injection for AMD treatment increased exponentially, from 210 in 2000 to 14,056 in 2003
- IVT injection performed in earlier years was predictor for endophthalmitis
  - Decreased from 1.9 / 100 injections in 2000/2001 to 0.4 / 100 injections in 2003

Jingping Mo, Yinkang Duan, Manju Patel, Ronald Klein, Ingrid U Scott, Kui Huang, Duanping Liao. Risk of Intravitreal Injection-Related Endophthalmitis in Patients with Age-Related Macular Degeneration (AMD) in the US Medicare Population. The 22nd ICPE & Therapeutic Risk Management, Lisbon, Portugal, August 24-27, 2006

Real World Database Studies

Phase II Medicare Study (Post-approval FDA commitment)

Objectives

- Estimate incidence of IVT injection-related endophthalmitis among AMD patients after Macugen launch

Design

- A cohort study of all Medicare beneficiaries who received an IVT injection for AMD in 2005-2006
- The use of IVT injection for AMD treatment increased significantly, 85,943 patients in 2005 and 160,560 patients in 2006

Key Findings

- The incidence of IVT injection-related endophthalmitis decrease over time
  - From 0.16 in 2005 to 0.12 per 100 injections in 2006

Duanping Liao, Jingping Mo, Yinkang Duan, Kui A. Huang, Ronald Klein, Ingrid Scott, Jiahao Liu. Incidence of Intravitreal Injection (IVT) related endophthalmitis among AMD patients. Annual Meeting of American Academy of Ophthalmology, Atlanta, Georgia, November 8-11, 2008

Risk Minimization

Need For Non-Routine Intervention

- Is routine pharmacovigilance sufficient?
- Are additional interventions needed to minimize an important risk?
  - "Risk minimization" includes interventions that may reduce the occurrence or severity (or both) of a risk or a harm or its outcome
  - What is the goal of each proposed intervention?
  - What interventions can be implemented and will they be effective?

Traditional and Non-Routine Interventions

- Traditional Risk Interventions
  - Label changes, Black Box labels
  - Dear HCP letters
- Non-Routine Interventions
  - Medication Guides
  - Patient Informed Consent
  - Physician education, authorization or registration
  - Registries or required surveillance
  - Restricted Distribution

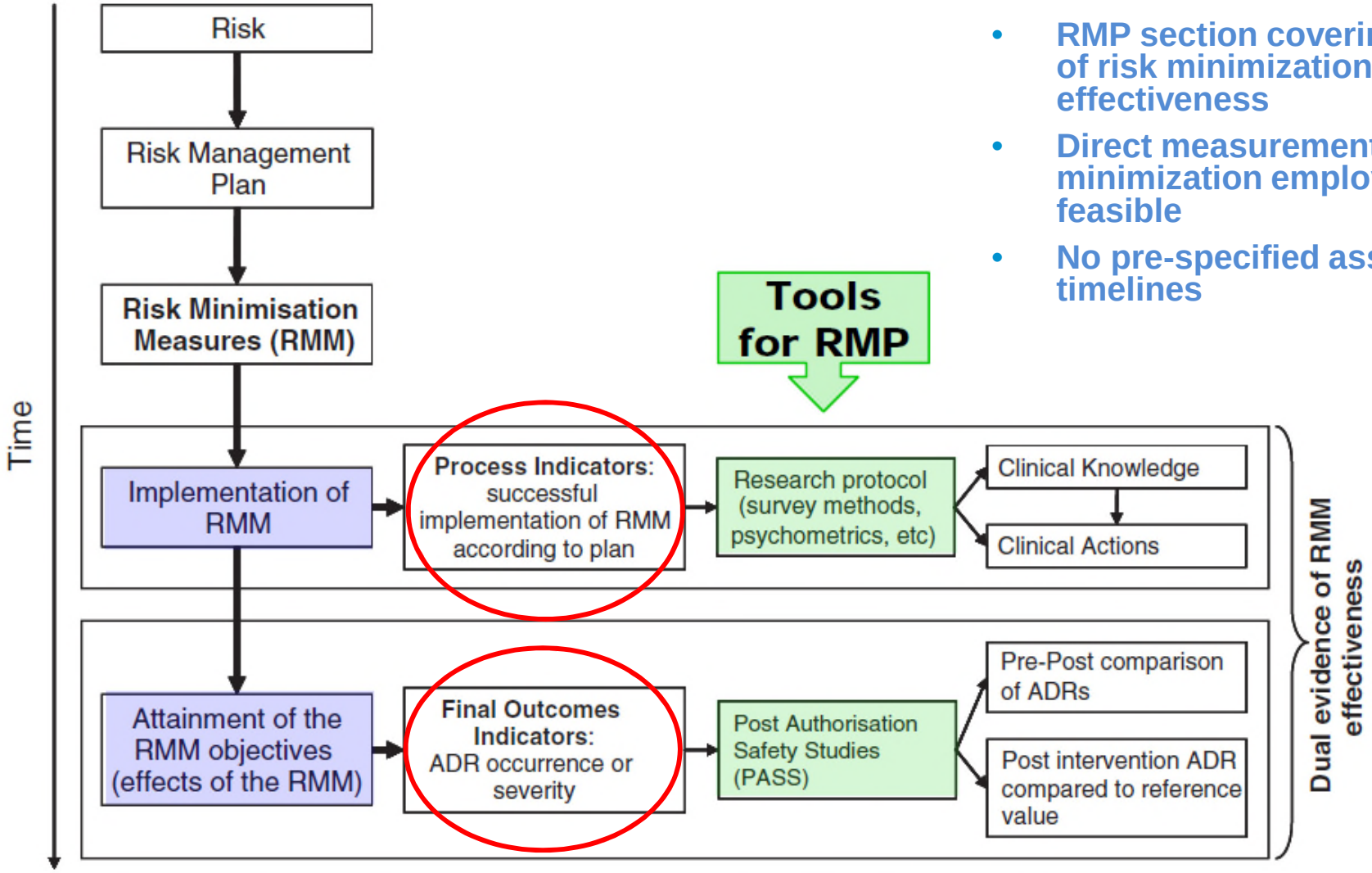
Risk Evaluation and Mitigation Strategies (REMS)
Effective 25Mar2008

- FDA can require for NDA or approved drug; sponsor can propose voluntarily
- FDA has authority to impose penalty for non-compliance
- Typically 30 or 60 days to submit response to REMS request

- May include:
  - Medication Guides
  - Risk communication plans
  - Elements to ensure safe use (“ETASU”), Restricted access to product

- **Required to Assess REMS**
  - Typically 18 months, 3 years, and 7 years from REMS approval date
  - May include: patients/physicians’ understanding of risks and safe use; compliance of prescribers to labeling; ultimately reduced event rates
  - Final assessment plans should be submitted to the FDA for approval at least 90 days before the initiation of the assessment

Risk Minimization Measures (RMMs) in the EU



- RMP section covering assessment of risk minimization tools' effectiveness
- Direct measurement of risk minimization employed whenever feasible
- No pre-specified assessment timelines

L Prieto et al., Pharmacoepidemiol Drug Saf 2012; 21: 896–899

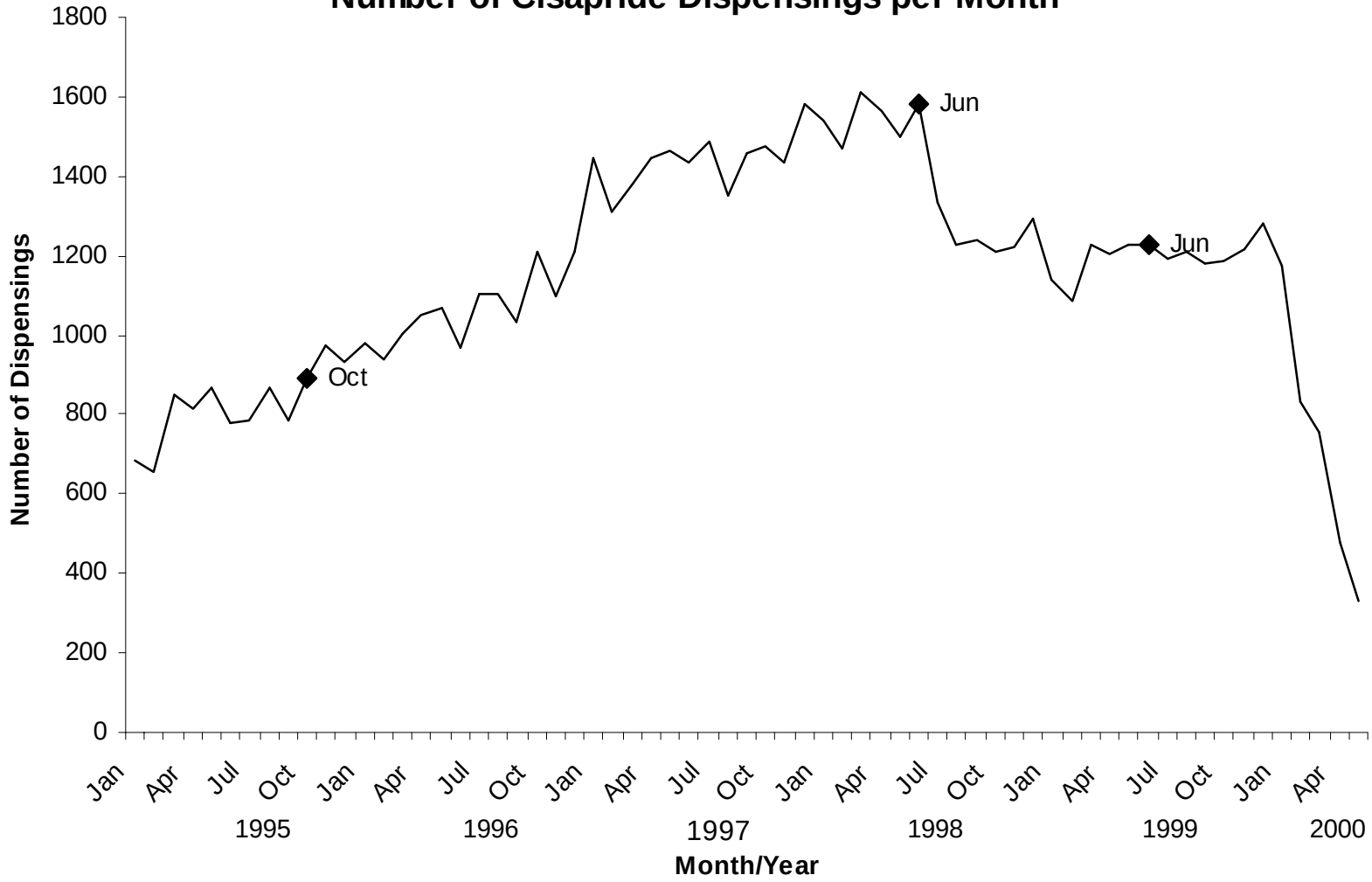
Risk Minimization
Case Studies

An Example of What to Measure

- **Aim:** Objective of Risk minimization tools (education program)
- **Risk Minimization tool:** Education brochure (MD/Pt); patient wallet card
- **Evaluation measure:**
  - **Survey** *(Process Indicator)*
    - Did the educational material arrive (for pts and MD)?
    - Did the MD/pt read it?
    - Did the MD/pt understand it (knowledge assessment)?
    - (Pre/post measurement once intervention has been implemented)
  - **Drug utilization/EMR/EHR study** *(Outcome Indicator)*
    - Has the educational materials/program or intervention impacted the MD/pt behavior
    - Is there evidence of behavior change- i.e. better alignment with treatment protocol and improved health outcomes or a reduction in adverse events)

Measuring the impact of 'Dear Doctor' letters on prescribing of contraindicated medications (1)

Figure 1
Number of Cisapride Dispensings per Month

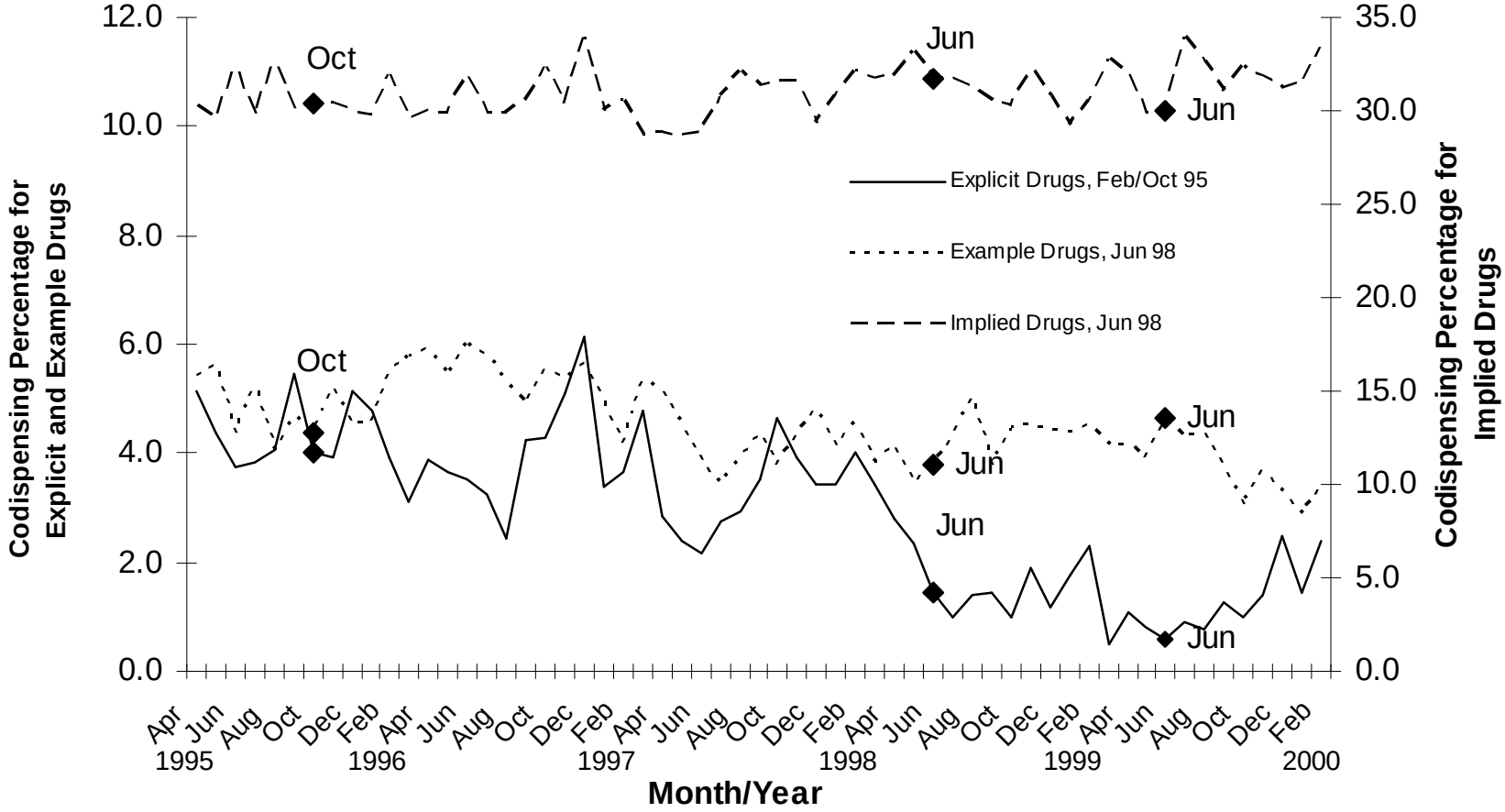


WORLDWIDE RESEARCH & DEVELOPMENT

Weatherby, L et al. *Pharmacoepidemiolgy and Drug Safety* 10:211-218, 2001

Measuring the impact of 'Dear Doctor' letters on prescribing of contraindicated medications (2)

Figure 3
Monthly Codispensing Percentages for Contraindicated Drugs: Overlapping Supply Days



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Weatherby, L et al. *Pharmacoepidemiolgy and Drug Safety* 10:211-218, 2001

Effectiveness of Risk Minimization Measures

REMS in the US

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3400

ORIGINAL REPORT

The effectiveness of varenicline medication guide for conveying safety information to patients: a REMS assessment survey†

Cheryl Enger[1]*, Muhammad Younus[2], Kenneth R. Petronis[2], Jingping Mo[2], Robert Gately[1] and John D. Seeger[1,3]

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ABSTRACT

Purpose Risk Evaluation and Mitigation Strategies (REMS) include various mechanisms to enhance safe use of medications, including a patient medication guide (MG) that provides key information regarding the potential risks associated with the medication. To evaluate the effectiveness of the varenicline MG as a REMS tool for educating patients, we undertook a survey among patients who were dispensed varenicline.

Methods Varenicline recipients within the Optum Research Database, a large U.S. administrative claims database, were invited to participate in a self-administered survey. Survey questions were general (receipt and reading of the MG) and specific regarding patient's understanding of the potential varenicline risks outlined in the MG (neuropsychiatric symptoms, skin reactions, and allergic reactions).

Results From 3568 varenicline recipients invited, 640 (18%) responded, with 633 completing at least one of three risk-comprehension questions. The majority (93%) indicated receiving the MG, and 86% read all or part of it. Ninety-one percent, 41%, and 53% correctly answered at least one question on neuropsychiatric symptoms, skin reactions, and allergic reactions, respectively. A higher proportion who read the MG had correct responses to the risk-comprehension questions than those who did not read it.

Conclusions The varenicline MG was widely received and read among survey respondents, and the information conveyed was generally well understood regarding potential risk of neuropsychiatric symptoms. This study provides an assessment of the effectiveness of the varenicline MG in communicating information about potential risks associated with varenicline. This assessment method may apply to the evaluation of the effectiveness of other MGs.

KEY WORDS—REMS; medication guide; varenicline; smoking cessation; survey; risk management; risk mitigation evaluation; pharmacoepidemiology

Cabergoline RMM Evaluation

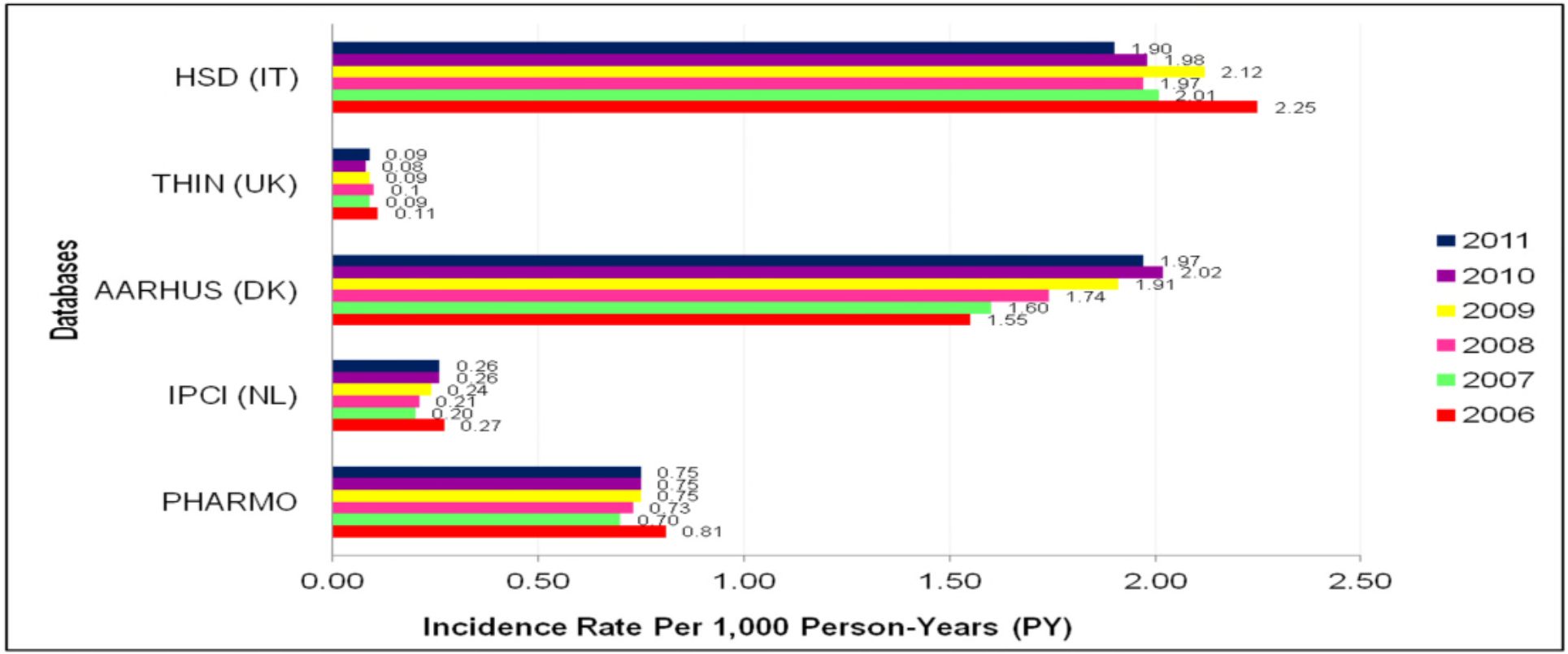
- **Assessment Objectives:** To assess compliance with and effectiveness of SmPC for cabergoline after changes were implemented in July 2008

- **Study Design:** Pre/Post Cohort study (Drug Utilization Study) of patients prescribed cabergoline Jan 2006 - Dec 2011
  - 5 EU databases, ~9.2M individuals
    - The Health Information Network (THIN) – (UK)
    - Integrated Primary Care Information (IPCI) - (NL)
    - PHARMO – (NL)
    - Aarhus healthcare registries – (DK)
    - Health Search Database (HSD) Thales – (IT)

  - *Substudy:* measure incidence/prevalence of CVR pre & post SmPC changes at 3 neurological centers in Italy (results not presented)

Cabergoline RMM Evaluation: Results

- >57 million person-years (PY) of observation
- Annual incidence of cabergoline use for the prolactin reduction indication [♀] declined slightly between 2006 (pre SPC changes) and 2011 (post SPC changes) except in Aarhus (DK)



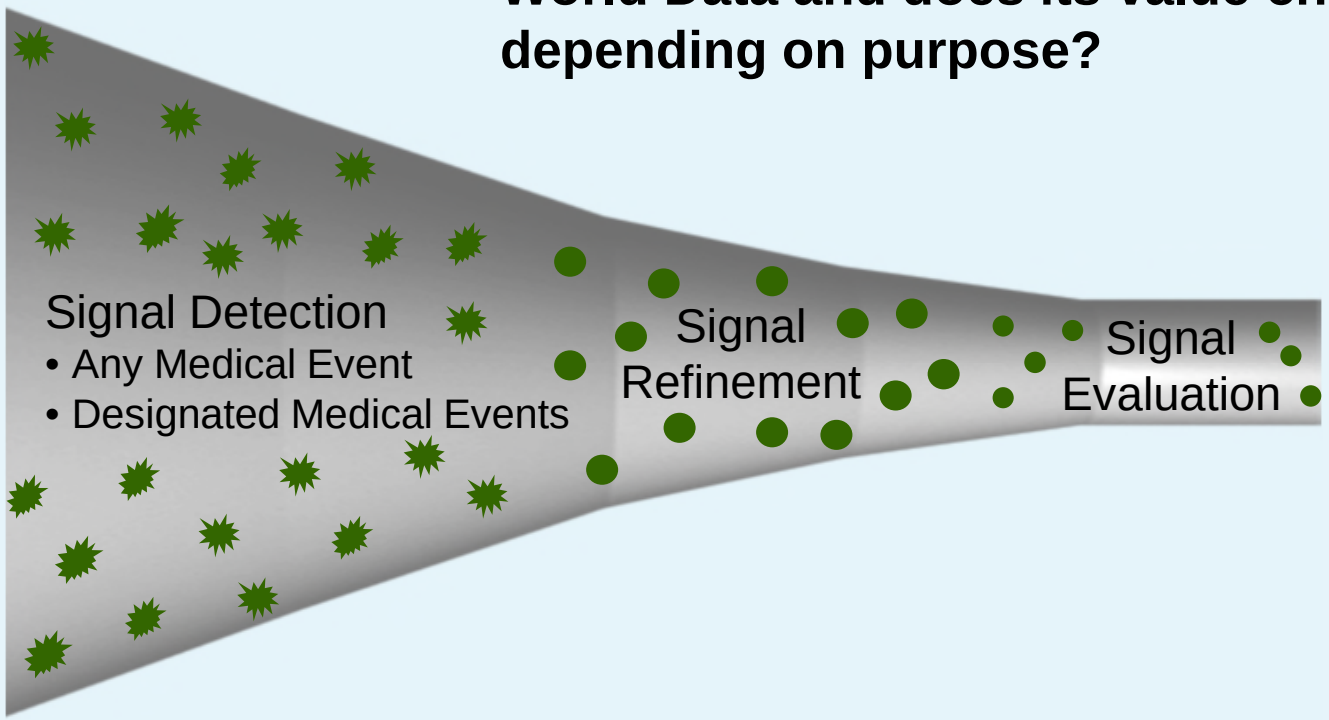
De Luise et al, *Pharmacoepi & Drug Saf* 2013;22:S461

“Big Epidemiology”

"Big Epidemiology"
Potential Use for Signal Detection and Refinement

How to best utilise the wealth of Real World Data and does its value change depending on purpose?

Product Approval & Launch

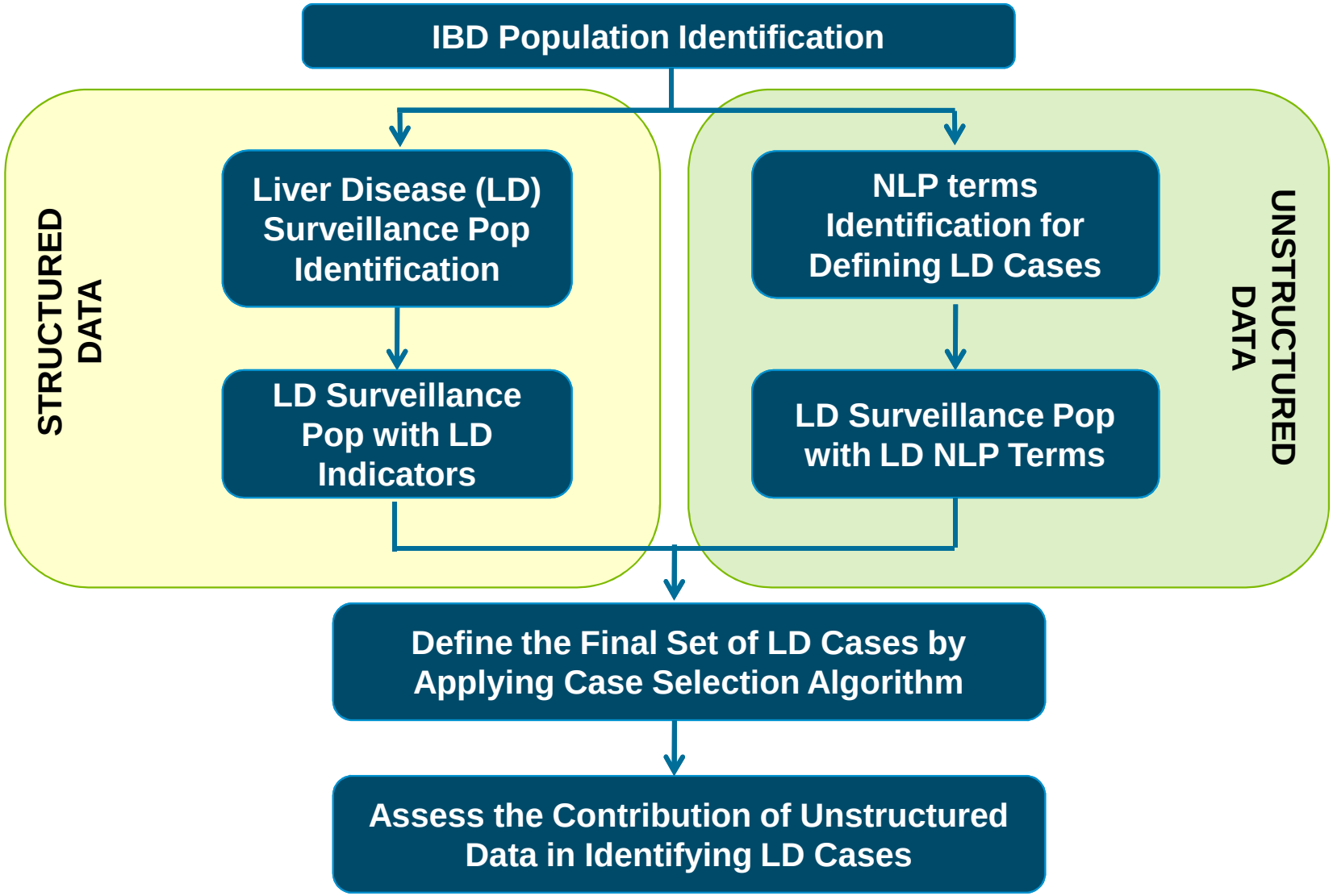


Rapid	⟷	**Time Consuming**
Detect the unexpected	⟷	**Test the anticipated**
Less persuasive	⟷	**Convincing**

Petronis K, Geier J, Reynolds R. "Observational Research in Risk Management and Epidemiology" in *Observational Research in Healthcare*, Eds. J Trotter and A Roddam (in press).

"Big Epidemiology"

Use of Natural Language Processing (NLP) in Humedica



X Zhou, L Weiss, AM Walker, A. Ananthakrishnan, R Shen, RE Sobel, A Bate, RF Reynolds. What does natural language processing add to the structured data available in medical records? Abstract to be presented at 2014 ICPE Taiwan and manuscript being prepared for journal submission.

Concluding Comments (1)

- Labeling is the cornerstone of risk management and the foundation for managing the risks of products
  - A formal Risk Management Plan is required in certain jurisdictions (may be disclosed to public)
  - Risk minimization or mitigation strategies may be needed to ensure that benefits outweigh risks
    - Science evolving rapidly
  - Effectiveness measurements may inform tool application and modification
- Risk management planning is iterative
  - A “Reference” RMP provides a cornerstone for global application that may require local adaptation

Concluding Comments (2)

- Epidemiology's contributions to risk management
  - A key component of development and post-approval safety assessment
    - Background epidemiology of indication(s) and adverse events
    - Active surveillance
    - Post-approval safety studies
    - Evaluation of risk management/minimization interventions
  - Focus early in candidate development leads to best outcomes
  - Evidence from real world important in benefit-risk decisions
- "Big Epidemiology" changing risk management and role of epidemiology
  - IMEDS (reaganudall.org), IMI PROTECT (imi-protect.eu), EU-ADR (eudar-project.org)

Thank You!