Orientation to Risk Evaluation and Mitigation Strategies (REMS)

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Background

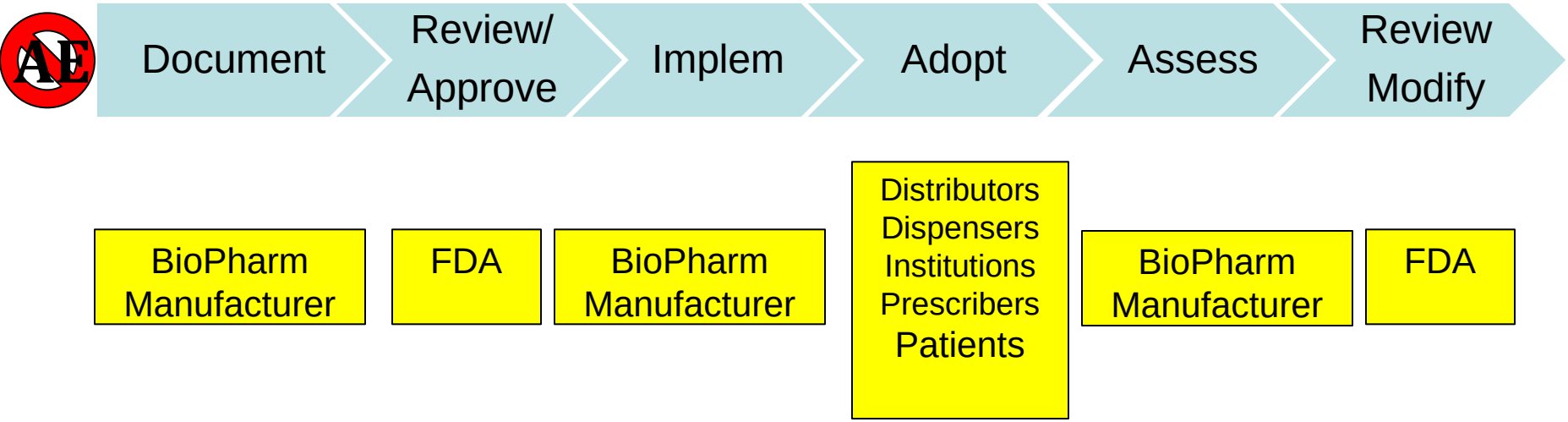
- The REMS provisions of the 2007 Food and Drug Administration Amendments Act (FDAAA) give FDA authority to require REMS if the Agency determines that a REMS is needed to ensure the benefits of the drug outweigh the risk.
- The REMS authority enables FDA to approve, and patients to have access to, certain drugs whose risks would otherwise exceed their benefits and may not be approvable.
- For the majority of approved products, FDA has determined that product labeling and routine AE reporting are sufficient and a REMS is not necessary to ensure a product's benefits outweigh its risks.

Background (2)

- By their nature, all REMS impose some burden on the healthcare system but they vary in how much.
  - multiple REMS place further burdens on the healthcare system.
  - classwide and shared system REMS have partially offset this
- Changes could be made to REMS to improve their efficiency and reduce burdens on the healthcare system.
  - standardization
  - integration
- PDUFA user fees provide support for enhancing REMS by
  - measuring their effectiveness and
  - evaluating, with stakeholder input, appropriate ways to better integrate REMS into the existing and evolving healthcare system.

What is a REMS

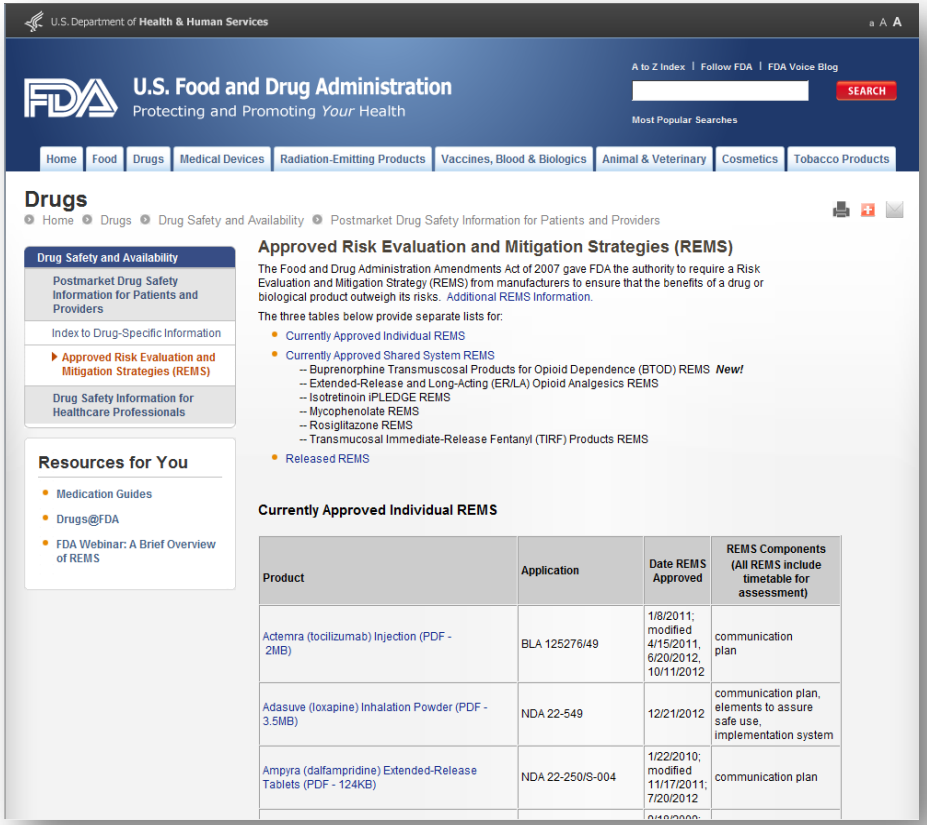
- A REMS is a healthcare intervention plan/program that is designed, implemented and assessed as follows:



What is a REMS (2)

- REMS include goals/objectives e.g., To mitigate the risk of [a serious AE] by…
  - (1) informing, educating and/or training
  - (2) facilitating, enabling, and/or coordinating
  - (3) managing, controlling and/or ensuring safer medication use
- They are comprised of a set of elements/tools
  - Patient-directed tools, e.g., Medication Guide, counseling sheet, website, physician-patient agreement, enrollment form
  - Physician/pharmacist directed tools, e.g., Letters, training, certification/enrollment form, CME, website, requirements
  - Setting/supply chain tools, e.g., Certification requirements, forms (safe use conditions), tracking
- They are assessed at a minimum of 18, 36 and 84 months

REMS Have Been Used Selectively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- Postmarket Drug Safety Information for Patients and Providers
- Index to Drug-Specific Information
- Approved Risk Evaluation and Mitigation Strategies (REMS)
- Drug Safety Information for Healthcare Professionals

Resources for You
- Medication Guides
- Drugs@FDA
- FDA Webinar: A Brief Overview of REMS

Approved Risk Evaluation and Mitigation Strategies (REMS)

The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. Additional REMS Information.

The three tables below provide separate lists for:
- Currently Approved Individual REMS
- Currently Approved Shared System REMS
  - -- Buprenorphine Transmuscosal Products for Opioid Dependence (BTOD) REMS *New!*
  - -- Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS
  - -- Isotretinoin iPLEDGE REMS
  - -- Mycophenolate REMS
  - -- Rosiglitazone REMS
  - -- Transmucosal Immediate-Release Fentanyl (TIRF) Products REMS
- Released REMS

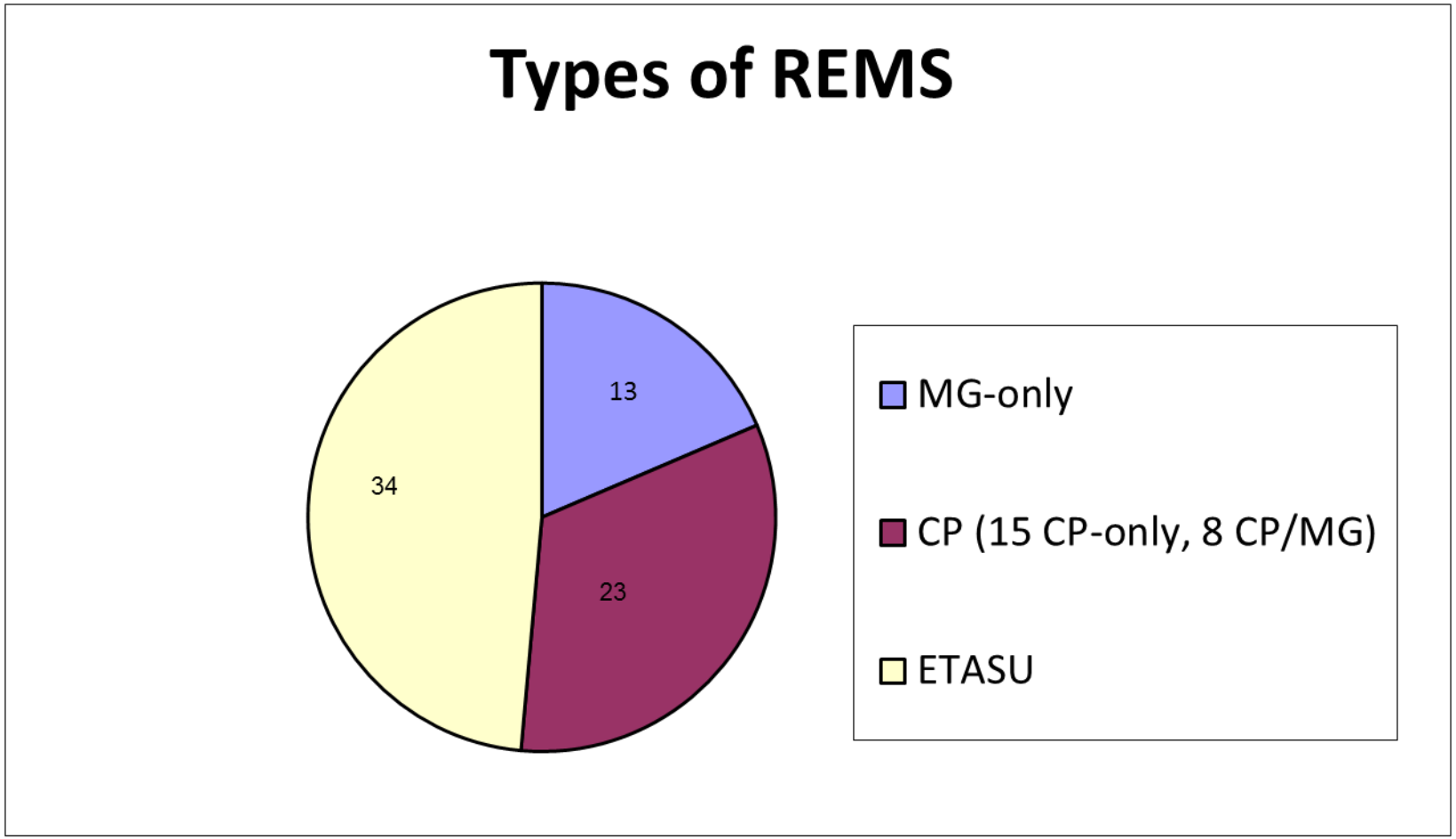
Currently Approved Individual REMS

Product	Application	Date REMS Approved	REMS Components (All REMS include timetable for assessment)
Actemra (tocilizumab) Injection (PDF - 2MB)	BLA 125276/49	1/8/2011; modified 4/15/2011, 6/20/2012, 10/11/2012	communication plan
Adasuve (loxapine) Inhalation Powder (PDF - 3.5MB)	NDA 22-549	12/21/2012	communication plan, elements to assure safe use, implementation system
Ampyra (dalfampridine) Extended-Release Tablets (PDF - 124KB)	NDA 22-250/S-004	1/22/2010; modified 11/17/2011; 7/20/2012	communication plan

- About 200 REMS have been approved since 2008.
- Many were “MedGuide only” REMS which have been released.
- As of July 2013, there are 72 REMS.
  - 66 individual drugs
  - 6 shared system REMS including 84 applications (NDA and ANDA)

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

Types of REMS (N= 70*)



*Numbers as of June 2013

How REMS Have Varied

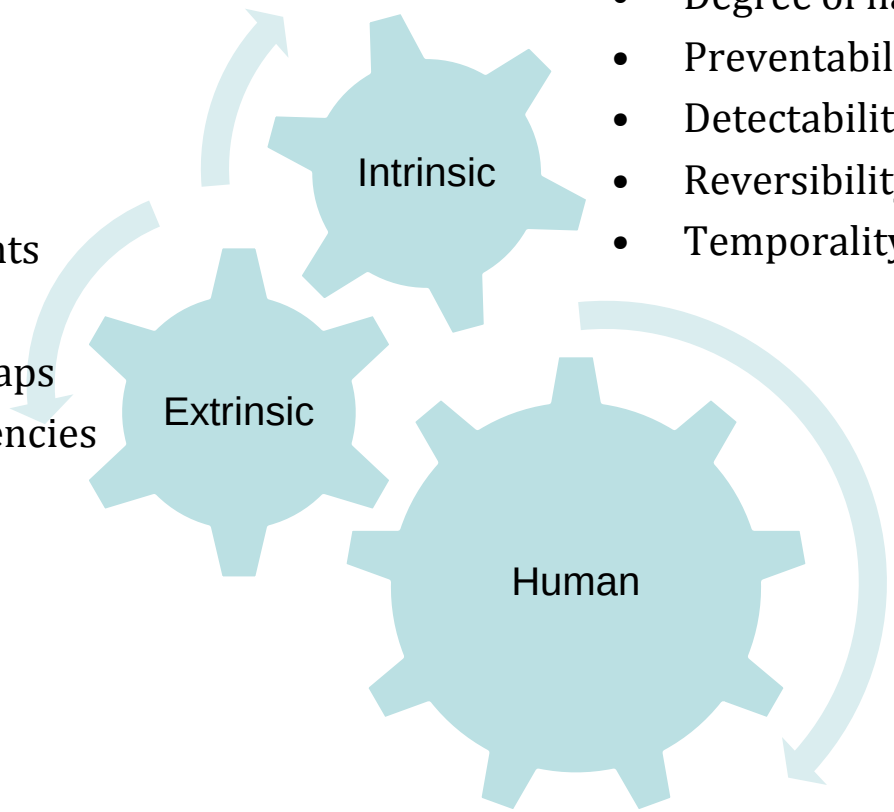
- Goals - some goals have been more general and others more specific
  - e.g., "to inform patients about the risks of Drug X"
  - e.g., "to mitigate the risk of Y associated with Drug X"
- Design –
  - targeted stakeholder(s); some include both patients and prescribers, others only include prescribers
  - variation in the element(s) used to address a given risk
    - e.g., for a given risk some REMS have required restrictions while others have not

How REMS Have Varied

- Selection of tools –
  - Patient directed tools have included Medication Guides, Patient Guides, Booklets, Brochures, Counseling Tools, Patient-Prescriber Agreement Form (PPAF), Patient Enrollment Form, REMS-dedicated Website
  - Prescriber directed tools have included REMS training materials, Prescriber Guides, Booklets, Brochures, Counseling Tools, Patient-Prescriber Agreement Form (PPAF), Prescriber Enrollment Form, REMS-dedicated Website
  - Dispensing settings have varied in degree of certification
- Assessment plan – metrics, data sources, data to inform redesign e.g., RCA

Diverse Factors Contribute to REMS Variation (Goals, Design, Tools)

- Sponsor proposals
- Regulatory constraints
- Lack of evidence
- Healthcare system gaps
- Precedent inconsistencies
- Unmet needs
- Burden/access
- Cost



- Degree of hazard
- Preventability (risk factors)
- Detectability
- Reversibility
- Temporality

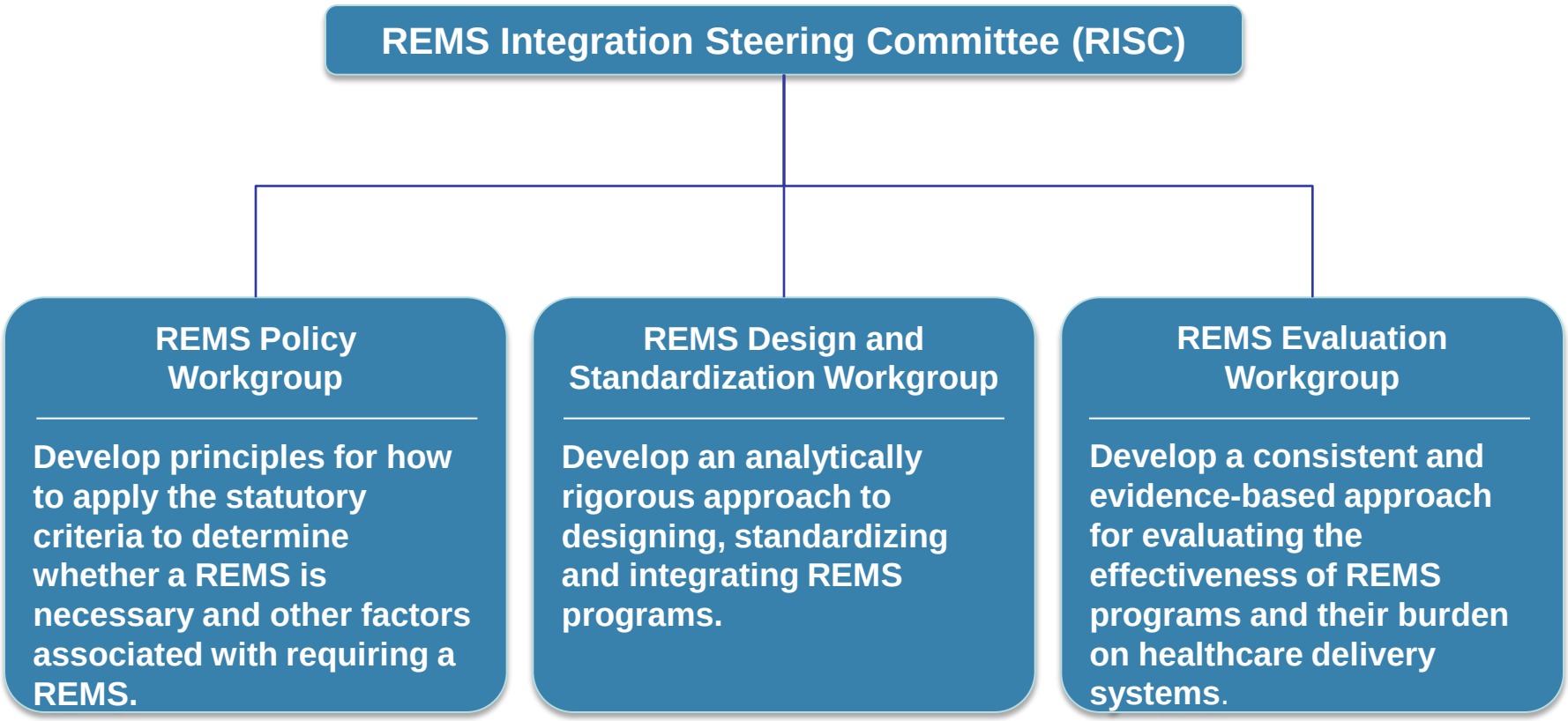
Variations Between REMS

- Explained/necessary variations e.g.,
  - Risks and circumstances vary requiring a degree of customization
  - Addressing diverse healthcare system with one single program design
  - Dispensing restrictions may be detrimental in some cases (anti-rejection)
  - Subpopulations may be at unequal risk (teratogens)
  - New legislation, new technology, new field
- Unexplained/unnecessary variations e.g.,
  - Human factors
  - Sponsor proposal have varied
  - Approaches to educating prescibers (training, attestation, certification)
  - Differing instructions for similar risks
  - Limitations to assessment methods and data
  - Other

Opportunities to Standardize REMS

- Extent of AE risk characterization
- Application of standard criteria for requiring a REMS
- **Systematic use of prospective "failure analysis" methods to inform:**
  - **Descriptions of desired program goals/objectives**
  - **REMS program design/re-design**
  - **Consistent selection and implementation of tools from a standardized REMS "toolkit" to each stakeholder**
  - **Assessment metrics and methods**

REMS Integration Initiative – Structure



Ideal Future State

Fully characterized AE risk	Prospective Failure Analysis	Goals & Objectives	Standardized REMS Toolkit	Standardized Assessments
• At risk pop. • Detectability • Temporality • Mitigability • Reversability	• Systematic • Evidence based • Stakeholders • Failures specify targets	• Consistent • Specific • Measurable	• By stakeholder • Integrated • Content/enablers • Nonburdensome	• Metrics • Systems • Domains • Inform

BackUp

Patient-Directed REMS Tools

- Medication Guides (MG)
- REMS Print Materials
  - Patient Guides, Booklets, Overviews, Brochures
  - Counseling Tools (*may be part of prescriber/healthcare provider materials*)
- Patient-Prescriber Agreement Form (PPAF)
- Patient Enrollment Form
- REMS-dedicated Website

Patient-Directed REMS Tools (1)

- **Medication Guides (MG)**
  - The most frequently-used patient educational materials in REMS
- Purpose: To provide information when the FDA determines in writing that it is necessary to patients' safe and effective use of drug products

  Length: 1 - 8 pages

  Format: Text, bullets

  Delivery Method: Provided to patient by pharmacist or healthcare provider, or accessed by the patient online

Patient-Directed REMS Tools (2)

- **REMS Print Materials**

  Patient Guides, Booklets, Overviews, Brochures

  Purpose: Focus on REMS risks and REMS program information

  Length: 2 - 18 pages

  Format: Text, bullets, tables, graphics

  Delivery Method: Provided to patient by healthcare provider.

  Can also be downloaded from REMS-dedicated website

Patient-Directed REMS Tools (3)

Counseling Tools for Healthcare Providers (Print materials)

Purpose: Tools used by healthcare providers to counsel patients about safe use of drug

– Include risks of the drug, patient responsibilities, and encourage patient-prescriber discussion

Length: 1 - 2 pages

Format: Text, bullets, tables

Delivery Method: Provided to patient by healthcare provider

Patient-Directed REMS Tools (4)

- **Patient-Prescriber Agreement Forms**

  Purpose: Used to document that an informed discussion of the drug's benefits and risks took place and that the patient understands the risks and REMS program requirements

  – Supports patient counseling by providing information for prescribers to review with patients

  Length: 1-2 pages

  Format: Text, bullets

  Delivery Method: Provided to patient by prescriber

Patient-Directed REMS Tools (5)

- **Patient Enrollment Forms**

  Purpose: Contain agreements and acknowledgements of safe use conditions

  – Used to enroll patients into REMS program in order to receive drug

  – Allows sponsor to track patients and ensure that only those who have completed the form can obtain drug

  Length: 1-2 pages

  Format: Text, bullets

  Delivery Method: Provided to patient by healthcare provider

Prescriber Tools for REMS (1)

- Product labeling
- REMS program communications
- REMS training materials
- Additional REMS materials
- Enrollment forms to support certification

Prescriber Tools (2)

REMS Program Communications

Purpose: Deliver messages to healthcare providers about drug risks and REMS programs

Examples: Dear Healthcare Provider Letters and e-mails, letters to professional societies, factsheets REMS-dedicated websites, journal information pieces

Prescriber Tools (3)

Training Materials

Purpose:

- Provide comprehensive training on risks addressed in REMS and how to mitigate risks
- Explain how the REMS program operates
- Describe prescriber roles/ requirements

Examples: Program Overviews, Prescriber Guides, Training Modules

Delivery: In person, by phone, print, electronic (online/DVD), with or without audio

Prescriber Tools (4)

Additional Materials

Purpose: Address specific issues related to safe use of drug; enabling tools to support ongoing patient care

Examples: Checklists, counseling tools, dosing and administration guides

Enrollment Forms

Purpose: Enroll prescriber into REMS program

Content: Prescriber demographic information, acknowledgements, agreements

Role of Dispensers/Dispensing Settings in REMS

REMS may require that:

- practitioners or settings that dispense the drug are specially certified
- the drug is dispensed only in certain healthcare settings
- the drug is only dispensed to patients with evidence or documentation of safe-use conditions

REMS Requirements for Dispensers (1)

To be certified to dispense, dispensers may be required to:

- Designate “Authorized Party”
- Train and/or ensure staff are trained
- Enroll
- Establish systems for tracking and/or document management
- Modify existing systems and/or processes (electronic and/or manual)

REMS Requirements for Dispensers (2)

At the time of dispensing, dispensers may be required to:

- Verify 'documentation of safe use conditions'
  - Record/document verification
  - Resolve verification *failures*
- Provide Medication Guide
- Counsel patients and/or caregivers

REMS Requirements for Dispensers (3)

Periodically, dispensers may be required to:

- Re-enroll
- Train new staff
- Participate in audits
- Implement new or modified REMS requirements

Towards a Systematic Approach to REMS Design

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September 25, 2013

Why do we need a systematic approach to REMS design?

A systematic approach to REMS design could help us…

- Document and communicate a "rationale" for each REMS.
- Comprehensively identify and anticipate failures.
- Address complexity of drug risk management.
- Reduce unnecessary variation in REMS design and tools.
- Increase predictability of review process.

REMS Design: Future State

Establish the Scope

- Characterize the risk that the REMS is trying to address and conditions for safe use of the drug.
- Establish the likely context of use for the drug.

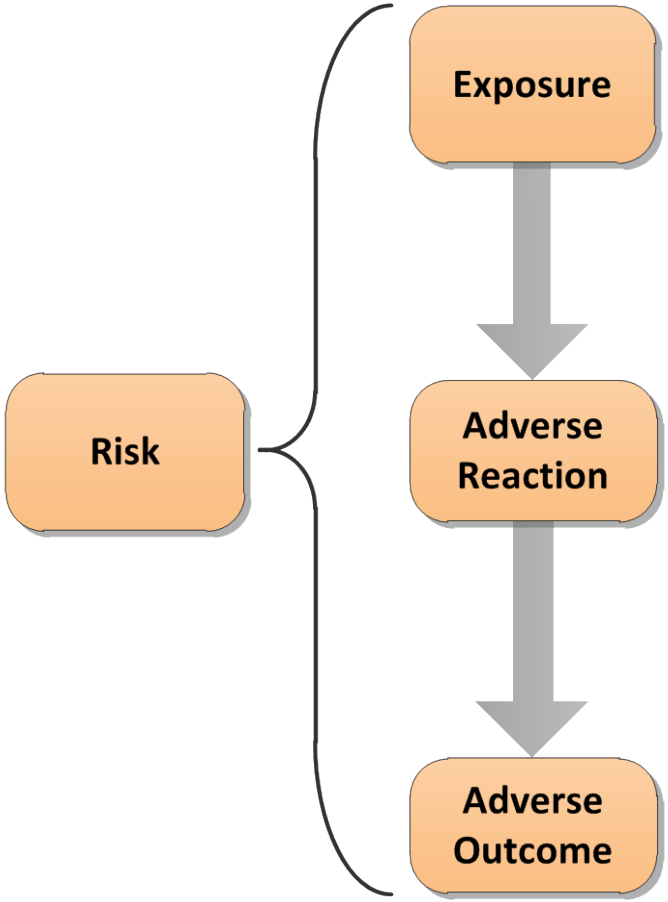
Analyze the Problem

- Identify failures in safe use that might lead to patient harm.
- Identify underlying causes of those failures.

Specify Interventions

- Specify key information / desired behaviors /process changes to address underlying causes.
- Develop interventions to convey information/ behaviors.

Characterize the risk and safe use of the drug



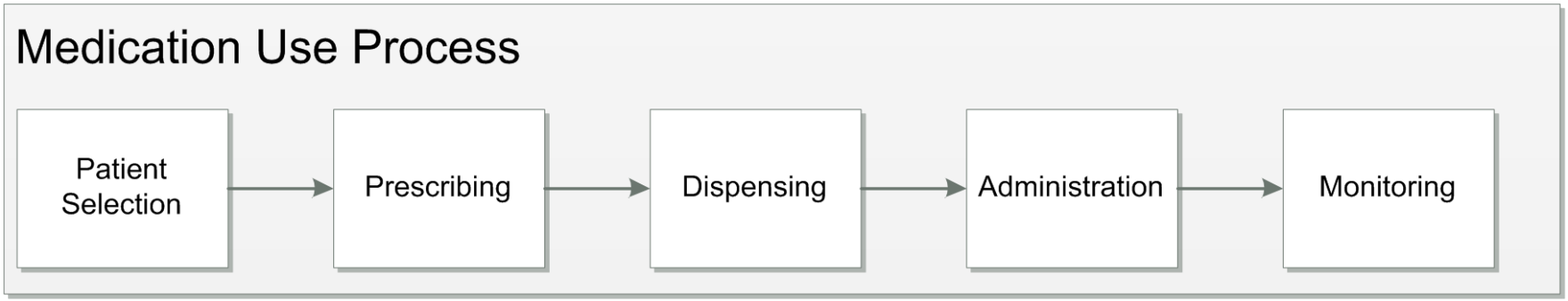
- How do patients become exposed to the risk?
- What is the relationship between exposure and the adverse reaction of concern?
- Can exposure be managed to reduce the likelihood of an adverse reaction? How?

- What is the adverse reaction (ADR) of concern?
- Can it be prevented, detected, or treated? How?
- What risk factors affect the likelihood of an ADR?
- Can they be prevented, detected, or treated? How?

- What are adverse outcomes that can result and how likely/severe are they?
- What factors affect their likelihood/severity?
- Can they be prevented, detected, or treated? How?

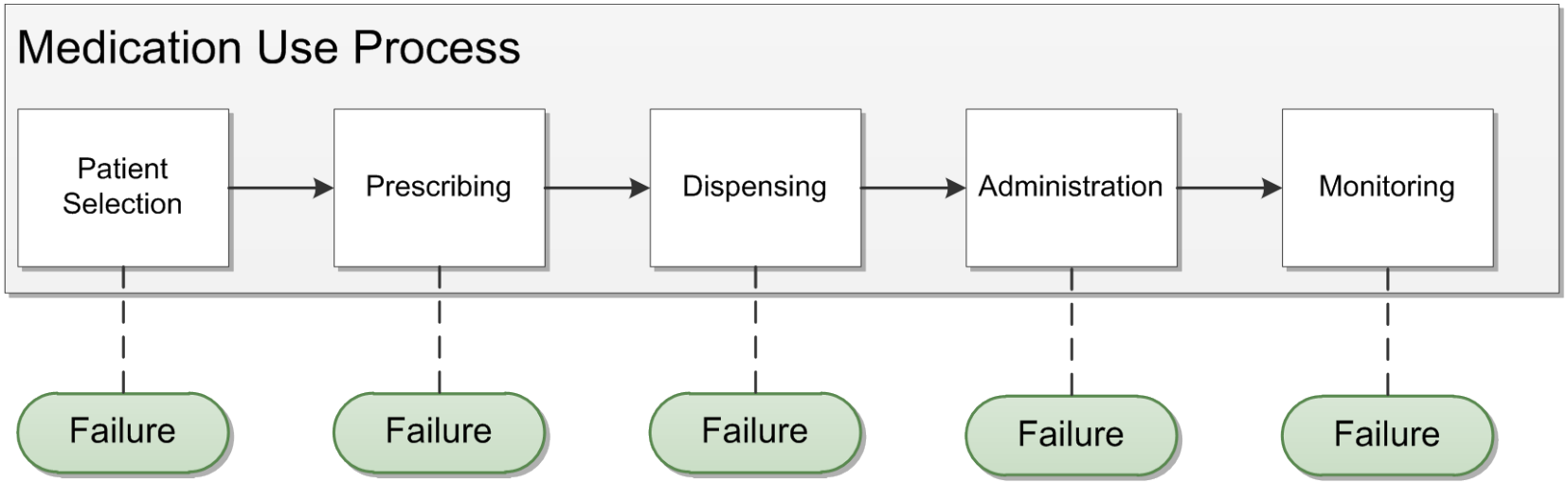
Establish the context of use

- Which patient populations that are likely to use the drug?
- In which healthcare settings is the drug likely to be prescribed?
- Which stakeholders will be involved in the patient's care?
- What is the process by which the patient is treated?



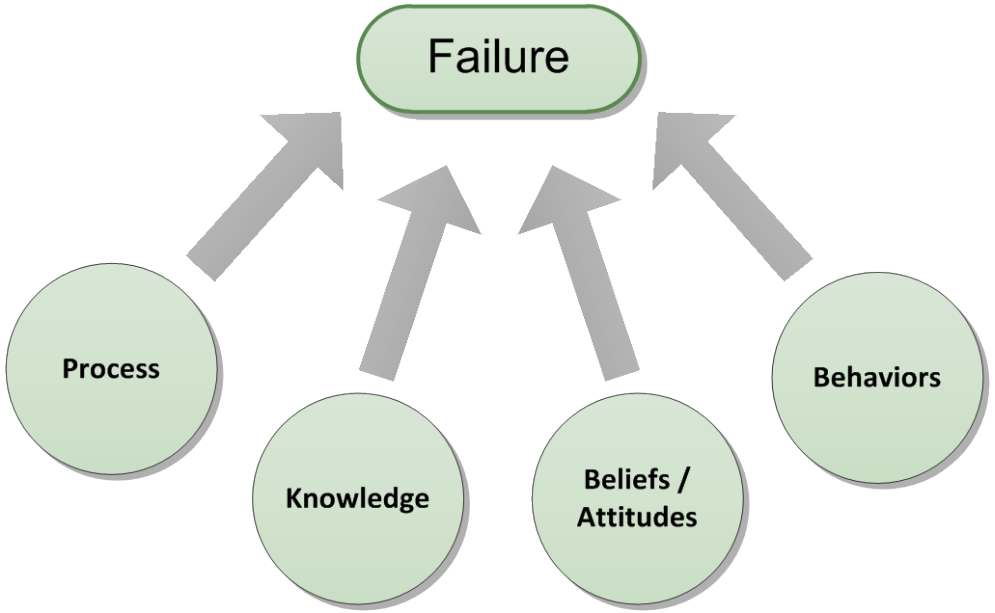
Identify possible failures

- What are the potential failures that could lead to unsafe use and patient harm?
- Where in the medication use process could these failures occur?



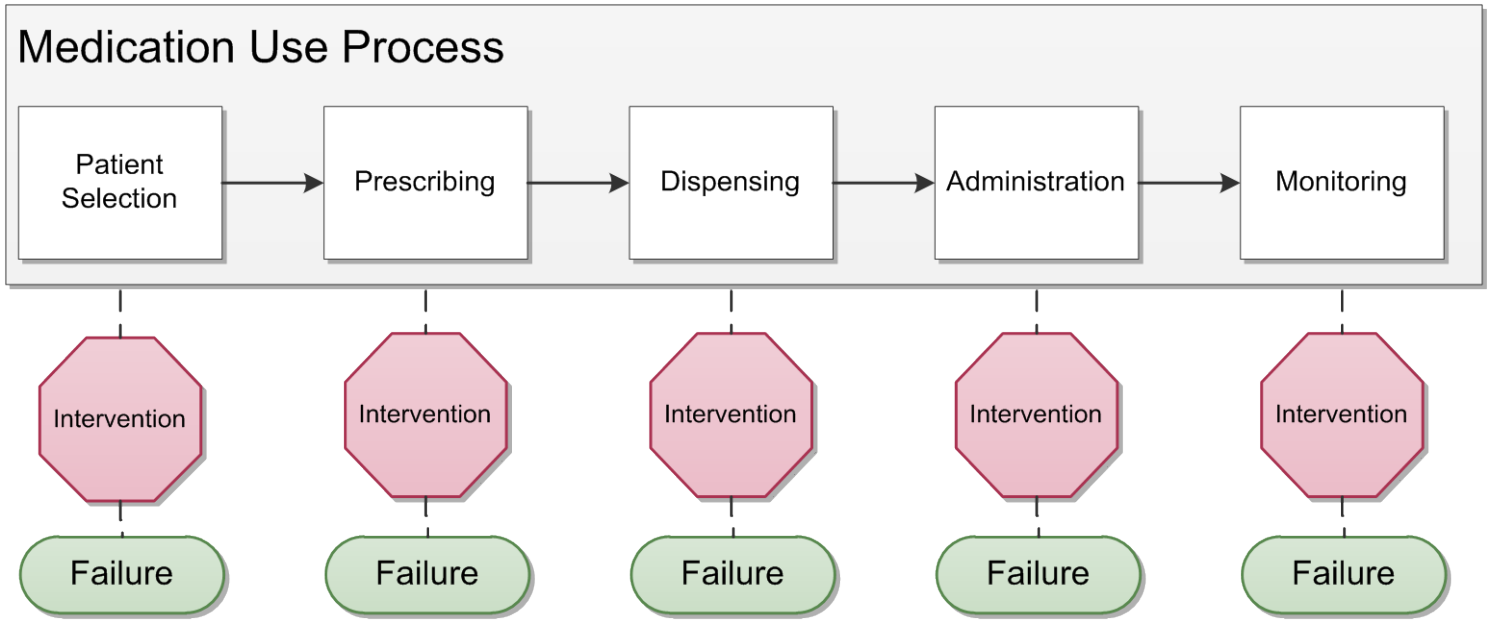
Identify underlying causes of failure

- How does the medication use process contribute to the failure?
- How do the knowledge, attitudes, beliefs, and behaviors of stakeholders contribute to the failure?

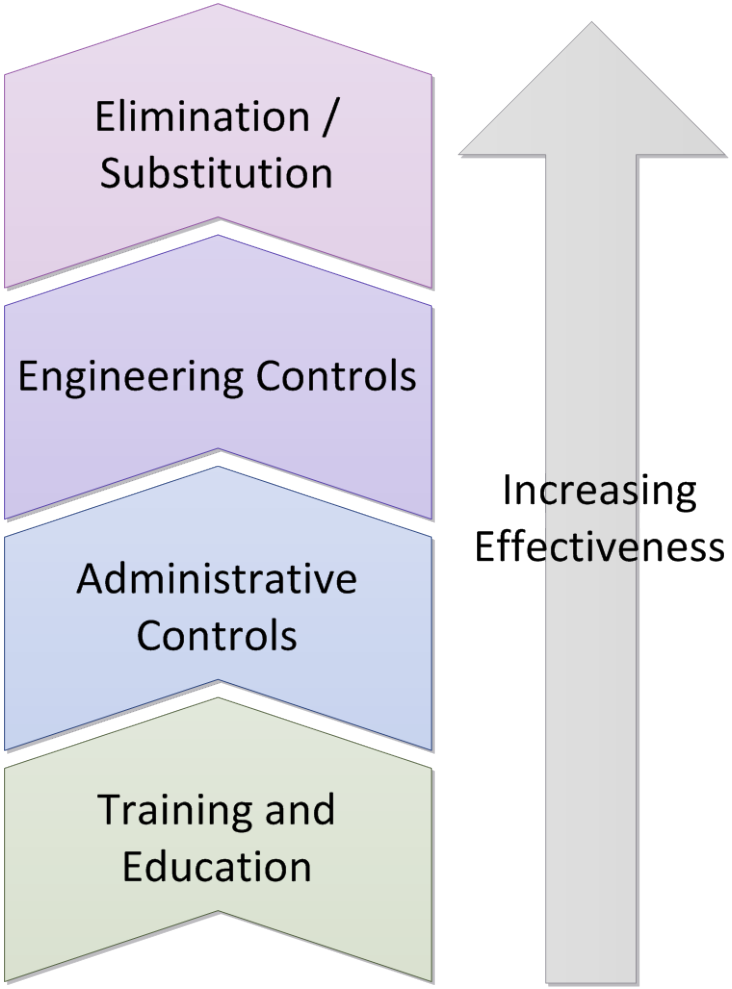


Identify key information, desired behaviors, interventions

- What information, behavior changes, or process changes are needed to address the underlying causes of failure?
- What interventions can effectively convey information and implement changes?



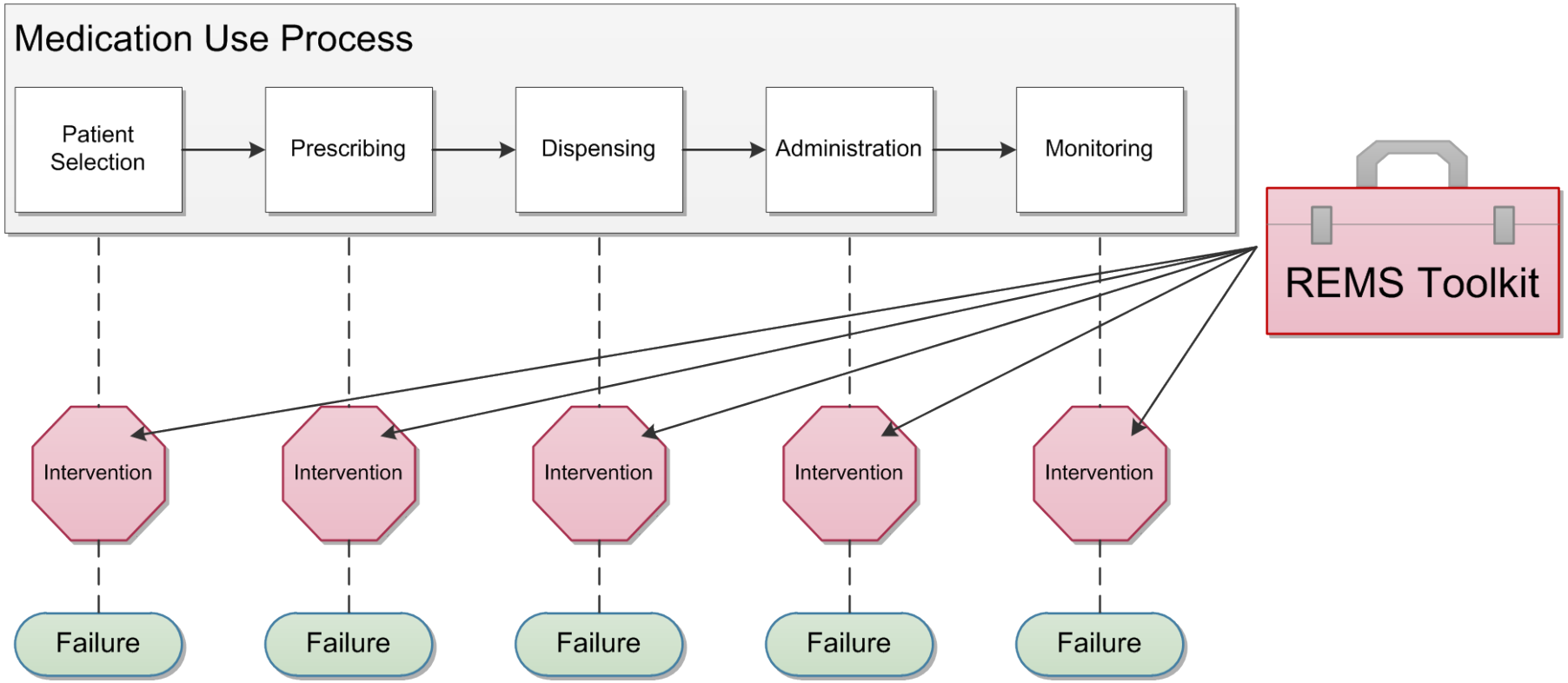
Develop tools



- When is it possible to use engineering or administrative controls?
- How do we balance tool "intensity" against access and burden considerations?

Use tools from a standard REMS "toolkit"

- What tools can we use from our REMS toolkit?
- How should they be customized to the individual REMS?



Practical Considerations

An effective approach should…

1. Work within the regulatory review process
   - Build an evidence base that permits informed decision-making
   - Consider time/resource and regulatory constraints
2. Focus on what's most important
   - Prioritize most important failures, root causes
   - Prioritize most effective/feasible interventions
3. Streamline to enhance efficiency
   - Share tools across programs
     (e.g., for similar risks, failures, and/or contexts of use)
   - Re-use analysis across programs
4. Design with evaluation in mind