RxFMEA® Discussion

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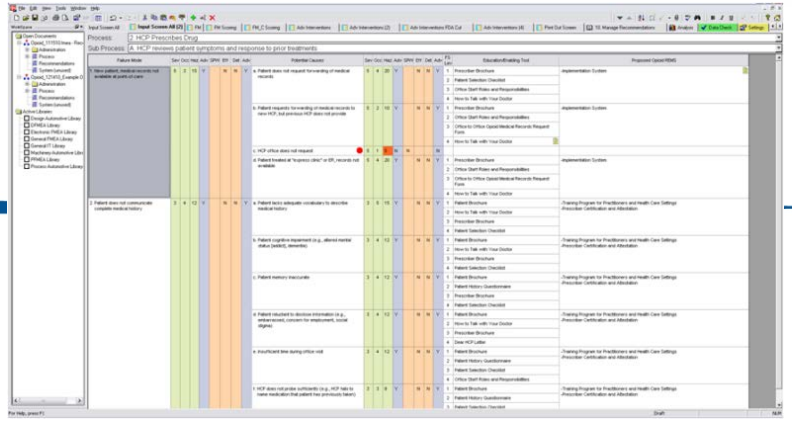
RxFMEA® Adaptations



- ☑ Procedures to characterize the process of medication use
- ☑ Customized database to track volume of data when analyzing “wild state” care process
- ☑ CIOMS III compatible scoring
- ☑ Specify interventions incorporating Human Factors and Adult Learning insights
  - ☑ At least two (2) stakeholders to address each failure (for back-up redundancy)
  - ☑ At least one (1) educational and one (1) enabling intervention for each stakeholder

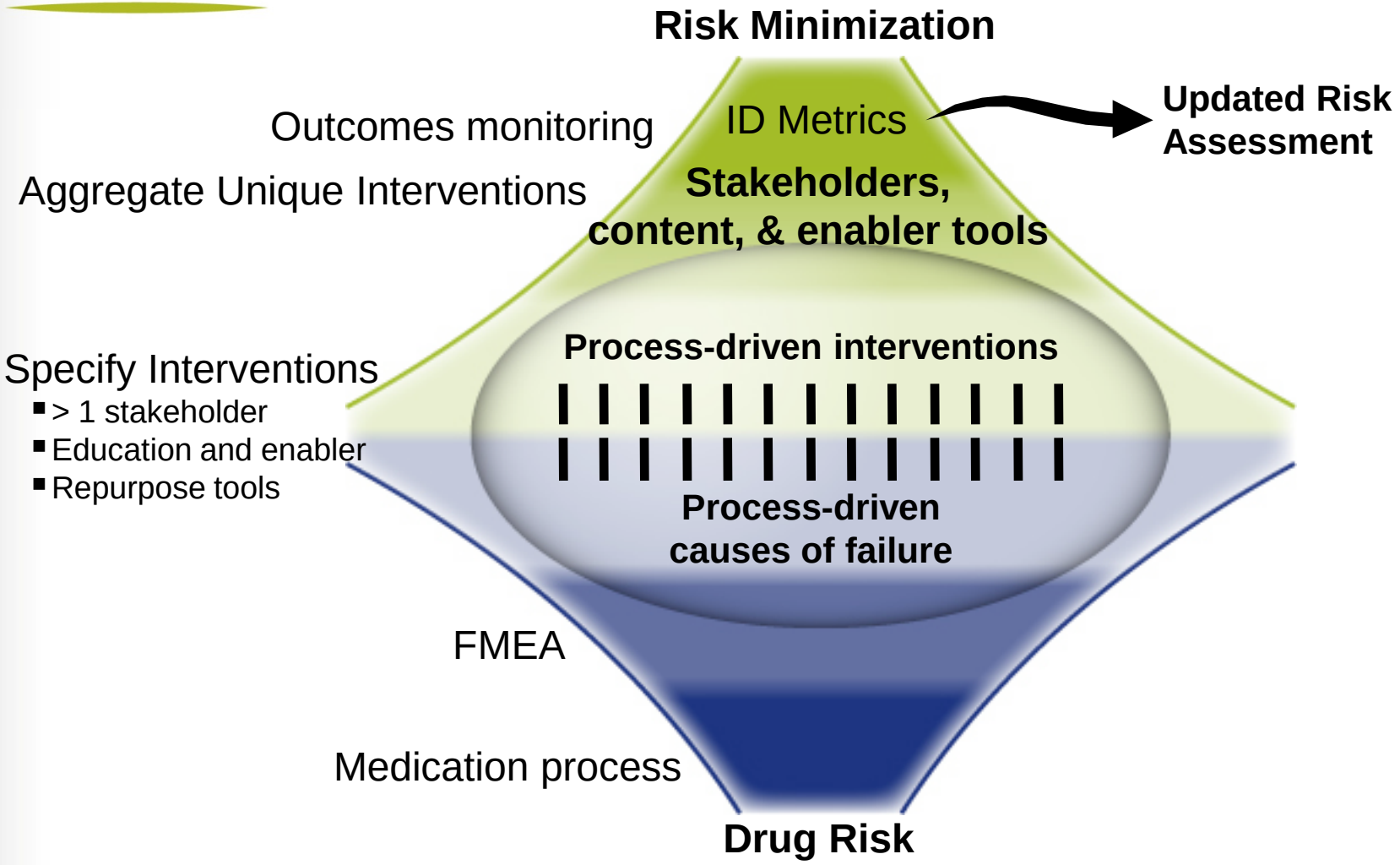
Severity

Value	Description	Examples
1	Negligible	Patient at no risk
2	Minor	Symptomatic adverse event, headache
3	Moderate	Impaired function (QOL), sever constipation
4	Major	Hospitalization, temporary disability, respiratory depression
5	Serious	Death, permanent disability

Occurrence

Value	Description	Examples
1	Very rare	Less than 1/10,000
2	Rare	From 1/10,000 - 1/1,000
3	Occasional	From 1/1,000 – 1/100
4	Frequent	From 1/100 – 1/10
5	Very Frequent	Greater than 1/10

RxFMEA Overview



Systematic Targeting

Process Step 2: HCP Prescribes Drug

Sub Processes:
A. HCP reviews patient symptoms and response to prior treatments

Failure: Patient does not communicate complete medical history

Potential causes of failure:
1. Patient lacks adequate vocabulary
2. Patient has cognitive impairment
3. Patient has poor memory
4. Patient is reluctant to disclose information
5. HCP does not probe adequately
6. There is Insufficient time during office visit

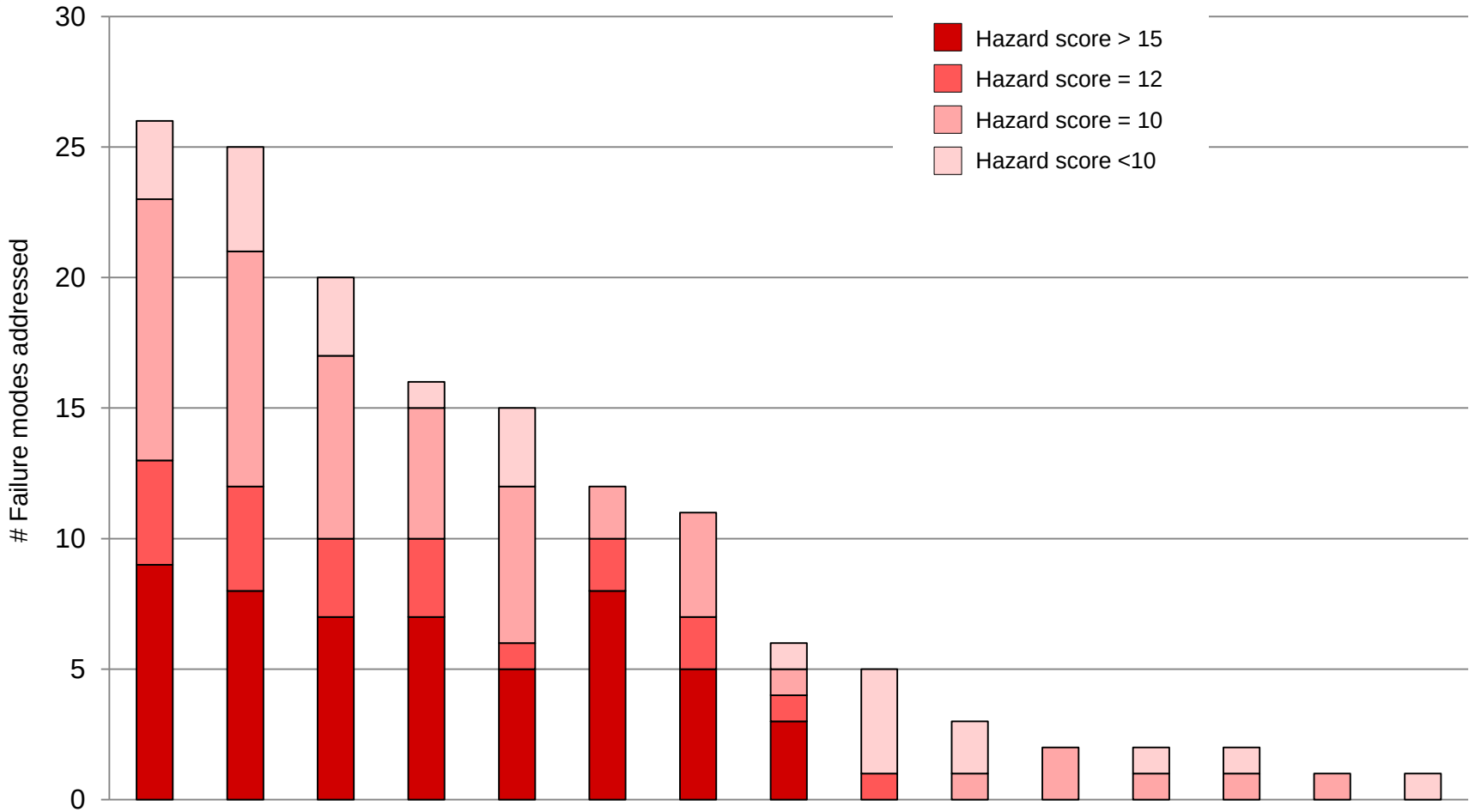
Interventions that may address causes of failure for each stakeholder:

1. Patient Stakeholder Education and Training
   - Patient Brochure
   - "How to Talk with Your Doctor"
   - Patient History Questionnaire
2. HCP Stakeholder Education and Training
   - Prescriber Brochure
   - Dear HCP Letter
   - Dear Pharmacist Letter
   - Patient Selection Checklist

Causes determine content for interventions

- Content must be written at an elementary level
- Content must include a glossary of terms and talking points for patients to use with HCPs
- Stress importance to patients of disclosing all medical information to HCPs
- Reinforce need for HCPs to obtain complete patient history
- List important questions HCPs need to ask patients

Sample Intervention Distribution



Case Example: Poster at the American Academy of Pain Medicine's 27th Annual Meeting, National Harbor, MD

A Science-Based Approach to Responsible Risk Management for a Novel Long-Acting Opioid Analgesic

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INTRODUCTION

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- Long-acting and extended-release opioid analgesics have potentially serious patient safety risks beyond the usual drug-associated adverse events, including overdose, abuse, misuse, and addiction; diversion is also an important concern and class-wide risk[1]
- Mallinckrodt Inc., a Covidien company based in Hazelwood, MO, received recent approval to market EXALGO® (hydromorphone HCl) extended-release tablets CII, indicated for once-daily administration in opioid-tolerant patients requiring around-the-clock opioid analgesia for an extended period of time
- To help ensure proper prescribing to mitigate patient safety risks, the science-based method of failure mode and effect analysis (FMEA) was employed to assist in the selection and design of risk mitigation tools to help ensure safer use
- This presentation illustrates how a Risk Evaluation and Mitigation Strategy (REMS) mandated by the US Food and Drug Administration (FDA) and a Covidien voluntary program work synergistically to achieve REMS goals to protect patient safety

BACKGROUND

EXALGO possesses unique challenges to both safe prescribing and use. The extended-release drug delivery system provides a gradual increase in hydromorphone, reaching 50% of peak concentration (C_{max}) by 6-8 hours and resulting in a 2-hour delay in onset of action after the initial dose. This presents a potential risk of overdose as:

- Patients may potentially dose with another opioid tablet prior to the onset of action of EXALGO
- Physicians may prescribe an immediate-release opioid to provide analgesia for breakthrough pain prior to the onset of action of EXALGO

The FDA specified that the approval of EXALGO would require an "Interim REMS" with the following objectives[2]:

- Educate prescribers about the risks of overdose, abuse, misuse, and addiction, including risks of:
  - Overdose by exposure to an essentially immediate-release form of hydromorphone created by breaking, chewing, crushing, or dissolving EXALGO
  - Addiction from exposure to EXALGO
  - Overdose with use in opioid-nontolerant individuals
- Educate prescribers on proper patient selection to help reduce risk of overdose, abuse, misuse, and addiction
- Educate prescribers on responsible prescribing practices, including risk assessment and stratification, periodic assessment and monitoring, and proper use and handling, to help reduce the risks of overdose, abuse, misuse, and addiction
- Educate prescribers and patients about safe use, handling, storage, and disposal of EXALGO
- Educate prescribers to counsel patients on the need to store opioid analgesics safely out of reach of children and household acquaintances

METHODS

FMEA is a proactive, science-based risk assessment methodology used to identify process system failures and underlying causes as targets for intervention. This technique has been employed by multiple governmental agencies, in healthcare, and in manufacturing. It is a valuable tool for improving patient safety.[3] FMEA has been utilized by The Joint Commission and hospitals in reducing medication errors and improving patient care.[4-7] RxFMEA® is a proprietary software application (ParagonRx, Wilmington, DE) enabling users to systematically identify, rank, and define potential human factors and other failures related to pharmaceutical product use and specify interventions to address those failures.

This method was used to assist and guide the development of the overall risk mitigation program to meet and exceed REMS objectives in a way consistent with company priorities and values to educate, collaborate, and innovate to improve patient safety. Additionally, important considerations were made to:

- Preserve access for patients, prescribers, and pharmacists
- Avoid prescriber burden and increase confidence by providing genuinely useful tools
- Ensure patients and prescribers understand key safe-use messages to reduce risk

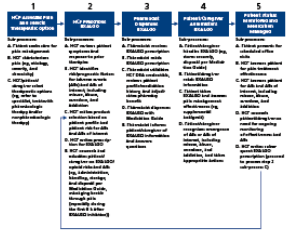
The RxFMEA consists of specific steps to ensure a systematic and reproducible method of analysis, as depicted in **Figure 1**. The team was multidisciplinary and comprised about 15 members who met in 6 half-day meetings. The team agenda was to thoroughly define the medication use process (MUP) for EXALGO—an integral part of the entire process. Once defined, the MUP served as a map of the patient care process.

Figure 1. The RxFMEA process

Steps involved in the RxFMEA process include the following:

- Define MUP processes and sub-processes (**Figure 2**)
- Define ways these sub-processes could fail (failure modes)
- Identify underlying behaviors (causes of failure) that can cause a sub-process to fail for each MUP sub-process
- Define the hazard score threshold (frequency x severity = hazard score)
- Prioritize each potential cause of failure by assigning it a hazard score
- Advance the analysis for those hazards that exceed the threshold
- Determine the types of interventions that could address each potential cause of failure that exceeded the hazard score threshold
- Create redundancy among interventions

Figure 2. EXALGO medication use process (MUP)

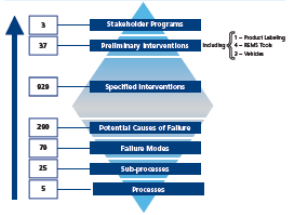


Causes of failure were defined as behaviors that could lead to unsafe actions. A cause of failure exceeding the hazard index threshold became the focus of a specific intervention. Interventions were selected to mitigate negative behavior and consisted of educational programs/materials and enabling tools. Metrics were defined to help measure how each intervention is accepted, understood, and utilized. Project briefs were created to aid in intervention tool development, specifically targeting one or more behaviors.

RESULTS

Results of the EXALGO RxFMEA analysis are shown in **Figure 3.**

Figure 3. Results of EXALGO RxFMEA analysis



RESULTS

A total of 30 processes and sub-processes were analyzed, yielding 79 failure modes and 290 potential causes of failure. These failures led to 929 identified interventions, for which 37 preliminary tools were specified to be distributed through physician, pharmacy, and patient/caregiver programs. The process also identified the 5 tools required by the FDA as meeting the REMS objectives, which are listed in **Table 1.**

Table 1. REMS tools

RxFMEA-identified tools currently implemented
• Medication Guide
• Dear Healthcare Professional Letter
• Prescribing Guide
• Dedicated REMS Web Site (www.exalgorems.com)
• Full Prescribing Information (not limited to REMS)

RxFMEA verified these 5 required REMS tools as necessary, but not completely sufficient, to be able to mitigate important patient safety risks. This previously unknown gap in protecting patient safety was closed with additional tools that were identified and specified. These tools, referred to as voluntary since they were not part of the REMS, were adopted and developed for implementation. Using the RxFMEA hazard index as a guide, 8 tools were deemed most critical and appropriate for implementation at product launch *in addition* to the REMS tools. These are listed in **Table 2.**

Table 2. Voluntary risk management tools identified by or derived from the RxFMEA process and currently implemented

• American Pain Society (APS) Opioid Treatment Guidelines
• *Responsible Opioid Prescribing: A Physician's Guide* (book by Scott Fishman, MD)
• EXALGO Healthcare Professional Education Program Kit expanded outreach mailing (beyond FDA mandate)
• EXALGO Healthcare Professional Education Program Kit sent to all retail pharmacies
• Patient Welcome Kit for first-time patients
• Welcome Video
• Patient Brochure
• Dose Alert 24-hour timer for EXALGO pill bottle cap

RxFMEA also identified additional tools to mitigate risks that met action criteria, but had a lesser combined severity or frequency of occurrence (hazard score) of the REMS or voluntary tools described above. Specifications were provided to draft, design, and implement these additional tools. These tools, listed in **Table 3**, will be implemented in a phased approach, with timing partially based on the REMS 6-month post-launch assessment learning.

Table 3. Additional voluntary risk management tools identified by or derived from the RxFMEA process to be phased in based on initial program performance

• Opioid Clinical Management Guide
• Opioid Clinical Management Checklist
• Clinical Management Educational Module CD/Slideshow Presentation
• Patient Safe Use and Handling Guide
• Urine Drug Testing Monograph
• Urine Drug Testing Primer for Clinicians
• Brief Pain Inventory (BPI)
• Numeric Rating Scale (NRS)
• Opioid Risk Tool (ORT)
• Pain Assessment and Documentation Tool (PADT)
• Prescriber Education Programs
• Extended-Release Opioid Patient-Prescriber Medication Agreement/Informed Consent
• Patient Environmental Checklist for Safe Opioid Storage, Use, and Disposal
• Ask an Expert Peer-to-Peer Live and Video Education Series for Prescribers
• Opioid Prescribing Toolkit by Nathaniel Katz, MD

RxFMEA provided the science-based "evidence for action" leading to the systematic identification, dissemination, and use of the most appropriate set of tools to mitigate each of the highest hazard safety risks. Such focused effort allowed for the most important and impactful tools, including both mandated (few) and voluntary (many), to be utilized early and often by stakeholders. It provides a solid foundation of reference for program redesign. Phased implementation of additional specified tools will aid in addressing identified risks and can be adapted based on real-world experience and results of program assessments.

CONCLUSIONS

- REMS tools were verified and specifically designed; however, RxFMEA identified additional tools to mitigate patient safety risks that were not mandated by the REMS
- These additional tools were voluntarily developed and implemented to help ensure patient safety, with additional tools to be implemented in a phased approach following the 6-month assessment of REMS performance
- The use of a science-based risk assessment approach to analyzing the patient care process led to deployment of tools beyond those mandated by the regulatory agency to further protect patient safety

REFERENCES

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Disclosures: EXALGO is a registered trademark of Mallinckrodt Inc.
ParagonRx furnishes consulting services to Mallinckrodt Inc., a Covidien company.

Case Study
Figure 3 – Results of EXALGO RxFMEA