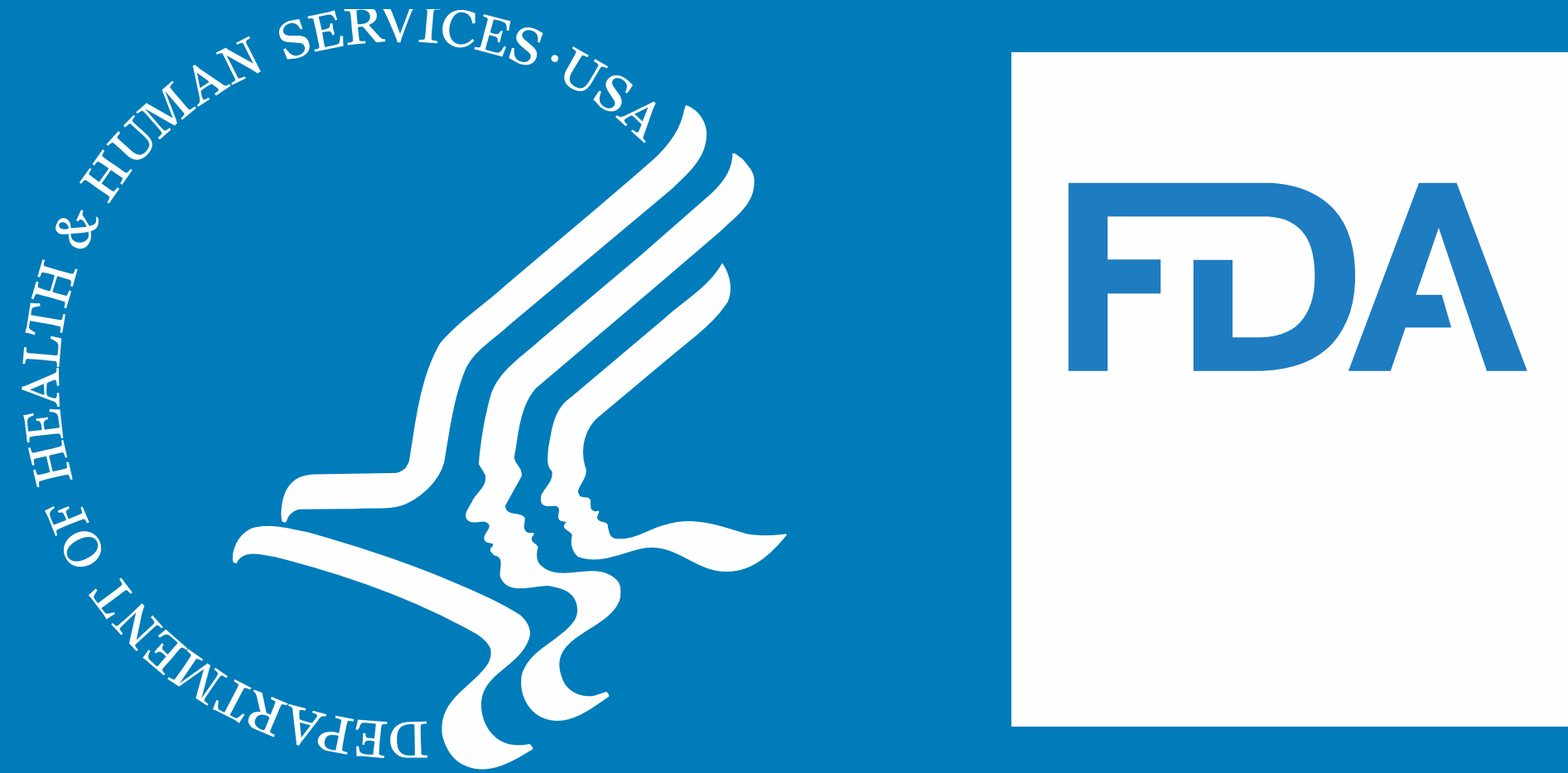


Impact of Risk Evaluation and Mitigation Strategy Programs on Product-Specific Guidances for Generic Drug Development

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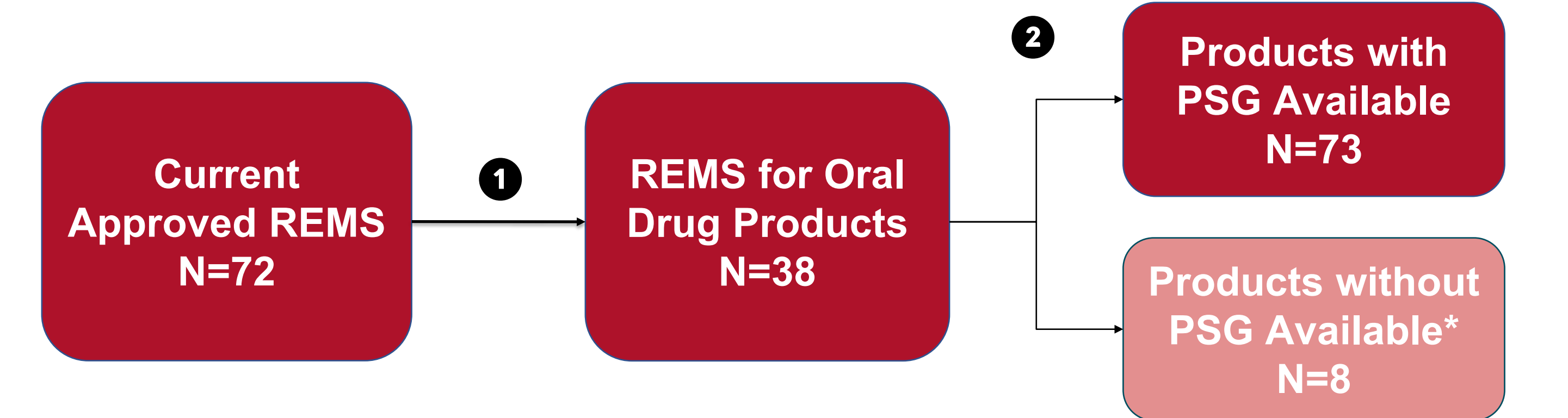
Introduction

- The United States Food and Drug Administration (FDA)'s approvals of certain drug products require Risk Evaluation and Mitigation Strategy (REMS) programs with(out) Elements to Assure Safe Use (ETASU) to ensure their benefits outweigh their risks.
- Product-specific guidances (PSGs) describe the FDA's current thinking on the most appropriate method for establishing therapeutic equivalence between generic drugs and their respective reference listed drugs (RLDs). The PSGs for REMS-covered RLDs often contain a general recommendation for generic drug applicants to incorporate all pertinent REMS elements into the protocol to ensure subject safety in pharmacokinetic (PK) bioequivalence (BE) studies.
- REMS may be modified post-approval; thus, there is a need to continually review the approved REMS programs. This project aimed to investigate the current status of REMS and -related recommendations in PSGs of oral drug products.

Materials and Methods

We compiled a list of approved REMS programs and of PSGs containing REMS recommendations for oral drug products. The following data were collected from the public REMS and PSG databases and analyzed: types of risks requiring REMS, modification history of the REMS programs, PSG availability, and REMS-related and other relevant PSG recommendations.

Results



- REMS for biologic and non-oral drug products were excluded.
- Certain shared REMS systems covered multiple drug products containing the same active pharmaceutical ingredient (API; e.g., Mycophenolate Shared System) or containing multiple APIs belonging to the same drug class (e.g., Opioid Analgesic Shared System)

*6 unique APIs/active moieties

- As of July 2024, there were 38 approved REMS programs for oral drug products. The most common types of risks covered by these programs were: embryo-fetal toxicity (n=14); overdose, abuse, misuse, addiction (n=6); and cardiotoxicity (n=6) [Figure 1].
- Of the 73 available associated PSGs (52 unique APIs), we identified 42 PSGs with up-to-date general REMS recommendations.
- The remaining 31 PSGs were identified to not align with the respective REMS programs and their modification history [Table 1] based on:
 - Release of REMS/ETASU requirements (5 PSGs),
 - Update of REMS program name (1 PSG), and
 - Lack of general REMS recommendations for REMS-covered RLDs (25 PSGs).

Results (cont.)

Figure 1. Risk Types of Approved REMS Programs for Oral Drug Products (N=38)

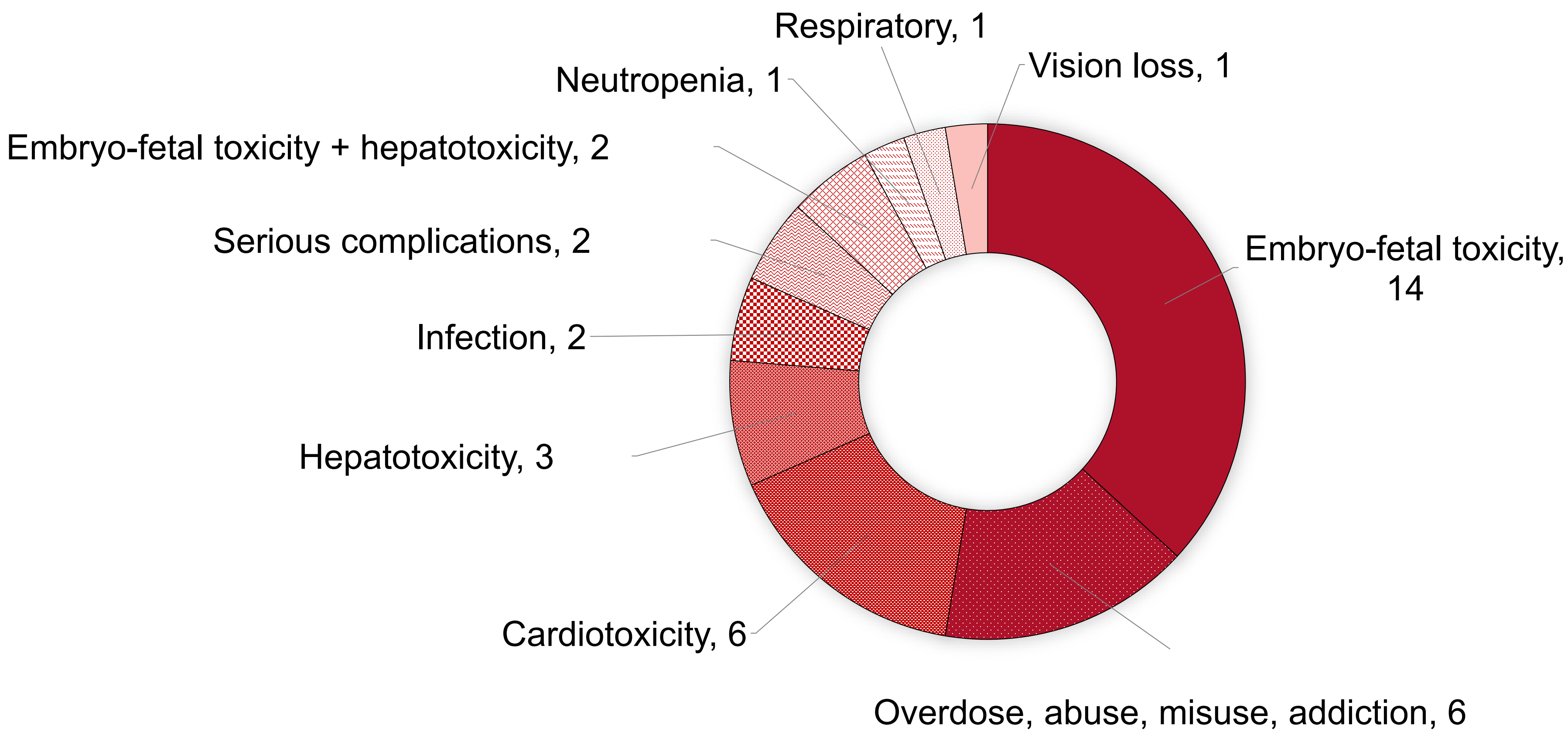
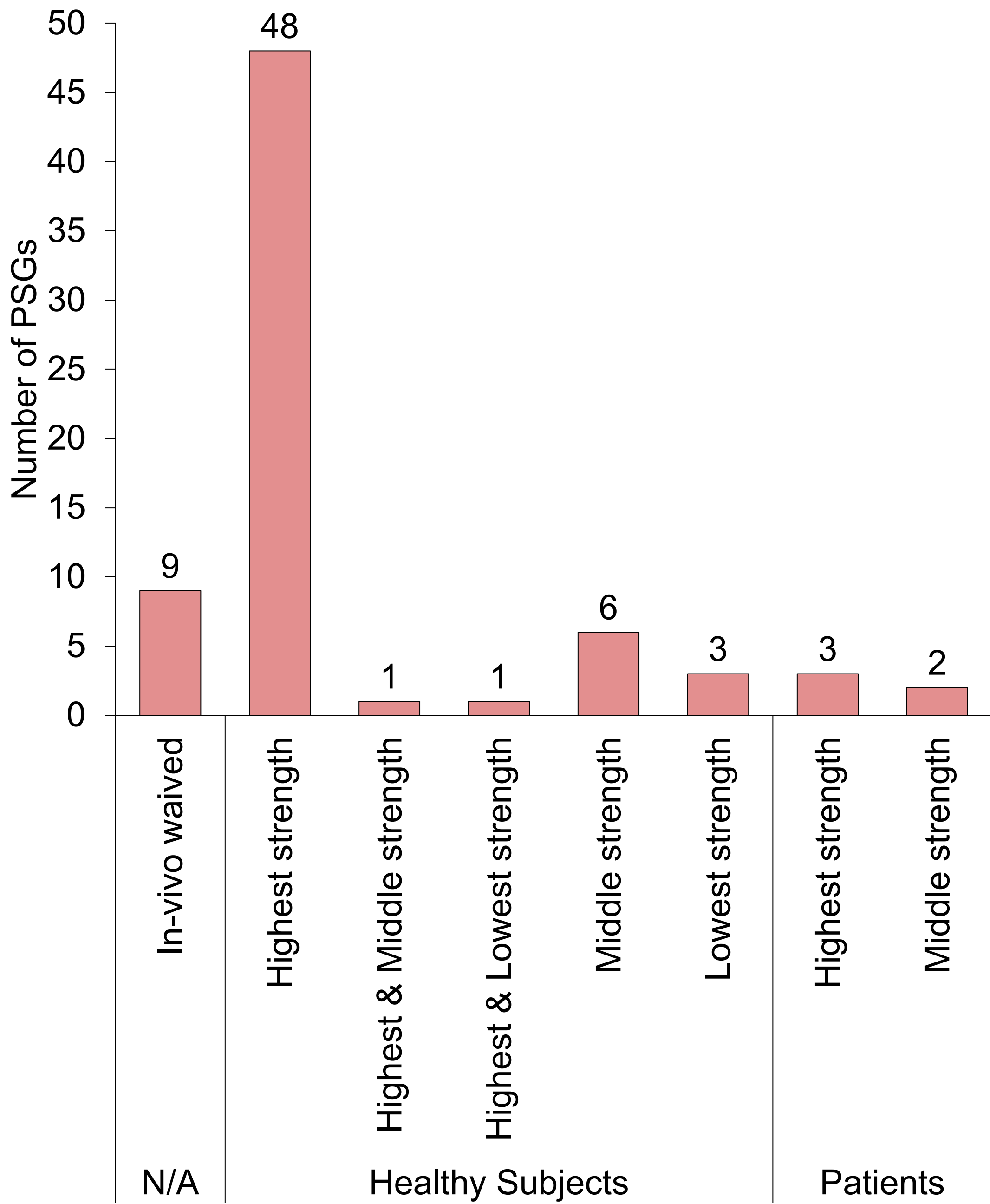


Table 1. Type of REMS Modification History and Number of PSGs Impacted

Type of REMS Modification History	Number of PSGs Impacted
Release of REMS/ETASU	
Clorazepate	1 PSG
Dronedarone	1 PSG
Emtricitabine; tenofovir disoproxil fumarate	1 PSG
Flibanserin	1 PSG
Quinine sulfate	1 PSG
REMS Name Change	
Thalidomide	1 PSG
REMS Approval	
Buprenorphine Transmucosal Products for Opioid Dependence Shared System	2 PSGs
Mycophenolate Shared System	4 PSGs
Transmucosal Immediate-Release Fentanyl Products Shared System	1 PSG
Opioid Analgesic Shared System	18 PSGs

Figure 2. Recommended Subject Population and Strength to be Studied in PSGs for REMS-Covered Products (N=73)



- The majority of PSGs for REMS-covered oral products still recommended PK BE studies in healthy subjects (59 of 73 PSGs), but 9 of these PSGs recommended using a non-highest strength [Figure 2].
- The majority of PSGs (47 of 73 PSGs) included safety additional comments (e.g., exclusion criteria, coadministration with an antagonist, monitoring parameters) to address REMS-covered risks in consideration of the actual practice in BE studies.

Discussion and Conclusion

- This project demonstrated that the impact of REMS programs on PSG recommendations varied depending on the type of risk covered and the intended study population.
- Pertinent PSG revisions as part of the FDA's efforts in global harmonization of BE recommendations pursuant to the Guidance for Industry, *M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms* (Oct 2024) have incorporated the proposed changes based on findings from this project.
- Close and continual review of the approved REMS and -associated regulatory actions are needed to provide up-to-date and relevant recommendations in PSGs, thereby ensuring the safety during generic drug development and facilitating their availability.

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Disclaimer

The poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

References

M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms - Implementing the Final Guidance. Webinar presented 11/21/2024. https://www.fda.gov/drugs/news-events-human-drugs/m13a-bioequivalence-immediate-release-solid-oral-dosage-forms-implementing-final-guidance-11212024?utm_medium=email&utm_source=govdelivery

