HAVE REMS PROGRAMS REACHED STABLE STATE 7 YEARS POST-APPROVAL?

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Abstract

Background: FDA can require applicants to develop and implement a REMS for certain prescription drugs to ensure the benefits outweigh the risks. REMS are continuously assessed to determine whether the programs are meeting goals and whether modifications are warranted. Per Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)(21 U.S.C. 355-1), applicants are required to conduct assessments of their REMS programs at a minimum of 18 months, 3 years, and 7 years after approval.

Purpose: To assess the stableness of REMS programs that have been approved ≥7 years.

Methodology: Active REMS programs approved ≥ 7 years were identified as of 9/5/2022 from the REMS@FDA website. The end date to calculate the duration since REMS approval was 12/31/22. The conclusion of the most recent FDA's internal reviews for all 26 REMS approved ≥7 years related to REMS meeting goals were summarized, and major modifications identified from the FDA website were categorized. Stableness of the REMS programs were assessed using descriptive analysis of both outcomes (effectiveness and major modifications). For the purpose of this work, *stableness* was defined as whether REMS are meeting goals and whether major REMS modifications related to safety or programmatic changes are occurring. Additionally, a retrospective summary of the effectiveness classification from year-1 through year-7 post approval was completed.

Results: Twenty-six of the 60 active REMS were identified as being approved ≥ 7 years. Nine out of the 26 programs were meeting goals in the most current assessment, four were partially meeting goals, four were not meeting goals, nine were unable to be determined. Of the nine programs meeting goals, six had been meeting goals since their first-year assessment. Thirteen of the 26 programs have experienced major modifications since the 7-year approval, of which four major modifications were for programs meeting goals.

Conclusion: The evaluation demonstrates most of the REMS programs have not achieved stableness at the 7-year approval and beyond. Regardless of the programs meeting goals, they continue to have major modifications; however, continued changes can be expected as programs are operating within the healthcare system which is continuously evolving and advancing.

Introduction

- A REMS is a drug safety program that FDA can require for certain medications with serious safety concerns to help ensure the benefits outweigh the risks.
- These programs are continuously evaluated to determine if the REMS goals are being met and if modifications are needed.[1]
- Applicants of new drug applications (NDA) and biologics license applications (BLA)s must submit assessments of their REMS programs at a minimum of 18 months, 3 years, and 7 years after the REMS is initially approved. However, FDA may require these assessments more frequently or at another frequency specified in the REMS.
- A REMS program may require modification that can be categorized as minor or major based on the potential effect on the risk message or safe use and/or the REMS requirements.[2]
- The evaluation of effectiveness of a REMS program and frequency of these modifications may indicate if a program has been optimized or has reached a stable state.
- Findings may inform if continued assessments are warranted and provide insight into the frequency and type of information that would be most informative.

Materials and Methods

On 9/5/2022 currently active REMS approved ≥ 7 years were identified from the REMS@FDA webpage and characterized (N=26). The results of REMS program effectiveness was summarized from FDA's internal reviews.

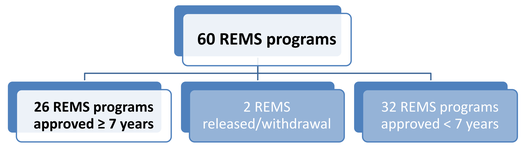

Figure 1. Selection of REMS programs included in the analysis

The outcomes of interest were divided into REMS program effectiveness and major modifications:

Effectiveness is defined as a program meeting the pre-specified REMS goals. Based on the last REMS assessment report, programs were classified as *meeting goals*, *partially meeting goals*, *not meeting goals*, and *unable to determine*. Posteriorly, we evaluated how these programs were classified since their first-year assessment report to identify how they have been evolving.

Major Modifications are defined as changes that have a substantial effect on the information contained in the REMS about the serious risk or safe use of the drug, or the actions REMS stakeholders must take to comply with the REMS.[2] For the purpose of this work, major modification were further classified into safety, programmatic, and administrative changes. Some of the changes qualified as administrative are considered major per REMS Modification Guidance.[2] (**Figure 3**)

Table 1. Summary of active REMS programs approved ≥ 7 years (N=26)

Characteristics	Number of REMS
Years of approval	
7-10 years	16
> 10 years	10
REMS elements	
Medication guide	8
Communication plan	3
Implementation system (IS)	19
Elements to assure safe use	24
Timetable for submission of assessments (TSA)	
Annual	17
Biannual	7
REMS goals	
Meeting goals	9
Partially meeting goals	4
Not meeting goals	4
Unable to determine	9
Deemed REMS*	8
Shared System REMS**	8

* Deemed REMS were existing risk management programs approved before REMS authorization in 2007 that were subsequently converted to REMS programs.
** Shared System REMS encompass multiple prescription drug products (e.g., generic and branded) and are developed and implemented jointly by two or more manufacturers.

Results and Discussion

REMS Program Review Statutory Requirements go up to the 7-year post approval

EFFECTIVENESS

Twenty-six (43%) programs are at or have passed the 7-year post approval:

- As of the latest assessment, nine are meeting goals, four are partially meeting goals, four are not meeting goals, and nine are unable to determine.
- Majority of the programs classified as *meeting goals* in the most current REMS assessment review, are meeting goals since the 1-year assessment, demonstrating the stableness of the programs for this subset.
- Among the *partially meeting goals* category and the *not meeting goals* category, there is much more variation on how they are classified over time.
- For the programs where FDA was *unable to determine* if the goals are being met in the most recent REMS assessment review (n=9) , five were meeting goals in the prior review. Of note, *unable to determine* classification comes from lack of available data at the time of the report.
- For the deemed programs (n=8), 50% of the programs are meeting goals. For the shared system programs, three out of the eight are meeting goals.
- When considering the timetable of assessment for the entire sample, 17 out of 26 products have annual submission. The assumption is that stable programs would allow for a longer time between assessments translating to more biannual than annual assessments. In this data, no trend was seen between the frequency of the assessment report and effectiveness.

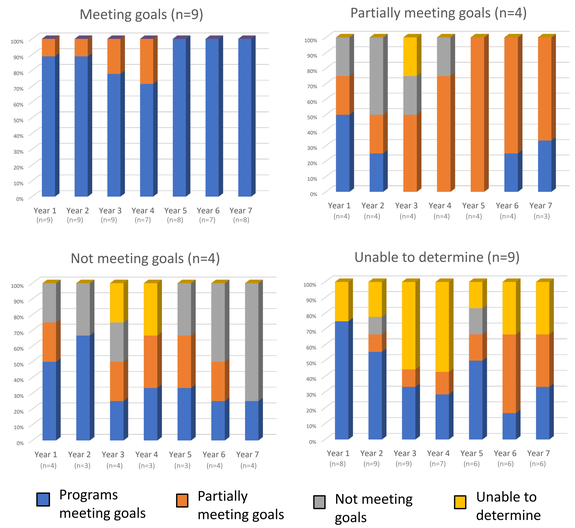

Figure 2. Classification of REMS effectiveness review from year 1 to 7 post-approval (year 7 may not represent the latest assessment)

MODIFICATIONS

Thirteen programs had major modification, representing a total of 24 changes.

- Modifications vary from changes to program goals to approval of a shared system REMS.
- It's expected that a stable program would have few to none major modifications after achieving the 7-year mark, however, of these 13 programs 9 were safety changes and 9 were programmatic changes.
- For the deemed programs (n=8) and shared system programs (n=8), nearly half of them continue to have major modifications.

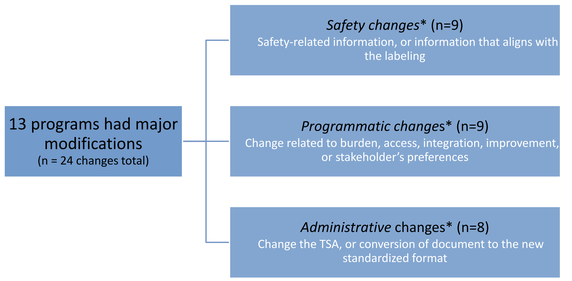

Figure 3. Classification of major REMS modifications

Conclusion

- Most REMS programs have not achieved stableness at and beyond the 7-year. Nine programs (34.6%) are meeting goals, most of them have been either meeting goals or partially meeting goals since year-one; thus, this subset seems stable in terms of effectiveness. However, major modifications in this subset–continue to occur post 7-year approval.
- Continued modifications are anticipated during the REMS life cycle because healthcare system, technology, and regulation are evolving.
- The results demonstrate that further work is needed to better identify the information required to define a stable program.
- Future work may include understanding the appropriate frequency past the 7th year approval and the type of information that would be most informative with respect to an assessment of an approved risk evaluation and mitigation strategy for these programs.

References

1. REMS assessment: Planning and Reporting Guidance (2019) U.S. Food and Drug Administration. (Accessed: April 3, 2023).
2. Risk evaluation and mitigation strategies: Modifications and revisions (2019) U.S. Food and Drug Administration. (Accessed: April 3, 2023).