Original Research

DIA

Therapeutic Innovation
& Regulatory Science
2020, Vol. 54(2) 318-323

https://doi.org/10.1007/s43441-019-00060-y

Evaluating REMS Burden: A Comparative Time Analysis of 3 Channels for REMS Stakeholders to Perform Mandatory REMS Tasks

Jennifer Chapman, BA[1], John Freeman, MSc, JD[1], Jorge Hechavarria, MBA[1], Pritam Dodeja, BS[1], and Paul Sheehan, MSJ, CPHIMS[1]

Abstract

Background: To determine the time taken to perform 5 Risk Evaluation and Mitigation Strategy (REMS) tasks across 3 channels for the Celgene REMS programs, with an aim to better understand which channels may minimize REMS administrative burden. *Methods:* Five mandatory REMS tasks (new prescriber and patient enrollments, prescriber and patient surveys, and pharmacy dispenses) were performed across applicable REMS channels (online portals, telephone interactions with customer care representatives [CCRs], or an interactive voice response [IVR] system). Five REMS representatives, who had $\geq$1 year of experience as a CCR, simulated the completion of the same set of testing activities across REMS channels. The execution time for each task by channel was measured and averaged across the participating CCRs. *Results:* Using the online portal, less time was taken to enroll a new prescriber (1.3 minutes) and adult male (6.7 minutes), compared to when the CCR channel was used (21.9 and 25.9 minutes, respectively). Similarly, completion of 3 AFRP prescriber surveys, the adult male patient survey, and 5 pharmacy dispenses was faster using the online portals (3.1, 1.3, and 1.7 minutes, respectively) compared to when the CCR (4.9, 1.8, and 3.4 minutes, respectively) and IVR (10.7, 4.0, and 11.3 minutes, respectively) channels were used. *Conclusion:* The use of online channels may alleviate some of the REMS burden by reducing the administrative time it takes for prescribers, patients, and pharmacy stakeholders to complete mandatory REMS tasks. More education and awareness of the available efficient channels should be provided to REMS stakeholders.

Keywords

ETASU, Pomalyst REMS, Revlimid REMS, Risk management, Thalomid REMS.

Introduction

Since 2007, the United States (US) Food and Drug Administration (FDA) has required sponsors to design and submit a Risk Evaluation and Mitigation Strategy (REMS) program, alongside their new and/or abbreviated applications for drugs, biologics, generics, or biosimilars, if the product risks may not be addressed by routine product labeling.[1] The stated purpose of REMS is to ensure that the benefits of a drug or biological product outweigh the risks. Product-specific REMS programs may include a communication plan, Medication Guide, patient package insert, Elements to Assure Safe Use (ETASU), and an implementation system. In a survey of health care practitioners in Southern California, most responders considered that REMS improved patient safety, with the most positive response (68%) being among oncology practitioners.[2]

While REMS programs have been acknowledged to improve patient safety, the additional administrative burden generated has been criticized.[3] In a 2009 Hematology Oncology Pharmacy Association survey, most of the 152 respondents that took part believed that 10% to 20% additional time was required to dispense a drug with a REMS program, but approximately one-third of respondents considered that more than 20% additional time was required.[4] A 2011 American Society of Clinical Oncology (ASCO) workshop with representatives from the FDA, pharmaceutical companies, and professional and patient organizations raised the concern that the administrative burden associated with REMS programs may distract health care professionals from maintaining direct patient care, which could result in the limitation of patient access to important therapies and increase cost.[5]

[1] Celgene Corporation, Summit, NJ, USA

Submitted 03-Jan-2018; accepted 29-Oct-2018; published online 6-Jan-2020

Corresponding Author:
Jennifer Chapman, Celgene Corporation, 556 Morris Avenue, Summit, NJ 07901, USA.
Email: Jchapman@celgene.com

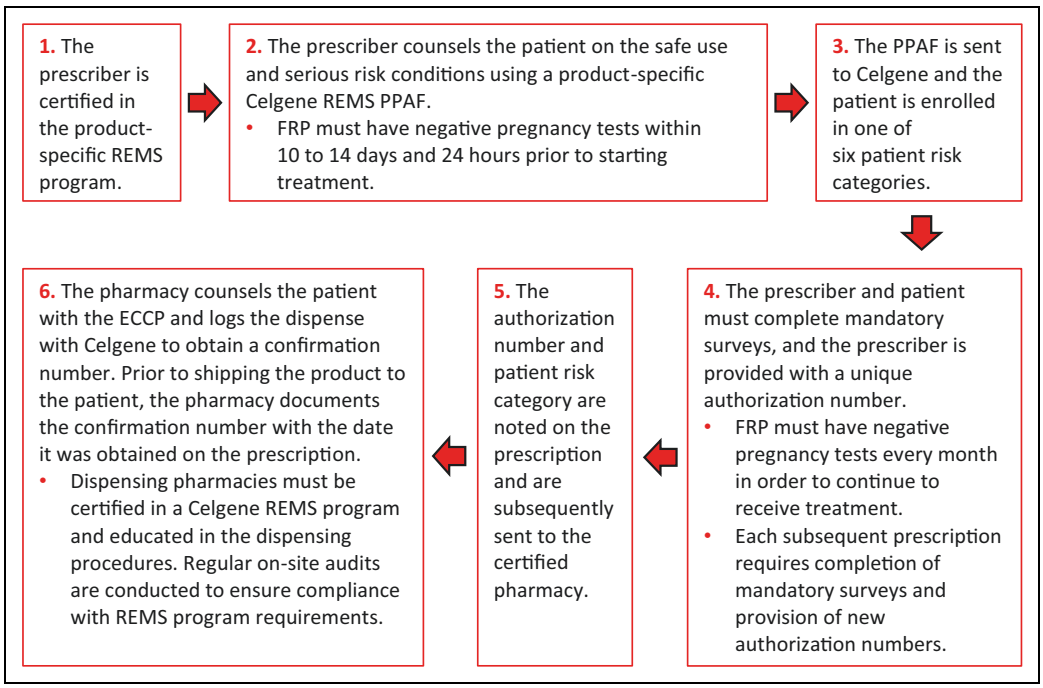

Figure 1. Flow chart of the major steps in the Celgene REMS process.
Note: In order to obtain each subsequent prescription, steps 4 to 6 must be repeated on a monthly basis. The frequency in which specific patient surveys are completed is dependent on risk class.
ECCP = Education and Counselling Checklist for Pharmacies; FRP = females of reproductive potential; PPAF = Patient-Physician Agreement Form; REMS=Risk Evaluation and Mitigation Strategy.

Since the development of the *S.T.E.P.S.* System for Thalidomide Education and Prescribing Safety,[6] a proactive approach has been taken toward improving and updating risk management programs and, subsequently, its REMS programs. Thalidomide (Thalomid) was approved by the FDA in 1998 for acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum. At this stage, the teratogenic potential of thalidomide was well known.[7,8] The purpose of the *S.T.E.P.S.* program was to allow access to thalidomide for those who would benefit from treatment, while preventing the exposure of unborn fetuses to the drug's teratogenic effects.[9]

Alongside the development of thalidomide, 2 additional chemical congeners (IMiD) compounds were developed, lenalidomide (Revlimid) and pomalidomide (Pomalyst), which share similar but not identical immune modulatory activities to thalidomide. In nonclinical studies, both IMiD compounds were also teratogenic, with lenalidomide and pomalidomide causing embryo-fetal defects in nonhuman primates and in the New Zealand White Rabbit, respectively.[10,11] These IMiD compounds are therefore only available to be prescribed, dispensed, and received by prescribers, pharmacists, and patients enrolled and participating in these REMS programs.

With the approvals of lenalidomide and pomalidomide REMS programs, Celgene has continuously updated its REMS programs with new technology and tools in an attempt to minimize stakeholder burden. Improvements have included standardization across the Revlimid REMS, Pomalyst REMS and Thalomid REMS programs, creation of online portals, and recently, the introduction of a mobile app.

The goals of these REMS programs are to prevent the risk of embryo-fetal exposure, and to inform prescribers, patients, and pharmacists of the serious risks and safe-use conditions for lenalidomide, pomalidomide, and thalidomide. Before those products can be taken by patients, the REMS programs require prescribers, patients and pharmacists to complete several mandatory REMS tasks, which are beyond the typical required prescription and dispense interactions. These tasks help to ensure that the REMS programs meet their goals. There are multiple channels for REMS stakeholders to perform the mandatory tasks for each REMS program. The 3 selected to include in this analysis are as follows: (1) online portals (www.CelgeneRiskManagement.com and www.CelgeneREMSPharmacyPortal.com), (2) telephone interactions with REMS customer care representatives (CCRs), and (3) telephone interactions with an interactive voice response (IVR) system.

The objective of the comparative analysis was to determine the time taken to perform selected REMS tasks across 3 available channels for the 3 REMS programs, with an aim to better understand which channels may minimize REMS administrative burden.

Materials and Methods

Revlimid REMS, Pomalyst REMS, and Thalomid REMS Programs

Details of the REMS process for lenalidomide, pomalidomide, and thalidomide are summarized in Figure 1.

Briefly, the prescriber, who is certified in the product-specific REMS program, counsels the patient on safe-use and serious risk conditions using a product-specific REMS Patient Physician Agreement Form (PPAF). The PPAF is sent to the REMS program, and the patient is subsequently enrolled in one of 6 risk categories. The prescriber and patient then undertake mandatory confidential surveys and the prescriber is issued with a unique authorization number. Once the certified pharmacy receives the authorization number and patient risk category, the dispense is logged to obtain a confirmation number within an allotted timeframe. After the pharmacy has completed the mandatory patient counseling and documented the confirmation number with the date it was obtained, the pharmacy can ship the product to the patient.

Measurement of Execution Time by Task

Five company representatives, who had $\geq$1 year of call center experience as a CCR, simulated the completion of the same set of testing activities using each applicable REMS channel. In order to reduce the variation in the data, the testing was consistently conducted in the work environment. The 3 channels were online portals, CCR, and IVR. The 5 mandatory REMS tasks performed were as follows: new prescriber enrollment, new adult male patient enrollment, 3 prescriber surveys for adult female of reproductive potential (AFRP) patients, one adult male patient survey, and 5 pharmacy dispenses. Notably, not every business process is supported on each channel (eg, patient and prescriber enrollments could not be completed using the IVR channel).

The execution time for each task by channel was measured using a stopwatch and was averaged across the participating CCRs. Survey tasks performed using the online channels commenced on logging into the portal, and for the CCR and IVR channels, when the toll-free number was dialed. Survey tasks performed using the online and IVR channels were considered to have ended at the completion of the survey disclaimer, and enrollment tasks conducted using the online channel were assessed as having ended when the person was enrolled online. Any task performed using the CCR channel was considered to have ended when the CCR wrapped up the call. For enrollment tasks, the time taken for the patient/prescriber to read and acknowledge the check boxes was added for all channels, and the 15-minute manual internal processing time was added for the CCR channel.

As patient risk categories have different safe-use and serious risk conditions to consider, they have specific questions and statements in their PPAF and surveys that vary in number. Therefore, the results for different REMS tasks were not aggregated across risk categories. Additionally, as some of these activities are time intensive to execute, they were not run the same number of times using each channel. It was assumed that the times recorded were representative of the REMS stakeholder (prescriber, pharmacy, and patient) population.

Table 1. Mean Time Taken to Perform Selected REMS Tasks Across Three Available Channels for the Celgene REMS Programs.

Task/Statistic	Web-Based Portals	CCR Channel	IVR Channel
New prescriber enrollment			
n	19	14	NA
Mean time, min	1.3	21.9	NA
P value[a]	–	$<2.2 \times 10^{-16}$	NA
Adult male patient enrollment			
n	22	17	NA
Mean time, min	6.7	25.9	NA
P value[a]	–	$<2.2 \times 10^{-16}$	NA
Prescriber survey (3 surveys performed for 3 AFRP patients)			
n	5	3	2
Mean time, min	3.1	4.9	10.7
P value[a]	–	0.001	0.018
Patient survey (1 survey performed for 1 adult male patient)			
n	10	11	8
Mean time, min	1.3	1.8	4.0
P value[a]	–	5.2×10^{-7}	6.8×10^{-7}
Pharmacy dispenses (5 prescriptions)			
n	6	6	5
Mean time, min	1.7	3.4	11.3
P value[a]	–	5.05×10^{-7}	6.0×10^{-12}

Abbreviations: AFRP, adult female of reproductive potential; CCR, telephone interactions with a customer care representative; IVR, interactive voice response; n, number of tests performed; NA, not applicable; REMS, Risk Evaluation and Mitigation Strategy.

[a] All comparisons were performed relative to values obtained using the relevant web-based portals.

Results

A total of 33 tests were performed to enroll a new prescriber over 2 channels, 39 tests were run to enroll a new adult male patient over 2 channels, 10 tests were performed for a prescriber to take 3 surveys over 3 channels, 29 tests were run for a patient to take one survey over 3 channels, and 17 tests were run for 5 patient dispenses over 3 channels. Results of these comparisons are summarized below and in Table 1.

Enrollment Tasks

Enrollment of a new prescriber through the online portal was completed in 1.3 minutes, which was approximately 20 minutes shorter than using the CCR channel (21.9 minutes, $p < 2.2 \times 10^{-16}$; Figure 2).

For the enrollment of a new adult male patient, the average execution time using the online portal took 6.7 minutes,

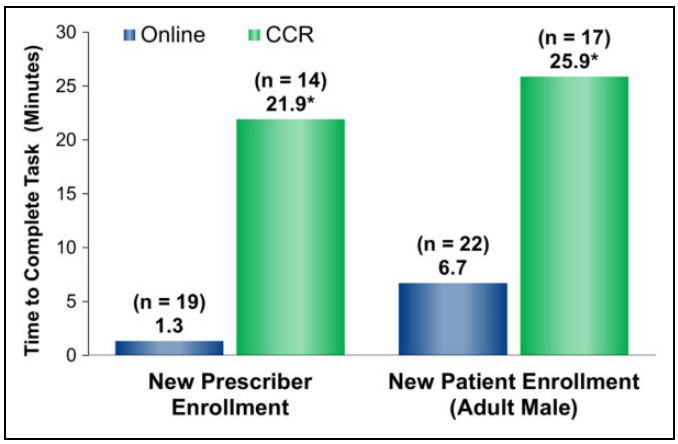

Figure 2. Mean time taken to complete enrollment of a new prescriber or a new adult male patient.
CCR = telephone interactions with a customer care representative; n = number of tests performed.
*The details of statistical significance are provided in Table 1.

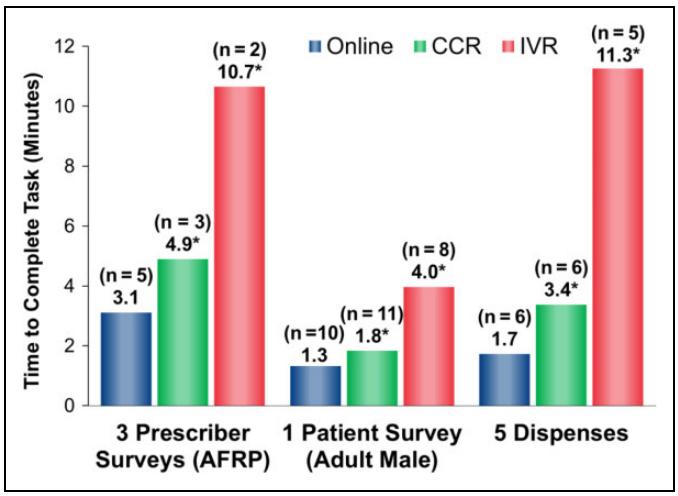

Figure 3. Mean time taken to complete tasks.
AFRP = adult female of reproductive potential; CCR = telephone interactions with a Customer Care Representative; IVR = Interactive Voice Response; n, number of tests performed.
*The details of statistical significance are provided in Table 1.

compared to 25.9 minutes with the CCR channel ($p < 2.2 \times 10^{-16}$; Figure 2).

Survey Tasks

Online completion of the 3 AFRP prescriber surveys (3.1 minutes) took 1.8 minutes less than the CCR channel (4.9 minutes; $P = .001$) and 7.6 minutes less than the IVR channel (10.7 minutes, $P = .018$; Figure 3).

The adult male patient survey was completed online in 1.3 minutes. However, this REMS task took 1.8 minutes to complete using the CCR channel ($P = 5.2 \times 10^{-7}$) and 4.0 minutes to complete using the IVR channel ($P = 6.8 \times 10^{-7}$; Figure 3).

Pharmacy Dispenses

The 5 pharmacy dispenses task took significantly less time to complete using the online pharmacy portal, at 1.7 minutes, than the CCR channel at 3.4 minutes ($P = 5.05 \times 10^{-7}$) and the IVR channel at 11.3 minutes ($P = 6.0 \times 10^{-12}$; Figure 3).

Discussion

We compared and evaluated the time taken to conduct selected REMS program tasks across the 3 different channels available for these programs. The administrative burden of REMS programs on health care providers is a recognized concern among oncology/hematology practitioners. Thus, there is a need to evaluate new methods and technologies that have the potential to decrease REMS burden without compromising patient safety.

The effectiveness of Celgene's risk minimization programs (including REMS) in preventing fetal exposure to potential teratogens has been demonstrated.[9,12,13] The company has been proactive in driving the evolution of their REMS programs, both to maintain focus on patient safety and to incorporate stakeholder feedback regarding administrative burden, which has been identified as a concern among oncology professionals.[3,5,14] Consequently, there are multiple channels through which stakeholders can interact with the REMS programs.

This study was intended to compare the relative administrative burden (measured in time spent) of routine mandatory REMS tasks between channels, and in this comparative analysis, there was considerable variability in the execution times for REMS tasks between channels. Notably, the performance of REMS tasks using available online systems was statistically significantly faster than other available channels to perform all of the REMS tasks assayed, while the IVR required the most amount of time. These findings support the implementation of the REMS online portals, which were designed to reduce the administrative burden for healthcare providers and patients when completing their required REMS tasks.

A limitation of this study is that only a small number of CCRs with $\geq$1 year of experience simulated the completion of the selected REMS tasks. The population studied was therefore not entirely representative of the patient, prescriber, and pharmacist stakeholder populations for whom the tasks were aimed. However, as the tasks were performed across channels by the same stakeholders, the differences observed between channels are still considered meaningful. Also, the controlled environment in which the study was conducted may not be truly representative of "real world" conditions.

The perception of REMS burden may be driven by the experience stakeholders have when interacting with REMS programs, their understanding of REMS program rationales to mitigate serious safety risks, and their awareness of product benefits. We acknowledge that stakeholder preference will determine how they perform REMS tasks and how they interact with REMS programs. Ultimately, REMS burden on

stakeholders is determined by multiple factors in addition to time spent on mandatory REMS tasks. Although stakeholder feedback was not collected in this study and stakeholder perceptions of the various channels could not be inferred, we are aware of the fast and near total uptake (>98%) of our online portal among pharmacy stakeholders through a separate analysis. These results were presented elsewhere.[15] Similarly, we have not directly measured learning efficacy; however, we can infer that it has not been a barrier to adoption.

Based on the findings of this comparison, we recommend that prescribers, patients, and pharmacy stakeholders should consider, if and when possible, using online systems to complete their REMS transactions to potentially lessen some of the REMS burden by reducing the time it takes to complete their mandatory REMS tasks. We also propose that more education and awareness of the available efficient channels for the completion of REMS tasks is provided to REMS stakeholders that display lesser adoption rates to help address their REMS burden concerns. These would include targeted communication and educational materials provided to existing users of the CCR and IVR channels by REMS program sponsors, providing information and advice on the online REMS channel. In addition, targeted onboarding procedures for new stakeholders could be developed to proactively present the online platforms as the default channel through which to access the REMS programs, thereby creating desired behaviors from the beginning of REMS program participation instead of trying to change stakeholder behaviors. We would also recommend that other REMS programs consider making electronic platforms available as a viable option for their stakeholders to perform mandatory program tasks.

Conclusion

As all selected REMS tasks were performed faster using online channels versus CCR and IVR channels, online channel usage may alleviate some of the REMS burden by reducing the time it takes for prescribers, patients, and pharmacy stakeholders to complete mandatory REMS tasks. This important confirmatory information indicates that an online portal could be used by program sponsors and administrators as a primary channel to execute mandatory REMS tasks. Finally, more proactive education, awareness, and efforts to encourage the use of the available efficient channels should be made available to stakeholders of REMS programs that provide these electronic channels for program participation.

Authors' Note

Data from this study have previously been presented at the Drug Information Association Annual Meeting; 26-30 June 2016, Philadelphia, PA, USA.

Acknowledgments

Medical writing and editorial support for the preparation of the manuscript was provided by James Williams, PhD, of Insight Medical Writing (Oxford, United Kingdom) and funded by Celgene Corporation.

Declaration of Conflicting Interests

All of the authors of this manuscript are current employees of Celgene Corporation.

Funding

This study was sponsored by Celgene Corporation.

ORCID iD

Jennifer Chapman, BA https://orcid.org/0000-0002-1251-1145

References

1. Food and Drug Administration Amendments Act of 2007, 505-1(f)(1). Sept 27, 2007. https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm. Accessed August 31, 2017.
2. Rashid N, Cheetham TC, Aranda G, Guerrero VN, Bartell H, Coghlan RJ. A descriptive evaluation of prescriber perceptions and experience with Risk Evaluation and Mitigation Strategy (REMS) programs in an integrated health care system. *Ther Innov Regul Sci*. 2015;49:503 510.
3. Johnson PE, Dahlman G, Eng K, et al. NCCN oncology risk evaluation and mitigation strategies white paper: recommendations for stakeholders. *J Natl Compr Canc Netw*. 2010;8(suppl 7):S7-S27.
4. Soefje S. Risk evaluation and mitigation strategies (REMS): survey results. *Hematology/Oncology Pharmacy Association Newsletter*. *Winter* 2010:3-4.
5. Frame JN, Jacobson JO, Vogel WH, et al. Assessment of risk evaluation and mitigation strategies in oncology: summary of the oncology risk evaluation and mitigation strategies workshop. *J Oncol Pract*. 2013;9:e24-e39.
6. Zeldis JB, Williams BA, Thomas SD, Elsayed ME. S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. *Clin Ther*. 1999;21:319-330.
7. McBride WG. Thalidomide and congenital abnormalities. *Lancet*. 1961;2:1358.
8. Lenz W. Kindliche missbildungen nach medikament einnahme während der gravidität? *Dtsch Med Wochenschr*. 1961;86: 2555-2556.
9. Uhl K, Cox E, Rogan R, et al. Thalidomide use in the US: experience with pregnancy testing in the S.T.E.P.S. programme. *Drug Saf*. 2006;29:321-329.
10. Revlimid prescribing information, revised February 2015. http://www.celgene.com/content/uploads/revlimid-pi.pdf. Accessed August 31, 2017.

11. Pomalyst prescribing information, revised June 2016. http://www.celgene.com/content/uploads/pomalyst-pi.pdf. Accessed August 31, 2017.
12. Castaneda CP, Zeldis JB, Freeman J, Quigley C, Brandenburg NA, Bwire R. RevAssist: a comprehensive risk minimization programme for preventing fetal exposure to lenalidomide. *Drug Saf*. 2008;31:743-752.
13. Brandenburg NA, Bwire R, Freeman J, Houn F, Sheehan P, Zeldis JB. Effectiveness of risk evaluation and mitigation strategies for lenalidomide and thalidomide: patient comprehension and knowledge retention. *Drug Saf*. 2017;40(4):333-341.
14. American Pharmacists Association, Bough M. APhA 2011 REMS white paper: summary of the REMS stakeholder meeting on improving program design and implementation. *J Am Pharm Assoc (2003*). 2011;51:340-358.
15. Chan Liston ML, Bourke JL, Sheehan PS, et al. REMS Pharmacy tasks: the adoption of an innovative electronic support system. *J Am Pharm Assoc (2003*). 2017;57(3): e1-142.