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REVIEW ARTICLE

Risk Evaluation and Mitigation Strategies (REMSs): Are They Improving Drug Safety? A Critical Review of REMSs Requiring Elements to Assure Safe Use (ETASU)

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Abstract Risk Evaluation and Mitigation Strategies (REMSs) with Elements to Assure Safe Use (ETASU) are requested for drugs with significant safety risks. We reviewed REMS programs issued since 2011 to evaluate their rationales, characteristics, and consistencies, and evaluated their impact on improving drug safety. We conducted a literature search and a survey of relevant websites (FDA, manufacturers, and REMSs). ETASU characteristics were summarized. REMS risks were compared with labeled risks, including black box warnings. Forty-two programs were analyzed. Seven incorporated drugs of the same class. Most drugs (57%) were indicated for an orphan disease. A single risk was mentioned in 24 REMSs, and multiple risks in 18. Embryo-fetal toxicity and abuse or misuse were the most frequent risks. All risks were identified during clinical development but some were hypothetical. Thirty-six drugs had a black box warning. REMS risks and black box risks differed for 11 drugs. A drug with multiple indications could have a REMS for one of them but not for another. Most REMSs required prescriber training and certification, half required dispenser certification and patient enrolment. REMSs were revised multiple times and only three (7%) were discontinued. No data were available to establish whether REMSs were effective in improving drug safety. Some REMSs were deemed inefficient. REMSs with ETASU continue to be implemented but their impact on improving drug safety is still not documented. Hence, one of the main requirements of the FDA Amendments Act of 2007 is not being addressed. In addition, REMSs are complex and their logic is inconsistent; we recommend a thorough re-evaluation of the REMS program.

Key Points

Risk Evaluation and Mitigation Strategies (REMSs), particularly ones that require elements to assure the safe use of drugs, are operationally complex and burdensome for physicians, pharmacists, drug distributors, regulators, and manufacturers.

A demonstration of the impact of REMSs on improving safety was a key request from the legislator but, based on our review of public information, this impact does not appear to have been evaluated or made public.

We recommend that REMS programs should be evaluated for their effectiveness to improve drug safety. The results of this evaluation should be made public.

1 Introduction

Approximately 10 years ago, the US Food and Drug Administration (FDA) implemented a safety risk monitoring system for new marketed drugs and for drugs already on the market and for which a new risk was identified. The Risk Evaluation and Mitigation Strategy, or REMS [1], requires multiple and complex processes, particularly REMSs that include Elements to Assure Safe Use

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(ETASU). REMSs with ETASU are requested for drugs that pose the most significant safety risks. These ETASU involve the participation of physician prescribers and drug companies but can also involve patients, pharmacists, and drug distributors [2, 3].

Pre-existing drug safety monitoring systems, such as the black box warning, have been frequently criticized [4–6] and, in particular, concerns were raised because their utility is difficult to evaluate [4]. Consequently, a key provision in the FDA Amendments Act of 2007 was the mandate to study the effectiveness of REMSs to evaluate their impact on improving drug safety [1]. Logically, the addition of a new and more complex system, such as REMSs with ETASU, could only be justified if evidence-based results demonstrate that such a process improves drug safety.

In 2013, the Inspector General of the Department of Health and Human Services conducted an extensive evaluation of REMSs launched between 2007 and 2011. The report concluded that the FDA could not determine whether REMSs were improving drug safety [7]. This report highlighted that the federal agency did not have the capacity to fulfill one of the most important aspects of the Amendments Act of 2007, which was to verify that the REMS system was efficient. Since this report, new REMSs have been implemented, and few have been discontinued. As REMSs accumulate, so does the administrative burden and workload on the health system [8].

This study evaluates REMSs issued, or modified, from December 2011 (right after the period covered by the Inspector General report) until August 2015. The study evaluates REMS rationale, characteristics, and consistencies and evaluates whether the impact of REMSs to improve drug safety could be documented. The focus was on REMSs with ETASU, as these plans concern drugs that pose the most significant safety risks.

2 Methods

REMSs requiring ETASU are requested for drugs that represent the highest known, and clinically relevant, safety concerns [9]. The main rationale for ETASU is to provide patients with safe access to a drug that would otherwise be unavailable to them. We evaluated the individual characteristics of REMSs with ETASU that were issued from December 2011 to September 2015. We searched the FDA website (http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm) to determine which of the following elements were incorporated into REMSs with ETASU (points 3–6 being specific for ETASU):

1. A medication guide. This could, for instance, takes the form of a patients' package insert.
2. A communication plan to healthcare providers. This plan may include letters or other means of communication (e-mail, website, professional societies).
3. An implementation system. This process is specific for ETASUs and is intended for the sponsor of the drug to monitor, evaluate, and eventually correct the level of compliance by healthcare providers and pharmacists. This system may also include wholesalers, distributors, or other parties.
4. The need for certification. For drug prescribers and drug dispensers (e.g., pharmacists), a certification may be required to demonstrate their ability to diagnose the condition, understand the risk/benefit of the drug, read the educational material, and, eventually, treat potential adverse drug reactions. The certification might be temporary and renewable. The certification process should be available online or via mail. The cost of the certification process is required to be 'reasonable' for the provider. Pharmacists' certifications might require an agreement to fill a prescription and dispense the drug only after receiving prior authorization, checking laboratory values, or checking for the presence of stickers. Providers affix these stickers to prescriptions. Stickers indicate that the patient has met all criteria for receiving the product ('qualification stickers') to fill a prescription. Pharmacists might also be required to dispense a drug only within a specified period, as well as to fill prescriptions only from enrolled prescribers.
5. The need to enroll patients. Patients may be required to enroll in a registry. The registry can be used to document that the drug is dispensed to patients with documentation of safe-use conditions, or to document that the patient is enrolled in a mandatory monitoring system. The registry can collect clinical outcomes, including safety information, compliance with prescribing protocols, and assessment regarding the impact of actions taken to ensure compliance.
6. The need to train prescribers. A prescriber's training generally requires the review of clinical documents, successfully answering questionnaires, and the documentation of these activities.

For each REMS with ETASU, the number of versions was documented, including the number of revisions following the first issue.

For each drug subjected to a REMS with ETASU, the dedicated REMS website was accessed and the information available on the FDA's website was eventually completed.

The following information was compiled: the drug name (USAN/trade name), the labeled indication(s), whether the indication was covering an orphan disease or not, and the clinical description of the safety risk(s).

We identified REMSs with ETASU that were discontinued. Discontinuations were first searched on the FDA website, verified on the drug's sponsor website by consulting the Press Release section, and confirmed on each REMS website address.

Last, for each drug subjected to a REMS with ETASU, the drug package insert was reviewed for the presence of a black box warning and to check whether the black box warning risks matched the risks mentioned in the REMS.

A PubMed search was performed (http://www.ncbi.nlm.nih.gov/pubmed) from 2007 to 2015 for publications concerning REMSs. The key words used in the title field were 'risk minimization', 'risk evaluation and minimization strategy', 'REMS', and 'REMS with ETASU'.

A similar search was conducted on the FDA website, with no time limits, with the additional term 'REMS working group' (www.fda.gov). This last search was done because the Inspector General and the FDA had agreed that a working group would report on an evidence-based approach that would evaluate the efficiency of REMSs by March 2015 [7].

3 Results

Forty-two REMSs with ETASUs were issued, or modified, during the study period.

We could not find data on the FDA's website or from FDA publications demonstrating the effectiveness of REMSs to improve drug safety.

From the general literature, we identified five publications of interest. One study was conducted by a drug safety consulting group on its claims database. It was a survey on the effectiveness of the REMS medication guide for conveying information on the risks of varenicline [10]. Of the 3458 recipients surveyed, 18% responded. The study concluded that the information received was generally well understood. A second study evaluated the bosentan REMS program for its compliance to a required monthly testing of liver function [11]. The study was conducted by the same consulting group in collaboration with the maker of the drug. The study concluded that compliance was not achieved. A third study evaluating retigabine/ezogabine REMS was conducted by the maker of the drug and surveyed pharmacists and physicians for their understanding of the risk of urinary retention associated with the drug [12]. Of the 1028 individuals surveyed, 22% of physicians and 82% of pharmacists responded. The study demonstrated an insufficient level of understanding of the risk, especially among pharmacists.

An additional study on lenalidomide was conducted right before REMS programs were implemented. The initial risk minimization program was later continued as part of a REMS with ETASU [13]. The study was conducted by the maker of the drug and concluded that, in the absence of pregnancy report in female patients or female partners of male patients, the program was effective in preventing fetal exposure to the drug.

A recent study reported on an education program for prescribers of extended-release/long-acting opioid analgesics [14]. This continuing education program, mandated by the FDA, was funded by the manufacturers of these products. In the immediate period following the implementation of the program, the 2850 participants surveyed demonstrated a significant improvement in the number of correct responses to knowledge questions (from 60 to 84%) and 82% of participants declared they were planning to change their practice. After 2 months, however, when a subset of 476 participants were tested, the results were an improvement from 60 to 69, and 67% of participants planned to change their practice, indicating that the positive effect was waning.

Of the 42 REMSs with ETASU, 35 were designed for a single drug (Table 1), and seven were shared programs that included multiple drugs of the same class (Table 2). These shared programs were implemented across multiple manufacturers.

The nature of the risks involved could be common to more than one REMS (Table 3). The risk of birth defect(s) or embryo-fetal toxicity and the risk of potential abuse or misuse were the most frequent risks addressed in REMSs with ETASU (8/42 [19%] and 6/42 [14%], respectively). Some risks were mentioned in only one REMS. These were biliary/pancreatic disorders; ischemic colitis and complication of constipation; delirium, sedation, and vision loss; severe neutropenia; and congestive heart failure. Three risks addressed the appropriate conduct of physicians' practice. These were the adherence to the prescribed regimen and counseling, mistake in blood glucose reading, and tendon or cavernous body rupture following a local drug injection.

The risk(s) mentioned in a REMS with ETASU could be single or multiple. For 24 REMSs, only a single risk was identified (e.g., hepatotoxicity for mipomersen or bronchospasm for Adasuve®). For 17 REMSs, multiple risks were mentioned (e.g., progression of myelodysplastic syndrome and acute myeloid leukemia, thromboembolism, and bone marrow fibrosis for romiplostim).

All the risks mentioned were identified during the clinical development program. Some, however, were not documented with clinical data and remained hypothetical (e.g., ischemic cardiac disease and possible acceleration of neoplastic growth for teduglutide). In that case, the risks could be inferred from the drug's mechanism of action or hypothesized based on non-clinical data. Some risks were difficult for individual prescribers to evaluate as they were

Table 1 Single REMSs with ETASU: drugs, sponsors, indications, nature of risk(s) and presence of a black box warning

Drugs	Sponsor(s)	Indication	Risk(s)	Black box
Loxapine	Teva	Acute agitation with schizophrenia or bipolar type I	Bronchospasm	Yes
Vandetanib	Astra Zeneca	Medullary thyroid K	Long QT syndrome	Yes
Alvimopan	Cubist/ Merck	Shorten GI recovery following bowel surgery	Increase incidence of MI	Yes
Icodextrin	Baxter	Peritoneal dialysis solution	Incorrect blood glucose results	Yes
Teduglutide	Shire	Short bowel syndrome	Possible acceleration of neoplastic growth and enhancement of colon polyp growth, GI obstruction, biliary and pancreatic disorders	No
Lomitapide	Aegerion	Homozygous familial hypercholesterolemia	Hepatotoxicity	Yes
Mipomersen	Sanofi	Homozygous familial hypercholesterolemia	Hepatotoxicity	Yes
Ambrisentan	Gilead	Pulmonary arterial hypertension	Serious birth defects	Yes
Alosetron	Prometheus	Diarrhea predominant IBS	Ischemic colitis	Yes
Alglucosidase alpha	Sanofi	Pompe disease	Anaphylaxis	Yes
Mifepristone	Danco	Medical termination of pregnancy	Life-threatening bleeding, infections, or other problems	Yes
Mycophenolate	Multiple	Prophylaxis of organ transplant rejection	Pregnancy loss and congenital malformations, other serious risks	Yes
Romiplostim	Amgen	Chronic immune thrombocytopenia	Progression of myelodysplasia and acute myeloid leukemia, thromboembolism, marrow fibrosis	No
Pomalidomide	Celgene	Multiple myeloma	Risk of embryo fetal exposure and other risks	Yes
Eltrombopag	GSK	Chronic immune thrombocytopenia	Hepatotoxicity, bone marrow fibrosis, thromboembolism	Yes
Phentermine/topiramate	Vivus	Chronic weight management	Birth defect (cleft lift/cleft palate)	No
Lenalidomide	Celgene	Myelodysplastic syndrome, mantle cell lymphoma	Embryo-fetal toxicity	Yes
Vigabatrin	Lundbeck	Refractory complex partial seizure	Vision loss	Yes
Eculizumab	Alexion	Paroxysmal nocturnal hemoglobinuria	Meningococcal infection	Yes
		Atypical HUS		
Thalidomide	Celgene	Multiple myeloma	Embryo-fetal toxicity	Yes
		Erythema nodosum		
Dofetilide	Pfizer	Atrial fibrillation	Arrhythmia	Yes
		Flutter		
Bosentan	Actelion	Pulmonary arterial hypertension	Birth defects, hepatotoxicity	Yes
Emtricitabine/ tenofovir/disoproxil	Gilead	Pre-exposure prophylaxis of HIV-1	Adherence to regimen, control of HIV-1 status, counseling	Yes
Natalizumab	Biogen	Multiple sclerosis	Progressive multifocal leukoencephalopathy	Yes
Clozapine	Jazz	Schizophrenia	Severe neutropenia	Yes

Table 1 continued

Drugs	Sponsor(s)	Indication	Risk(s)	Black box
Collagenase clostridium histolyticum	Endo	Dupuytren disease Lapeyronie disease	Tendon rupture, anaphylaxis, corporal rupture	Yes
Olanzapine	Lilly	Schizophrenia	Mitigate risk of post-injection delirium/sedation syndrome	Yes
Macitentan	Actelion	Pulmonary arterial hypertension	Serious birth defect	Yes
Riociguat	Bayer	Pulmonary arterial hypertension	Teratogenicity	Yes
Sacrosidase	QOL Medical	Sucrase-isomaltase deficiency	Severe allergic reaction	No
Testosterone undecanoate	Endo	Primary hypogonadism Hypogonadotropic hypogonadism	Pulmonary oil micro-emboli, anaphylaxis	Yes
Metreleptin	Aegerion	Generalized lipodystrophy	Neutralizing antibodies, risk of lymphoma	Yes
Alemtuzimab	Sanofi	Relapsing multiple sclerosis	Auto-immune conditions, infusion reactions, malignancies	Yes
Sodium oxybate	Jazz	Narcolepsy	CNS and respiratory depression, potential abuse/misuse, CI with hypnotics and alcohol, handling and storage	Yes
Alosetron	Boehringer Ingelheim	Chronic IBS	Ischemic colitis, serious complication of constipation	Yes

CI contra-indicated, *CNS* central nervous system, *ETASU* Elements to Assure Safe Use, *GI* gastro-intestinal, *HUS* hemolytic uremic syndrome, *IBS* irritable bowel syndrome, *MI* myocardial infarction, *REMS* Risk Evaluation and Mitigation Strategy

Table 2 Common REMSs with ETASU: drugs, sponsors, indications, nature of risk(s) and presence of a black box warning

Drugs	Sponsor(s)	Indication	Risk(s)	Black box
Epoetin alpha	Amgen, Janssen	Anemia of chronic kidney disease and chemotherapy	Shortened survival, increased risk of tumor progression/ recurrence	Yes
Darbepoetin alpha	Amgen			Yes
Buprenorphine	Multiple	Opioid dependence	Accidental overdose, misuse or abuse	No
Buprenorphine and naloxone	Multiple	Opioid dependence	Accidental overdose, misuse or abuse	No
Extended-release and long-acting opioid analgesics	Multiple	Analgesia	Addiction, abuse, and misuse	Yes
Isotretinoin	Multiple	Severe recalcitrant nodular acne	Severe birth defects	Yes
Rosiglitazone and its combinations	GSK	Type 2 diabetes	Ischemic cardiovascular risk	Yes
Fentanyl	Multiple	Analgesia in cancer patients	Mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors	Yes

ETASU Elements to Assure Safe Use, *REMS* Risk Evaluation and Mitigation Strategy

clinical events that could have multiple etiologies (e.g., myocardial infarction with alvimopan) or were too rare to be encountered in a practice with a limited number of patients. For such rare events, the collection of data from a large population and/or multiple prescribers could only document an increased risk.

Of the 42 REMSs with ETASU, 36 drugs (including 31 individual drugs and five classes of drugs) had a label that contained a black box warning. Six REMSs with ETASU concerned a drug that did not have a black box. These REMSs concerned four individual drugs (teduglutide, romiplostim, phentermine/topiramate, and sacrosidase) and

Table 3 Risks addressed in REMSs with ETASU

Risks	Number of drugs
Birth defect(s) or embryo-fetal toxicity	8
Potential abuse or misuse	6
Allergic reaction	5
Tumor or neoplastic progression	4
Hepatotoxicity	4
Infection	3
Thromboembolism	3
Cardiac arrhythmia	2
Myocardial infarction	2
Bone marrow fibrosis	2
Biliary/pancreatic disorders	1
Ischemic colitis and complication of constipation	1
Delirium, sedation, and vision loss	1
Severe neutropenia	1
Congestive heart failure	1
Adherence to regimen and counseling	1
Incorrect blood glucose reading	1
Tendon or cavernous body rupture after a local injection	1

ETASU Elements to Assure Safe Use, *REMS* Risk Evaluation and Mitigation Strategy

two classes of drugs (buprenorphine-containing products—including transmucosal formulations—and buprenorphine/naloxone product combinations). There was no apparent difference in the type of risks for drugs with a black box warning and drugs without such a warning. For instance, the same risks (misuse or abuse, thromboembolism, birth defect, or acceleration of tumor growth) were mentioned for drugs with or without black box warnings. Apart from information contained in the drug label, the severity or the frequency of the risk was generally not quantified in REMS documents.

When a drug had a black box warning, the risks mentioned in the REMS with ETASU were similar to risks mentioned in the black box for 33 drugs (23 individual drugs and two grouped REMSs). Risks were dissimilar for 11 drugs (eight individual REMSs and three common REMSs). In eight instances, fewer risks were mentioned in the REMS than in the black box (six single REMSs and two common REMSs). In three instances, more risks were mentioned in the REMS than in the black box (two single REMSs and one common REMS). No rationale could be identified to explain these discrepancies. For extended-release and long-acting opioid analgesics, REMSs included drugs with and without black box warnings.

A drug approved for multiple indications could be submitted for a REMS with ETASU for one indication but not for another indication. For instance, topiramate was subjected to a REMS when used in combination with phentermine, indicated for weight management, but was not submitted for a REMS when indicated for epilepsy and migraine. Similarly, mifepristone was subjected to a REMS with ETASU for the medical termination of intra-uterine pregnancy (one 600-mg dose) but not for the treatment of Cushing's syndrome (300 mg daily, continuously).

Some medical specialties, such as neuropsychiatry, cardiovascular medicine, endocrinology and metabolic diseases, and oncology, were more frequently concerned by REMSs with ETASU than other specialties (Table 4).

Most drugs (24/42, or 57%) that were subjected to REMSs with ETASU were indicated for an orphan disease. The most frequent indication was pulmonary arterial hypertension for which four drugs shared a risk of birth defects. Each of these drugs had an individual REMS program.

The processes that were included in REMSs with ETASU were, in order of decreasing frequency, an implementation system (81% of REMSs), prescriber training (71%), prescriber certification (69%), a medication

Table 4 Medical specialty concerned with REMS with ETASU

Specialty	Number of REMSs with ETASU
Neurology/psychiatry	7
Cardiology/vascular	7
Endocrinology/metabolic disease	6
Oncology/hematology	5
Hepato-gastro-intestinal	4

ETASU Elements to Assure Safe Use, *REMS* Risk Evaluation and Mitigation Strategy

Table 5 Discontinuation of REMS with ETASU

Drug	Indication	Risk	Reason for discontinuation
Eltrombopag	Thrombocytopenia in chronic immune thrombocytopenia	Progression of MDS and AML, thromboembolism, marrow fibrosis	Not available
Romiplostim	Thrombocytopenia in chronic immune thrombocytopenia	Hepatotoxicity, bone marrow fibrosis, thromboembolism	Not available
Lumizyme	Pompe disease	Anaphylactic reactions	Drug considered similar to Myozyme
Rosiglitazone and its combinations	Type 2 diabetes mellitus	Ischemic cardiovascular risk	Risk not documented (replaced by risk of congestive heart failure)

AML acute myeloid leukemia, *ETASU* Elements to Assure Safe Use, *MDS* myelodysplastic syndromes, *REMS* Risk Evaluation and Mitigation Strategy

guide (67%), dispenser certification (48%), patient enrolment (43%), and a communication plan (26%).

REMSs with ETASU had to go through multiple revisions. The mean number of revisions was 3.3 (range 1–11).

Three of the 42 REMSs with ETASU (7%) were discontinued (Table 5).

4 Discussion

A REMS is mandated by law and includes specific measures to ensure that the benefits of a drug outweigh its risks [1]. A REMS may be required by the FDA as part of a new drug approval process, or for an approved product when new safety information emerges. One of the key provisions in establishing REMSs was to ensure that the FDA can evaluate the impact of such programs and thus demonstrate their relevance in addressing and preventing safety risks [1, 7]. In February 2013, the Office of the Inspector General issued a comprehensive report covering REMSs issued since their implementation in 2007 until the end of 2011 [7]. This report concluded that the FDA did not have relevant data to determine whether REMSs improve drug safety and, despite the significant burden and cost associated with the REMS system, the relevance of these programs could not be established.

Our study's first objective was to establish whether the situation regarding the relevance of REMSs has changed since the Inspector General's report and whether the impact of REMSs to improve drug safety could now be established. Our second objective was to establish the characteristics of REMSs with ETASU, as these REMSs address drugs with the most significant safety risk.

Since the report from the Office of the Inspector General, 42 new REMSs with ETASU have been issued (35 programs for individual drugs, and seven programs incorporating more than one drug). Our study confirms that there is still only very limited information publicly available to demonstrate that REMSs with ETASU address and/or prevent safety risks [14]. While data on REMS effectiveness might have been collected, they have not generally been made public by regulators, sponsors, or scientists. This is contrary to the public commitment made by the FDA in its response to the Inspector General's report [7]. Despite the burden that REMSs represent, it is still not possible to conclude whether they are useful or not. REMSs continue to be requested and continue to be implemented despite the fact that the original intent of the law that established the REMS system has not been fulfilled.

The two most frequent risks addressed in the REMSs with ETASU we reviewed were the risk of embryo-fetal toxicities and the risk for drug abuse.

Since the thalidomide tragedy [15], the risk of embryo-fetal toxicity has been a priority for regulators; it is thus not a surprise to see this risk prominently addressed in REMSs. More surprising, however, is the great variability of the level of embryo-fetal risk associated with drugs submitted to a REMS. The very high risk of embryo-fetal toxicity of oral retinoids used to treat severe and refractory acne is well known. This risk is further amplified as patients affected by this type of acne are mostly young females of reproductive age [16]. Over the years, multiple initiatives have been taken to try to prevent women from becoming pregnant while on retinoids. Few have been judged satisfactory [17]. It is thus logical to incorporate the prescription of oral retinoids into a REMS with ETASU. Oral retinoids are included in a common REMS that is shared between manufacturers. To our knowledge, it is not known whether this program adequately addresses and prevents the risk of embryo-fetal toxicity [18].

For other drugs, the risk of embryo-fetal toxicity is variable. For thalidomide itself and lenalidomide, a derivative of thalidomide, the potential of these drugs to induce embryo-fetal toxicity is evidently high. These drugs, however, are indicated for the treatment of multiple myeloma and the population affected by this disease is generally not at risk of pregnancy. Indeed, a multiple myeloma is very rarely diagnosed during a woman's reproductive years [13, 19]. Additionally, the treatment of

multiple myeloma incorporates multiple chemotherapeutic drugs that, while they are themselves embryo-toxic, are not submitted to a REMS with ETASU [19]. While the situation is somewhat illogical, regulators probably could not avoid including thalidomide and its derivative into a REMS. In these cases, the logic could be to prevent reproductive-aged females in contact with patients to have access to the drugs or could be more an issue of public perception in the context of the tragedy mentioned.

The case of topiramate is also interesting. When indicated for the management of obesity, topiramate is formulated in an extended-release form. Topiramate is known to be associated with a risk of birth defect, however the risk appears relatively low [20]. At the same time, when used to treat migraine (a disease that mostly affects women in their reproductive age), topiramate is not subject to a REMS. It could be speculated that the true intent of the REMS was to limit prescriptions for the management of obesity, as the risk of birth defect would have increased with a large number of prescriptions, or to indirectly address other potential risks associated with the drug, such as the cardiovascular risks [21].

Four drugs indicated for chronic pulmonary hypertension, a rare orphan disease, share a risk of embryo-fetal toxicity. Each drug is subjected to an individual REMS with ETASU. The patient population is not only at high risk for pregnancy, but is also one for whom a pregnancy could have severe consequences for the health of the mother. In this case, the request for a REMS with ETASU appears logical. Unfortunately, each individual REMS has its own specific processes, and the burden for patients and prescribers would certainly be minimized with the implementation of a shared REMS.

The risk of drug abuse, particularly opioid abuse, with pain medications has been a longstanding and vexing problem. Despite multiple actions taken over the years, a definitive solution has not been found [22]. The implementation of REMSs with ETASU is another attempt to control access to opioids. While there are no data to indicate that this shared REMS is more effective than previous attempts, the recent admission by the FDA that a complete overhaul was necessary [23] indicates that the current system is no better than its predecessors. Beyond embryo-fetal toxicity and opioid abuse, the other risks identified in REMSs, such as allergic reaction, hepatotoxicity, or thromboembolism, were of varying severity. These risks are also associated with drugs that are not submitted to REMSs. For instance, allergic reactions with commonly prescribed drugs not subjected to a REMS can nevertheless be life-threatening or fatal and continue to affect many patients [24]. The same is true for the risk of thromboembolism, which can be fatal and is associated with widely prescribed drugs that are not subjected to REMSs [25, 26]. Overall, the rationale that supports the incorporation of a drug into a REMS is certainly difficult to establish for regulators and this issue was not foreseen by the legislator.

The risks addressed in a REMS with ETASU were generally documented during the drug development program of a candidate drug and were identified before the drug was approved. Some risks, however, such as an increased incidence of tumor progression or an increase in cardiovascular events, could not be documented with the available data and remained speculative. Such risks, because of their lack of specificity and their rarity, cannot be identified at the level of individual prescribers. It thus remains questionable whether such REMSs fulfill the initial intent of the program.

Most drugs that were included in a REMS with ETASU also had a black box warning in their label. The content of black box warnings and the content of REMSs were frequently divergent without apparent reasons. The black box warning system has been previously criticized and is generally considered inefficient [4–6, 27, 28]. In this context, regulators might be tempted to supplement a black box warning with a REMS with ETASU. REMSs, however, are immensely more complex and logistically challenging that black box warnings. There is thus a legitimate concern that the legislator added an unproven, cumbersome system on top of a potentially ineffective but simple system. Additionally, a significant number of REMSs with ETASU were requested for drugs that did not have a black box warning in their label. The rationale for requesting a REMS in such cases could be debatable.

Most REMSs with ETASU were implemented for drugs that were indicated for a rare orphan disease. In this case, regulators might be requesting REMSs with the objective to continue to collect safety information while favoring early patient access to life-saving medication. However, in the absence of data to evaluate the efficiency of REMS, this remains speculative. In the context of conditional approval for orphan drugs and for oncology drugs, post-marketing data collection is necessary to get a final approval [29, 30] and can be more informative that REMS. Also, patient registries that become the norm for rare orphan diseases provide useful clinical information, including safety information [31]. For many orphan drugs, registries are an efficient way to collect safety information that could be evaluated against the REMS system. Finally, most patients affected by an orphan disease are under the care of highly specialized physicians who are likely to manage any risks in a prudent and efficient way. With these considerations, the benefits of orphan diseases REMSs remain unproven. Having multiple REMSs for the same orphan indication renders medical practice more cumbersome and, ultimately, could result in limiting patient access to lifesaving

medications, which would be the exact opposite of the legislator's intent.

The processes requested as part of a REMS with ETASU highlight their complexity and administrative burden. Multiple parties are involved and significant operational challenges must be addressed. REMS revisions, mostly dedicated to procedural details, are frequent and slow to implement. Very few REMSs with ETASU were discontinued and when they were, no rationale was made publicly available, or the rationale was difficult to understand [32]. While REMSs can be negotiated between the FDA and a drug manufacturer, the FDA has sole decision power. In this context, the negotiation, implementation, or potential discontinuation, of a REMS is particularly challenging for small drug manufacturers who do not have the necessary staff and must contract these functions out at a significant additional cost. It also appears challenging for regulators to implement REMS programs across multiple review divisions in a consistent and logical manner.

5 Conclusion

The current REMS system does not appear to meet the intent of the law which requested a mandatory evaluation of these programs to demonstrate that they were improving drug safety. The decision-making process to require a REMS is not transparent and results in programs that contain inconsistent processes and unclear objectives. Each year, new REMS are issued, and very few are discontinued, but today, it is still unknown whether the REMS system is useful or not. While risk minimization strategies are always difficult to implement [33, 34], we have identified multiple challenges that need to be addressed.

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Compliance with Ethical Standards

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