FDA's Application of Statutory Factors in Determining When a REMS Is Necessary

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Aaron Sherman, Office of the Center Director, 240-402-0493, or (CBER) Office of Communication, Outreach, and Development, 240-402-8010 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2016
Drug Safety

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FDA's Application of Statutory Factors in Determining When a REMS Is Necessary

Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to clarify how the Food and Drug Administration (FDA or Agency) applies the factors set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) in determining whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks.[2] This guidance is one of several being developed to fulfill performance goals that FDA agreed to satisfy in the context of the fifth reauthorization of the prescription drug user fee program (the Prescription Drug User Fee Act (PDUFA) V).[3] By providing greater clarity about FDA's application of these statutory factors, FDA hopes to increase understanding about how and when FDA determines that a REMS is required.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of New Drugs, Office of Surveillance and Epidemiology, Office of Medical Policy, and Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration.

[2] Section 505-1 of the FD&C Act applies to applications for prescription drugs submitted or approved under subsections 505(b) (i.e., new drug applications) or (j) (i.e., abbreviated new drug applications) of the FD&C Act and to applications submitted or approved under section 351 (i.e., biologics license applications) of the Public Health Service Act (42 U.S.C. 262). For the purposes of this document, unless otherwise specified, the term *drug* refers to human prescription drugs, including those that are licensed as biological products (biologics).

[3] Section XI.A.1 of "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017" (PDUFA V), available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf.

II. BACKGROUND

The Food and Drug Administration Amendments Act of 2007 (FDAAA)[4] created section 505-1 of the FD&C Act, which authorizes FDA to require a REMS for certain drugs if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.[5] A REMS is a required risk management strategy that can include one or more elements to ensure that the benefits of a drug outweigh its risks.[6] A REMS may consist of a Medication Guide,[7] a patient package insert,[8] and/or a communication plan.[9] FDA may also require certain elements to assure safe use (ETASU) as part of a REMS.[10] The ETASU can include, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe use conditions.[11] Certain REMS with ETASU may also include an implementation system through which the sponsor is able to monitor and evaluate implementation of the ETASU and work to improve their implementation.[12] Finally, REMS generally must have a timetable for submission of assessments of the strategy.[13] FDA can require a REMS before initial approval of a new drug application or, should FDA become aware of new safety information[14] about a drug and determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks, after the drug has been approved.[15]

Before FDAAA was enacted, FDA approved a small number of drugs and biologics with risk minimization action plans (RiskMAPs).[16] A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing the known risks of a drug while preserving the drug's benefits. RiskMAPs were developed for products that had risks that required additional risk management strategies that went beyond the provision of FDA-approved labeling, including

[4] Public Law 110-85.

[5] See section 505-1(a) of the FD&C Act.

[6] See section 505-1(e) of the FD&C Act.

[7] Section 505-1(e)(2) of the FD&C Act.

[8] Id.

[9] Section 505-1(e)(3) of the FD&C Act.

[10] See Section 505-1(f) of the FD&C Act.

[11] Id.

[12] Section 505-1(f)(4) of the FD&C Act.

[13] See section 505-1(d) of the FD&C Act.

[14] Section 505-1(b)(3) of the FD&C Act.

[15] See section 505-1(a)(2) of the FD&C Act.

[16] Some of these drugs were approved under either subpart H (21 CFR 314.520) or subpart E (21 CFR 601.42) with restrictions on their use or distribution to assure safe use.

the prescribing information.[17] In 2005, FDA issued a guidance for industry, *Development and Use of Risk Minimization Action Plans* (RiskMAP Guidance),[18] which provides guidance on designing RiskMAPs to minimize identified risks, selecting tools to minimize those risks, evaluating RiskMAPs and monitoring tools, and communicating with FDA about RiskMAPs.[19] Many of the principles described in the RiskMAP Guidance are reflected in the REMS provisions set forth in FDAAA[20] and have been incorporated into FDA's REMS decision-making process. The purpose of this new guidance is to explain FDA's current application of previously articulated risk management principles and considerations under the REMS regulatory paradigm.

III. MANAGING DRUG RISKS

The statutory standard for FDA approval of a drug is that the drug is safe and effective for its labeled indications under its labeled conditions of use.[21] FDA's determination that a drug is safe, however, does not suggest an absence of risk. Rather, a drug is considered to be safe if the clinical significance and probability of its beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a drug is considered safe if it has an appropriate benefit-risk balance.

Over the past several years, FDA has been developing an enhanced, structured approach to its benefit-risk assessment in regulatory decision-making for human drugs and biologics. In 2012, the FDA Safety and Innovation Act (FDASIA)[22] charged FDA with implementing "a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decision-making, and the communication of the benefits and risks of new drugs."[23]

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[17] A drug's *prescribing information* (PI) contains a summary of the essential scientific information needed for the safe and effective use of the drug. 21 CFR 201.56(a)(1). The PI is updated from time to time to incorporate information from postmarketing surveillance or studies, for example, revealing new benefits or risk concerns.

[18] The RiskMAP Guidance is available at http://www.fda.gov/downloads/RegulatoryInformation/guidances/ucm126830.pdf.

[19] Certain products that were subject to elements to assure safe use prior to enactment of FDAAA were deemed to have in effect an approved REMS (section 909(b) of FDAAA; see also 73 FR 16313 (Mar. 27, 2008)). Some of these products were approved under subpart H or subpart E. Others were not approved under those provisions but contain elements to assure safe use for the drug that were agreed to by the sponsor and the Secretary. After 2005, these elements typically appeared in approved RiskMAPs. Many RiskMAPs that were in effect when FDAAA was enacted have been replaced by or included in a REMS.

[20] See section 505-1(a)(1) of the FD&C Act.

[21] See section 201(p)(1) of the FD&C Act (21 U.S.C. 321(p)) and section 505(d) of the FD&C Act (21 U.S.C. 355(d)).

[22] Public Law 112–144. FDASIA amended section 505(d) of the FD&C Act (21 U.S.C. 355(d)).

[23] Section 905 of FDASIA. Section 905 of FDASIA then notes that "[n]othing in the preceding sentence shall alter the criteria for evaluating an application for premarketing approval of a drug."

The performance goals that FDA agreed to in connection with the authorization of PDUFA V include creation of a five-year plan to further develop and implement this structured benefit-risk assessment framework in the new drug approval process.[24] FDA's benefit-risk framework includes the following categorization of key decision factors: analysis of condition, current treatment options, benefit, risk, and risk management.[25]

Risk management is a key factor in FDA's risk-benefit assessment. As described in previous guidances, risk management consists of both risk assessment and risk minimization: it is an iterative process involving (1) assessing a drug's benefit-risk balance, (2) developing and implementing tools to minimize the drug's risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a drug's life cycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.[26]

IV. THE USE OF REMS IN MANAGING DRUG RISKS

The goal of risk mitigation is to preserve a drug's benefits while reducing its risks to the extent possible. For the majority of drugs, routine risk mitigation measures, such as providing health care providers with risk information through FDA-approved prescribing information, are sufficient to preserve benefits while minimizing risks. In some cases, however, FDA may consider whether a REMS would help ensure that the benefits of the drug outweigh its risks.

If FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks, the Agency will impose one or more of a number of REMS elements, as described below. For example, FDA may require a Medication Guide or a patient package insert as part of the REMS[27] if the Agency believes that doing so may help mitigate the particular risk of the drug.

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[24] See section X of PDUFA V.

[25] FDA, February 2013, Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA V Implementation Plan (FY 2013-2017), available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf.

[26] See the following FDA guidances for industry: *Premarketing Risk Assessment Development*, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126958.pdf; RiskMAP Guidance; and *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, available at http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071696.pdf.

[27] Section 505-1(e)(2) of the FD&C Act. FDA has the authority to determine, based on the risks of a drug and public health concern, whether a Medication Guide should be required as part of a REMS (when the standard for requiring a Medication Guide in 21 CFR part 208 is met), and may decide the Medication Guide should be required as labeling but not part of a REMS if FDA determines that a REMS is not necessary to ensure the benefits of the drug outweigh its risks. For more information about when FDA intends to require a Medication Guide as an element of a REMS, see FDA's guidance for industry *Medication Guides – Distribution Requirements and Inclusion in Risk*

FDA may also require a communication plan[28] to health care providers as part of a REMS if it determines that the plan may support implementation of the REMS. For example, FDA may require a communication plan as part of a REMS to (among other things) disseminate information to health care providers regarding REMS requirements or to explain certain safety protocols, such as medical monitoring through periodic laboratory tests.

Under section 505-1(f)(1) of the FD&C Act, FDA may also require that a REMS include one or more ETASU, if FDA determines that

1. A drug has been shown to be effective, but is associated with a serious adverse drug experience, and can be approved only if, or would be withdrawn unless, the ETASU are required as part of the REMS to mitigate a specific, serious risk listed in the labeling of the drug; and
2. A communication plan, Medication Guide, patient package insert, and a timetable for assessments are not sufficient to mitigate this serious risk.[29]

The ETASU must be commensurate with a specific, serious risk in the drug labeling and, considering that risk, must not be unduly burdensome on patient access to the drug.[30]

FDA may use ETASU to address risk in a variety of ways. For example, if the goal of a REMS is to help prevent a serious outcome associated with a drug-induced adverse event, FDA may require that patients only receive the drug in a closely monitored health care setting. The REMS might include ETASU stipulating the type of prescriber training or education and monitoring protocols that are necessary to ensure that the drug is used safely. For instance, if the goal of the REMS is to help ensure that only certain patients are prescribed the drug in order to mitigate a serious risk associated with its use, FDA might approve a REMS that requires that health care providers who prescribe the drug be specially certified so that they receive training about the risk and appropriate patient selection.

FDA's determination as to whether a REMS is necessary for a particular drug is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case. In conducting this analysis, FDA considers whether (based on

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Evaluation and Mitigation Strategies (REMS), available at http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm244570.pdf.

[28] Section 505-1(e)(3) of the FD&C Act.

[29] Section 505-1(f)(1)(A)-(B) of the FD&C Act.

[30] Section 505-1(f)(2) of the FD&C Act. To minimize the burden on the health care delivery system, to the extent practicable, the ETASU must: (1) conform to ETASU in REMS for other drugs with similar, serious risks; and (2) be designed to be compatible with established distribution, procurement, and dispensing systems for drugs (section 505-1(f)(2)(D) of the FD&C Act). When assessing burdens on patient access, FDA considers, in particular, patients with serious or life-threatening diseases or conditions and patients who may have difficulty accessing health care (such as patients in rural or medically underserved areas) (section 505-1(f)(2)(C) of the FD&C Act).

premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.

If FDA determines that additional interventions are necessary to ensure that the benefits of a drug outweigh its risks, FDA considers what the goals of a proposed REMS to address these risks would be and what specific elements could help meet those goals. The REMS should be designed to meet the relevant goals and not unduly impede patient access to the drug. If FDA believes that the drug's risks would exceed its benefits even if FDA were to require a REMS for the drug, FDA will not approve the drug or may consider seeking withdrawal of the drug if it is already being marketed.

V. APPLICATION OF STATUTORY FACTORS IN REMS DECISION-MAKING

FDAAA requires FDA to consider the following six factors[31] in making a decision about whether to require a REMS:

- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
- The expected benefit of the drug with respect to the disease or condition
- The seriousness of the disease or condition that is to be treated with the drug
- Whether the drug is a new molecular entity
- The expected or actual duration of treatment with the drug
- The estimated size of the population likely to use the drug

These six factors influence FDA's decisions with respect to both whether a REMS is required for a particular drug and what type of REMS might be necessary (i.e., what specific elements or tools should be included as part of the REMS). FDA makes decisions about requiring a REMS as part of a benefit-risk determination for a drug after an evaluation that includes integrated consideration of each of the statutory factors. No single factor, by itself, is determinative as to whether a REMS is necessary to ensure that the benefits of a drug outweigh its risks.

[31] Section 505-1(a)(1) of the FD&C Act. The FD&C Act requires that FDA consider these factors in determining whether a REMS is necessary for a new drug. FDA also generally considers these factors in determining whether (based on new safety information) a REMS is necessary for a drug that is the subject of an approved application.

A. Seriousness of Known or Potential Adverse Events That May Be Related to the Drug and the Background Incidence of Such Events in the Population Likely to Use the Drug

The more serious[32] a drug's known or potential associated risks relative to its benefits, the more likely it is that a REMS will be necessary to ensure a favorable benefit-risk balance, without which the drug could not be approved. In determining whether to require a REMS, FDA considers the source, nature and reliability of available scientific evidence about the adverse events as well as the characteristics of the risks, including the severity, frequency, temporality, preventability, reversibility, background incidence, and likelihood of occurrence of the adverse events.

For drugs associated with adverse events that are reversible or preventable if particular measures are taken promptly, FDA may consider requiring a REMS to help ensure that such measures are undertaken in a timely manner to minimize or prevent a serious adverse event. For example, for a drug that is associated with liver abnormalities that are reversible with drug discontinuation, the REMS may require that the patient be monitored through laboratory studies so that the drug can be discontinued if and when hepatic enzyme elevations are observed.

A drug that is associated with a risk of a serious adverse event that is irreversible, such as one that causes a permanent disability or persistent incapacity, may be particularly likely to have a favorable benefit-risk profile only in the presence of a REMS that helps minimize drug exposure and the associated occurrence of the adverse event. In such cases, a REMS may include, for example, a prescriber certification requirement that includes prescriber training and patient counseling on the nature of the associated risk and on the drug's benefit-risk balance to facilitate informed patient and prescriber decisions about treatment with the drug. Such REMS are designed to ensure that patients are fully informed of the serious risk before beginning therapy and may involve patient acknowledgment forms or other methods of documenting that such patient-provider discussions have taken place. This kind of REMS is particularly important for drugs with limited available methods of preventing the actual occurrence of drug-associated adverse events.

The frequency and severity of adverse events associated with the use of a drug may also affect FDA's determination of whether a REMS is necessary. While a high frequency of adverse events may necessitate a REMS to mitigate this risk, FDA may also require a REMS for an infrequent adverse event, if the adverse event is particularly severe.

[32] Section 505-1(b)(4) of the FD&C Act defines an adverse drug experience as serious if it results in death, immediate risk of death, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect (or, based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent the above-described outcomes).

As part of its assessment of whether a particular adverse event is drug-associated, FDA examines the rate of the adverse event in individuals exposed to the drug relative to the background incidence of the adverse event in the population likely to use the drug. If an adverse event is determined to be drug-associated, FDA may determine that treatment with the drug unacceptably increases the frequency and/or severity of the adverse event in the patient population and that this risk needs to be mitigated through a REMS.

As part of its evaluation of the risks associated with the use of a drug, FDA also takes into consideration whether information about managing the particular risk is widely available and whether risk management measures are being widely implemented. FDA may also consider factors such as the specialties of the healthcare providers who may prescribe, dispense or administer the drug. The Agency also takes into account the health care setting(s) in which the drug is used or is likely to be used. For drugs intended for use in an outpatient setting, FDA considers the degree to which patients can be expected to reliably recognize symptoms as being associated with a drug and to take necessary actions to address adverse events. If, for example, FDA expects that a drug will likely be used in a setting where patient monitoring and certain medical equipment are not available, and believes that such measures are needed to mitigate the risks associated with the use of the drug, FDA may require a REMS with ETASU to limit use of the drug to settings in which these measures are available.

In making these determinations, FDA may take into consideration information from a variety of sources, including FDA's internal and external experts with specialized expertise relevant to a particular risk, other centers within FDA, other government agencies, advisory committee meetings, the Drug Safety Oversight Board, literature, and professional societies. FDA may also gather information from post-approval adverse event reports and active surveillance, as well as from post-approval clinical trials and other post-approval studies, including epidemiological studies, when evaluating whether a REMS is necessary for approved drugs.

B. Expected Benefit of the Drug With Respect to the Disease or Condition

When assessing a drug's expected benefits with respect to a specific disease or condition in considering whether a REMS is necessary, FDA may evaluate information about the drug's effectiveness, whether the drug treats a serious disease or condition, whether it fills an unmet medical need, and whether it can cure the disease or alleviate its symptoms. FDA may also consider the extent to which new dosage forms enhance convenience of administration and/or improve adherence to prescribed regimens, and whether new formulations or delivery mechanisms may extend treatment to patient populations who were formerly unable to use the drug.

A drug's expected benefits, however, are not considered in isolation. In determining whether a REMS is necessary, FDA's assessment of a drug's benefit is balanced against consideration of the risks associated with its use. For example, a once-a-month oral dosage form of a drug that was previously only available as a daily oral dosage form may offer a qualitative benefit in terms of convenience to the patient and adherence to medication therapy, but may have a different risk profile (e.g., a new risk associated with the new formulation, or with the longer half-life of the

drug) that makes it more likely that FDA would determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.

C. Seriousness of the Disease or Condition to Be Treated

The seriousness of the disease or condition[33] to be treated is a part of FDA's analysis of the benefits of a drug: the more serious the disease or condition to be treated, the greater the potential benefit of the drug's measured effect in the benefit-risk assessment. Nevertheless, even for drugs intended to treat serious or life-threatening diseases or conditions, the severity, irreversibility, or duration of an associated risk may weigh in favor of a REMS. For example, if a drug indicated for long-term treatment of an indolent, asymptomatic, or slowly progressing cancer also has a more immediate risk of serious and potentially fatal cardiac arrhythmias, FDA may conclude that, without a REMS, the risk of serious cardiac arrhythmias outweighs the potential benefits of this kind of cancer treatment. In this example, a REMS may be required to educate prescribers about the risk, appropriate monitoring, and management of cardiac arrhythmias to help minimize the occurrence of the adverse event associated with the drug.

D. Whether the Drug Is a New Molecular Entity

For new molecular entities (NMEs)[34] and Biologics License Applications (BLAs), available information about the drug can be limited and, as a result, there may be greater uncertainty about risks associated with the use of the drug that might emerge in the post-approval setting. When available safety information about a NME or BLA indicates a serious risk, there may be uncertainties about the nature of the serious risk (e.g., the strength of the association of the adverse event with drug treatment, the likelihood of occurrence of the adverse event, and the accuracy and/or reliability of the data). Depending on the nature of the uncertainties about the risks associated with the use of the drug, FDA may require a REMS to help ensure that the

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[33] FDA has defined *serious disease or condition* as

> "a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."

(21 CFR 312.300(b)); see also FDA's guidance for industry on *Expedited Programs for Serious Conditions – Drugs and Biologics*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf.

[34] FDA has defined the term "new molecular entity" as an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Act (in any application approved or deemed approved from 1938 to the present), or has been previously marketed as a drug in the United States. See Manual of Policies and Procedures (MAPP) 5018.2 NDA Classification Codes, available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm

benefits of the drug outweigh its risks, require a postmarketing study or clinical trial to further characterize the risk associated with the drug, or both.[35]

E. Expected or Actual Duration of Treatment with the Drug

The duration of treatment with a drug and the impact of treatment length on the likelihood and severity of adverse events also affect FDA's decision-making with regard to the need for a REMS. If long-term therapy with a drug appears to increase the likelihood of a serious adverse event, FDA may require a REMS either to limit the duration of treatment or to ensure that patients on long term treatment are monitored, e.g., for liver function if the drug is associated with liver toxicity.

A REMS may also be required for a drug with a relatively short duration of treatment, depending on the nature of the associated risk. For example, FDA may require a REMS for a drug indicated for a short duration of use, such as for the acute treatment of a condition, if the drug is associated with a serious adverse event that occurs immediately after administration. Such a REMS may require that the drug only be administered in a setting in which monitoring is available to ensure that the adverse event can be appropriately managed or in a setting in which, for example, providers have received particular risk management training. Similarly, a REMS may be required for a drug that is only intended to be administered once or twice if FDA determines that specialized training is necessary to prevent the occurrence of an adverse event associated with improper drug administration. In some cases, serious adverse events may occur even after treatment with a drug has ended. In such cases, FDA may determine that a REMS is required to ensure proper monitoring of patients for a period of time following completion of treatment.

F. Estimated Size of Population Likely to Use the Drug

In making a decision about whether to require a REMS, FDA also evaluates the estimated size of the population likely to use the drug. In considering size, FDA considers, among other things, the extent to which the population likely to use the drug includes a significant number of patients expected to use the drug for unapproved uses and the risks and potential benefits associated with those uses. In certain cases where the risks associated with unapproved uses of a drug are significant in relation to potential benefits, FDA may consider whether a REMS designed specifically to mitigate the risks associated with those uses is appropriate.

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[35] Section 505(o)(3)(A) of the FD&C Act states that postmarketing studies and clinical trials may be required for any or all of three purposes listed in section 505(o)(3)(B):

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

See FDA's guidance for industry *Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*, available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172001.pdf.

VI. ADDITIONAL CONSIDERATIONS: POTENTIAL BURDEN ON THE HEALTH CARE DELIVERY SYSTEM AND PATIENT ACCESS

FDA understands that REMS, particularly those with ETASU, may impose some measure of burden on patients and/or health care providers. When considering this burden on patient access and the health care delivery system, FDA takes into account existing REMS elements for other drugs with similar risks and whether the REMS under consideration can be designed to be compatible with established medical drug distribution, procurement, and dispensing systems. FDA also considers how patients for whom the drug is indicated currently access health care (such as whether patients are in rural or medically underserved areas) and whether the REMS may impose additional access difficulties. FDA also takes into account the consequences of potential treatment interruption or delays, particularly where patients have serious or life-threatening conditions and/or have difficulty accessing health care. In such circumstances, FDA takes steps, to the extent possible, to ensure that REMS are designed to minimize delays or interruptions in drug therapy that may have untoward clinical impact. Particularly for a REMS that requires additional procedures and controls in the patient care process, FDA also considers the characteristics, experience, and size of the likely prescriber population; how the drug will likely be dispensed in the setting in which it will likely be used; and the patient population likely to use the drug.

The selection of REMS elements and tools may be influenced by the extent to which they have already been used in the clinical trials to evaluate the drug's safety and efficacy, and by what is known about the effectiveness of the elements and tools more generally. Selection of risk management elements and tools is also informed by any regulatory precedent for addressing similar risks.[36] For example, if a serious risk is common to all members of a drug class, FDA will consider, as appropriate, how the Agency has previously managed the risk, including whether there has been a uniform approach to risk management. In such cases, FDA seeks opportunities to standardize the approach to managing that risk. FDA also encourages sponsors to submit REMS proposals that are compatible with established distribution, procurement, and dispensing systems. Following approval of a REMS, FDA continues to evaluate the impact of the REMS on patient access and the health care delivery system.

[36] In addition, the elements and tools may be driven by results of previous REMS assessments for REMS designed to address a similar risk, a similar patient population, or a similar drug distribution or dispensing system to the product under review.