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Client Alert

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FDA Issues Draft Guidance for Industry on Risk Evaluation and Mitigation Strategies (REMS)

On September 30, 2009, the Food and Drug Administration issued a draft guidance for industry on better understanding and implementing Risk Evaluation and Mitigation Strategies ("REMS"), which FDA requires for certain drugs or biologics when the agency believes additional precautions are necessary to ensure that the benefits of a drug or biologic outweigh its risks. FDA is placing increased reliance on its REMS authority and, as a result, REMS assessments and implementation have placed increased demands on time, money, and resources for sponsors and for physicians and hospitals.

The 36 page draft document, *Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modification* ("REMS Guidance"), reveals the Agency's current thinking on the format and content that manufacturers should use in developing proposed REMS.

The REMS Guidance focuses on three main points: 1) the content of a proposed REMS submission; 2) REMS assessment and modification of proposed REMS; and 3) communicating with FDA about REMS. In addition, the REMS Guidance also provides useful background information about REMS and RiskMaps and includes an example of a REMS for a fictitious product. This Bulletin summarizes the statutory REMS provision and highlights of the REMS Guidance.

A. Background on REMS

Section 901 of the Food and Drug Administration Amendments Act ("FDAAA"), amended the Federal Food, Drug, and Cosmetic Act ("FDCA") to add Section 505-1, 21 U.S.C. § 355-1, which allowed FDA to require applicants to submit a proposed REMS as part of certain drug or biologics applications to ensure the benefits of the drug or biologic would outweigh the risks.[1] In addition, FDA was authorized to require holders of applications approved without a REMS to submit a proposed REMS if the Agency became aware of new safety information indicating that such action would be necessary to protect the public health. Applicants may also voluntarily submit a proposed

1 Section 505-1 for REMS only applies to "covered applications," defined as new drug applications ("NDAs"), abbreviated new drug applications ("ANDAs"), and biologics license applications ("BLAs"). FDAAA allows FDA to require REMS for generic drugs whose reference product has an approved REMS, which will be addressed in future guidance. At this time, the REMS Guidance provides that ANDAs, based on a reference listed drug with a REMS, will be approved with any applicable elements of the REMS.

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REMS for the Agency's approval. [2]

A drug is considered misbranded, under 502(y) of the FDCA, if the applicant or the holder of the approved application fails to comply with a requirement of the approved strategy. 21 U.S.C. § 352(y). Violations of a REMS requirement can result in civil monetary penalties of up to $250,000 per violation, not to exceed $1 million in a single proceeding. 21 U.S.C. § 333(f)(4)(a). Penalties significantly increase for violations continuing for more than thirty days after FDA has provided notice of violation, doubling for the second thirty-day period and any subsequent thirty-day periods, up to $1 million per period and $10 million per proceeding. In addition, a product may not be introduced or delivered for introduction into interstate commerce if non-compliant with a REMS. 21 U.S.C. § 355(p).

B. Summary of Draft Guidance

Point 1. Content and Format of a Proposed REMS Submission

The REMS Guidance provides that a REMS submission include two parts: (a) a proposed REMS, the primary document describing the proposed goals and elements of the REMS, and (b) a REMS-supporting document, which explains the rationale for the content of the proposed REMS and provides additional information. Prior to approval, FDA may require applicants to revise proposed REMS to ensure that the product's benefits will outweigh the risks.

a. Part One: A Proposed REMS

A proposed REMS should include concise information on the goals and elements of the REMS and clearly describe the responsibilities of the applicant in implementation, with a date of implementation for each REMS element. All materials proposed to be included as part of the REMS (*e.g.*, communication and education materials, Medication Guide, patient package insert, enrollment forms, prescriber and patient agreements) should be attached with the proposed REMS. A template REMS document may be accessed here, on FDA's website. Further, FDA has confirmed that it will not review or require REMS in foreign languages.

A proposed REMS should contain the following elements or include a statement that the element is unnecessary:

- Product and Contact Information – The application number, proprietary and established names, dosage form, drug class according to the product label, and applicant's name and address. Contact

2 Prior to enactment of the FDAAA, FDA approved a limited number of drug and biological products, whose risk could not be managed by labeling and safety reporting requirements, by requiring a risk minimization action plans ("RiskMAPs"). Much like REMS, RiskMAPs are a strategic safety program with specific goals and objectives for limiting the known risks of a product while preserving its benefits. FDA anticipates that, where the statutory requirements for a REMS are met, REMS will replace the need for RiskMAPS, but the Agency also notes that RiskMAPs in place prior to the effective date of the FDAAA, but not replaced or included in a REMS, will remain effective. FDAAA also provided for the small number of drugs and biologics approved prior to its effective date, with postmarketing restrictions on distribution or other Elements to Assure Safe Use to have an approved REMS.

information, including position titles, should be provided for persons responsible for the REMS policy, management, and implementation.

- Goals – All REMS should include a statement of one or more overall goals. If the REMS includes an Element To Assure Safe Use ("ETASU"), at least one goal must address mitigating a serious risk listed in the labeling of the drug, for which ETASUs are required.[3] In general, a proposed REMS goal should focus on the achievement of particular health outcomes or increasing awareness of safety risks to target maximum risk reduction in absolute terms. For instance, examples of REMS goals are "Fetal exposures to Z drug should not occur" or "Patients on X drug should not also be prescribed Y drug."

- Additional Potential REMS elements – The development of a Medication Guide ("MedGuide"), Patient Package Insert ("PPI"), or Communication Plan may be required as one REMS element.

  i) *MedGuide* – A MedGuide may be required if: patient labeling may help to prevent a serious adverse effect; patient awareness of the serious risks of the product (relative to the benefits) could affect the patients' decision for use or continued use; or patient adherence to instructions for use is crucial to the product's effectiveness. If a MedGuide is required, the REMS should describe the mechanisms intended to be used for distribution.
  ii) *PPI* – A PPI may be required to help mitigate a serious risk of the product. FDA indicates that very few products will require both a MedGuide and a PPI, although a PPI may be converted to a MedGuide if FDA finds that patient labeling must meet MedGuide requirements. Editorial changes to a PPI or changes related to use a product will not trigger the need for conversion, unless the changes are to mitigate a serious risk, such as an overdose.
  iii) *Communication Plan* – A communication plan may include sending letters or disseminating information about REMS elements to healthcare providers or professional societies to encourage REMS implementation or explain safety protocols. Notably, if an NDA-approved product with a REMS Communication Plan is the basis for a subsequent ANDA, FDA must carry out the Communication Plan once the ANDA is approved, instead of the NDA or the ANDA holder. However, both the NDA and the ANDA holder will still be responsible for implementation of tools that were previously part of the Communication Plan which may be covered under an ETASU (*e.g.*, training materials, specified procedures, patient/physician agreements, patient educational materials, safety protocols).

- ETASUs – The proposed REMS should describe any ETASUs and the tools designed to implement them and contain copies of all relevant materials as attachments. The categories of ETASUs include:

3 In order to provide patients with safe access to drugs with known serious risks that would otherwise be unavailable, ETASUs must be put in place to mitigate a specific serious risk listed in the labeling of a product. Before requiring an ETASU, FDA must determine that the product is effective but is associated with a serious adverse drug experience and can only be approved if the ETASU were required. If the product was initially approved without an ETASU, FDA must also find that other possible elements of a REMS are not sufficient to mitigate the serious risk.

i) *Healthcare providers who prescribe the drug have particular training or experience, or are specially certified* – Elements under this category may relate to certification, training, or attestation of specific experience or knowledge before a healthcare provider can be enrolled in a prescriptive program. The program may require periodic recertification and enrollment, and the opportunity to obtain training or certification must be available to any provider at a reasonable cost.

ii) *Pharmacies, practitioners, or health care settings that dispense the drug are specially certified* – Elements under this category may require certification, training, or attestation of specific experience or knowledge before the pharmacy, practitioner, or health care setting can be enrolled in a prescriptive program. The program may require periodic recertification and enrollment, and the opportunity to obtain training or certification must be available to any provider at a reasonable cost.

iii) *The drug be dispensed to patients only in certain healthcare settings, such as hospitals* – Elements under this category may include restrictions on dispensing the product to patients in specific settings. Examples of implementation include ensuring the drug is dispensed only to patients in hospitals that have met certain conditions or to physicians' offices equipped to treat any potential risks after administration of the drug.

iv) *The drug be dispensed only to patients with evidence of other documentation of safe-use conditions, such as laboratory test results* – Elements under this category may include restrictions on dispensing the product to patients that meet specified criteria before exposure. *See* 21 U.S.C. § 355-1 (f)(3)(D). Examples of implementation include counseling patients about risks and benefits or ensuring patients receive a drug only after specified authorization is obtained and verified by a pharmacy.

v) *Each patient using the drug be subject to certain monitoring* - Elements under this category may require that patients be monitored or that specific follow-up occur at specific times. Examples of implementation include having patients' lab tests monitored on a specified periodic basis or requiring that patients contact the prescriber periodically during and after treatment.

vi) *Each patient using the drug be enrolled in a registry* - Elements under this category may require that patients enroll in a program as part of the overall strategy to mitigate a specific serious risk listed in the product labeling. Use of the registry may be combined with other ETASUs, and drug access may be contingent on patient enrollment.

- Implementation System – FDA may require an implementation system for any REMS, which include the ETASUs outlined in (ii), (iii) and (iv) above. The applicant would be expected to take reasonable steps to monitor, evaluate and improve the implementation of the ETASUs by other parties who are responsible for implementation, such as healthcare providers and pharmacists. FDA may require a description of the product's distribution or the certification of wholesalers or distributors to ensure the product is dispensed only to appropriate parties.

- Timetable for Submission of Assessment of the REMS – A description of the proposed timetable for submission of REMS assessments for NDAs and BLAs is required, but FDA does not require that REMS for ANDAs have a timetable at this time. FDA provides that:

  i) At a minimum, each timetable must, include assessments submitted by 18 months, by 3 years,

and in the 7th year after the REMS is initially approved. Additional dates for assessments may be required as necessary, and factors influencing this determination include, among others, the estimated size of the patient population for the product, the seriousness of known or potential risks, and knowledge about the effectiveness of the REMS elements to mitigate the risk.

ii) The 18 month and 3-year requirement can be met by assessments submitted at specified, but earlier dates, and the dates specified must relate to the submission, not the performance, of the assessments.

iii) The reporting interval for an assessment should conclude no earlier than 60 days before its submission date to facilitate the full inclusion of all available information.

b. Part Two: REMS Supporting Documentation

The REMS supporting document should include a detailed explanation of the rationale for the proposed REMS, including how and when each REMS element will be implemented and the basis for the timeline, in addition to all supporting information for the REMS. The REMS Guidance notes that a template for the REMS supporting document is available here on FDA's website. FDA notes the document should include the following sections listed as well as a table of contents:

- Background – This section should provide a concise summary explaining the necessity of the proposed REMS and how the plan will verify that the benefits of the product outweigh the risks. In addition, FDA provides that:

  i) An initial REMS for a previously approved product should describe the new safety information suggesting the need for the REMS.

  ii) Detailed information about the risk to be minimized should be provided, and the following factors, which FDA must consider in determining whether a REMS is necessary, should be addressed: the estimated size of the patient population; the seriousness of the disease or condition treated; the expected benefit of the product to the disease or condition; the duration of treatment; the risks and benefits of alternative therapies; and whether the drug is a new molecular entity.

  iii) Discussion of historical information about any successes and failures related to mitigating the risks for the specified product or similar products may be provided, as well as any information on relevant past experiences that would help in the development of the proposed REMS.

- Goals – A summary of the rationale for the proposed goals of the REMS, describing how the elements will individually and collectively contribute, should be provided.

- Supporting Information About Proposed REMS Elements – Describe why each element or tool was chosen for the proposed REMS and indicate how each tool contributes to the goals of the REMS. FDA notes:

  i) Each method used to monitor and evaluate the implementation system should be discussed along with any plans to improve implementation.

ii) The rationale and supporting information for the proposed timetable should be provided, addressing each interval that each assessment will cover as well as the planned date for submission to FDA.

iii) The applicant should give a thorough description of the available evidence, indicate whether any input was obtained from patient or health care interests, and discuss any feedback was received regarding the feasibility of the proposed REMS.

- Supporting Information with ETASUs - Proposed REMS which include ETASUs should include:

i) An explanation of how the ETASUs correspond to the specific serious risks listed in the labeling;
ii) An explanation of how the ETASUs mitigate the observed serious risk;
iii) Verification that the elements proposed are not unduly burdensome on patient access, for patients with serious or life-threatening disease or difficulty with access to health care;
iv) A description of how the ETASUs will minimize the burden on the healthcare delivery system, including discussion of any other drugs which pose similar risks to provide further information about the proposed ETASUs compatibility with established healthcare delivery systems.

- REMS Assessment Plan – REMS Assessments measure whether the goals are being met, and the proposed plan to assess the REMS should be fully explained in this section. Information should include the proposed evaluation methods, targeted values and timeframes for each measure, the type of data collected and timing for data collection, and any applicable plans to assess unintended or unfavorable consequences. Plans to obtain information on the effectiveness of REMS elements to meet the stated goals or the need to modify the goals or the REMS elements should be included. FDA requires that specific assessment instruments and methodology should be identified, and such information, once it is available, should be submitted to FDA to update the REMS supporting document at least 90 days before the assessments are conducted. In general, each assessment should contain sufficient detail to identify any need for changes to the REMS. In addition:

i) For REMS that include an ETASU, the assessment must consider the extent to which the ETASUs are meeting the goal.
ii) For REMS with a MedGuide, the assessment should include a survey of the patients' understanding of the risks of the product, a report on periodic assessments of the distribution of the MedGuide, and a report on any failures as well as corrective actions to address non-compliance.

- Required Postapproval Studies or Clinical Trials – The status of any postapproval study required or otherwise undertaken to investigate a safety issue must be included in the assessment. Specifically, the assessment must include the status of each clinical trial, the number of participants enrolled, the expected completion date, any difficulties encountered with completing the trial, and the clinical trial's registration information. A reference to the relevant information in the applicant's most recent annual report, with any updates since the report was prepared, may suffice to satisfy the requirement

for information on the status of the postapproval study or clinical trial.

- Other Relevant Information – This section should include information on positions within the applicant's company responsible for REMS policy, management, and implementation, with organizational charts, and any other information that is relevant to the proposed REMS.

Point 2. REMS Assessment and Proposed Modifications of REMS

As noted above, REMS assessments must be submitted in accordance with the timetable included in the proposed REMS. Applicants may voluntarily submit assessments, and FDA may also require additional REMS assessments. For example, FDA may require an assessment when a supplemental application is submitted for a new indication for use or where the Agency determines that new safety or effectiveness information suggests that the assessment timetable requires modification or that a cause for withdrawal or suspension of the approved REMS exists.

After approval of the REMS, applicants may request proposed modifications to enhance or reduce the REMS requirements, including potential changes to any materials included as part of the REMS. Applicants may also ask for changes to the assessment timetable, including the elimination of any assessments after the 3-year submission.

Proposed modifications should be submitted to FDA using a new prior-approval supplemental application and may not be implemented until FDA gives approval. Each proposed modification should include the new proposed REMS with the previous approved REMS, with all proposed modifications highlighted, along with an update to the REMS supporting document for the rationale and the impact of the changes on other REMS elements. FDA intends to provide more detailed guidance on assessments and modifications to approved REMS in the future.

Point 3. Communicating with FDA about REMS

A proposed REMS may be submitted in the product's original drug application, a supplemental application, or as an amendment to an original or supplemental marketing application. FDA specifically provides that:

- All supplemental applications that include a proposed REMS or for proposed modifications to an approved REMS should be submitted as prior-approval supplements;
- A proposed REMS submitted after approval, which is not associated with an existing supplemental application should be filed as a new supplemental application;
- Although a REMS assessment alone, without a proposed modification, is not considered a supplemental application, REMS assessments with a proposed modification to the approved REMS may be submitted as either a new supplemental application or a related supplemental application, at the time of admission or as an amendment;
- With few exceptions for those drugs not subject to Section 503(b) of the FDCA (*e.g.*, non-prescription drugs) where the REMS includes only the timetable for the submission of assessments, a supplemen-

tal application for a new indication for use for a product with an approved REMS must include a REMS assessment and may propose modifications to the REMS.

A template for submissions of proposed REMS and proposed modifications of approved REMS is available here on FDA's website. The Agency also requests that applicants also include electronic versions of the documents to facilitate processing. In addition, the REMS Guidance emphasizes that each submission, whether a proposed REMS application or REMS assessment, should provide identifying information to allow for tracking and provides detailed instructions for the labeling of each type of submission. FDA notes that applicants may contact the regulatory project manager in the division assigned to the drug for questions, while the Director of the Division of Labeling and Program Support in the Office of Generic Drugs will be the primary contact for ANDA applicants.