FDA's Recent Guidance on REMS

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PRACTICES Pharmaceuticals, FDA Regulatory and Compliance, Intellectual Property

This April the Food and Drug Administration ("FDA") issued a final guidance ("REMS Guidance") clarifying how FDA applies the factors in section 505-1 of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") (21 U.S.C. § 355-1) to determine whether a risk evaluation and mitigation strategy ("REMS") is necessary. A REMS is a required risk management plan to ensure that the benefits of a drug outweigh its risks.

The REMS Guidance explains that determining whether a REMS is necessary for a particular drug is a complex analysis, specific to a given drug. In conducting this analysis, FDA considers information from before and after marketing regarding whether risks associated with the use of the drug outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks. REMS Guidance at 4. When determining if a REMS is needed, FDA considers information from a variety of sources, such as experts, other FDA centers, government agencies, advisory committees, etc. *Id.* at 4-5.

In considering whether to require a REMS and what type of REMS should be required, FDA considers the six factors required by Section 505-1(a)(1) of the FD&C Act, discussed in more detail below. All six factors are considered together, and no single factor is determinative as to whether a REMS is necessary. *Id.* at 5.

1. **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 more serious a drug's known or potential associated risks relative to its benefits, the more likely it is that a REMS will be necessary." *Id.* at 6. FDA will also consider the frequency and severity of adverse events associated with the use of a drug. *Id.* A high frequency of adverse events can necessitate a REMS, as can an infrequent adverse event, if the adverse event is particularly severe. *Id.*

   As part of its evaluation of whether a REMS is needed, FDA also considers additional factors, including the availability of information about the risk and the levels of knowledge about the risk and risk management measures in healthcare professionals and patients. *Id.* at 7.

2. **The expected benefit of the drug with respect to the disease or condition.** In evaluating a drug's benefit, FDA considers information about the drug's effectiveness, the seriousness of the disease or condition treated, whether it fills an unmet medical need, and whether it can cure the disease or alleviate its symptoms. *Id.* For new dosage forms, FDA may also consider "the extent to which the 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." *Id.* These benefits are weighed against the risks associated with the drug. *Id.*

3. **The seriousness of the disease or condition that is to be treated with the drug.** "[T]he 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." *Id.* at 8. However, even for drugs intended to treat serious or life-threatening diseases or conditions, an associated risk may be sufficiently severe, irreversible, or long to warrant a REMS. *Id.*

4. **Whether the drug is a new molecular entity**. When safety information about a new molecular entity or Biological License Application indicates a serious risk and there are uncertainties about the nature of the serious risk, a REMS may be required to assure that the benefits of the drug outweigh its risks. *Id.*

5. **The expected or actual duration of treatment with the drug.** A REMS may be necessary when long-term therapy with a drug appears to increase the likelihood of a serious adverse event. *Id.* at 9. Such a REMS would likely limit the duration of treatment or ensure that patients on long-term treatment are monitored for the adverse event. *Id.* A REMS could also be necessary for a drug with a relatively short duration of treatment if that treatment is associated with serious risks. *Id.*

6. **The estimated size of the population likely to use the drug.** FDA will consider whether the expected patients are likely to use the drug for unapproved uses, and what are the risks associated with those unapproved uses. *Id.* A REMS can be designed to ensure that a drug's use is limited to its approved indication. *Id.*

The REMS Guidance recognizes that REMS can be a burden on the healthcare delivery system and patient access and notes that FDA considers these factors when deciding whether a REMS is necessary. *Id.*

The REMS Guidance further notes that the features of a REMS can be influenced by the extent to which they have already been used in clinical trials to evaluate the drug's safety and efficacy and by regulatory precedent for addressing similar risks. *Id.* at 10.

The REMS Guidance concludes: "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 healthcare delivery system." *Id.*

FDA's REMS Guidance provides useful information to pharmaceutical manufacturers about the basis for adopting a REMS and the considerations involved.