REMS Industry Consortium℠
Innovating Patient Safety. Mitigating Risk.

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SUBMITTED ELECTRONICALLY

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2023-N-0573 for "Changes to Third-Party Vendors for Risk Evaluation and Mitigation Strategies; Establishment of a Public Docket; Request for Comments"

To Whom It May Concern:

The REMS Industry Consortium® ("RIC") is pleased to provide these comments to the Food and Drug Administration's ("FDA's" or "Agency's") public docket on "Changes to Third-Party Vendors for Risk Evaluation and Mitigation Strategies." 88 Fed. Reg. 17578 (Mar. 23, 2023). This letter responds to the Agency's solicitation for comments on "factors that generally should be considered by the Secretary of the Health and Human Services ("Secretary") when reviewing modification requests from sponsors of drugs subject to Risk Evaluation and Mitigation Strategies ("REMS") related to changes in third-party vendors engaged by sponsors to aid in the implementation and management of the strategies."

A. Overview of RIC

RIC is the sole organization of its kind that is singularly dedicated to REMS-related issues. It is comprised of (i) twenty-five (25) organizations that commercialize (or anticipate commercializing) prescription drugs or biologic products subject to REMS ("sponsors"), and (ii) nine (9) industry partners (e.g., service providers and suppliers) that provide technology and other service provider solutions for REMS programs. Notably the sponsors who are members of RIC participate in nearly half of the sixty-four (64) REMS programs that are currently in effect. Individuals at RIC member companies have extensive experience with single drug REMS programs, as well as shared-systems REMS programs (that brand and generic drug companies jointly set up to implement REMS program requirements for a particular drug or class of drugs).

RIC was formally established in September 2021 to foster collaboration and innovation to advance the objectives of patient safety, appropriate access to medicines, and best practices in REMS-related drug and biologic risk management. The RIC Vision Statement reflects that our

members are committed to "improving patient safety and access to medicines through REMS innovation."

RIC has a variety of Working Groups dedicated to various portions of REMS practices. For example, RIC has a dedicated Vendor, Innovation & Technology Working Group that explores ways to increase vendor capabilities and identify tactics to spur technological improvements. The Best Practices Working Group focuses on advancing standardization across REMS programs when such standardization is useful and justified. These comments reflect the work of the FDA Interactions Working Group that is, among other things, committed to maintaining open lines of communication between RIC and FDA. While RIC is still relatively new, over time RIC hopes to offer forums where REMS stakeholders (e.g., FDA, sponsors, vendors, health care providers, and patients) can share their perspectives and work together with RIC to address and improve REMS operations.

Our consortium was initially comprised of six founding members, and it has grown to now include two different classes of members – manufacturers and service providers. Over time, we will expand our reach to engage with, and further benefit from, the input and perspectives of the wide array of stakeholders that engage with REMS. We will do this because RIC members are committed to our primary and most compelling of objectives - delivering on our industry-wide mission to deliver medicines to patients in a manner that is prompt, efficient and safe.

B. Background on REMS

Before we address the five questions that FDA has posed, it is helpful to consider the background of REMS and why FDA is undertaking this solicitation of comments at this time.

A federal statute, commonly referred to as the FDA Omnibus Reform Act ("FDORA"), that President Biden signed into law on December 29, 2022, required that a public docket be opened to "solicit comments on factors that generally should be considered by the Secretary when reviewing requests from sponsors of drugs subject to risk evaluation and mitigation strategies to change third-party vendors engaged by sponsors to aid in implementation and management of the strategies." That statute specifically focused attention on the "potential effects of changes in third-party vendors on patient access," as well as "prescribing and administration of the drugs by health care providers." Notably, the statute includes the important provision entitled "No Delay" that states: "Nothing in this section shall delay agency action on any modification to a risk evaluation and mitigation strategy."

The statute also requires the Comptroller General of the United States to submit a report by December 31, 2026, to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate ("GAO Report") on the following topics:

(1) the number of changes in third-party vendors (engaged by sponsors to aid implementation and management of risk evaluation and mitigation strategies) for an

approved evaluation and mitigation strategy the Secretary has approved under section 505-1(h) of the Federal Food, Drug, and Cosmetic Act (21 USC 355-1(h));

(2) any issues affecting patient access to the drug that is subject to the strategy or considerations with respect to the administration or prescribing of such drug by health care providers that arose as a result of such changes; and

(3) how such issues were resolved, as applicable.

Thus, this FDA solicitation of comments is statutorily mandated, as is a GAO assessment of REMS-related topics. Both initiatives arise fifteen years after REMS were first established. REMS are an updated version of Risk Minimization Action Plans ("RiskMAPs") and were first addressed in the Food and Drug Administration Amendments Act of 2007 ("FDAAA"). That Act included adoption of section 505-1 of the Food, Drug, and Cosmetic Act ("FFDCA"), which granted FDA authority to require persons submitting certain drug and biologic applications to include a REMS so that the benefits of the drug or biologic outweigh its risks. The authority for FDA to mandate a REMS became effective on March 25, 2008 – 180 days after enactment of FDAAA.

While sponsors may implement some aspects of REMS programs directly, third-party service providers (a/k/a REMS administrators) are a critical contributor to effective execution of REMS programs (a/k/a REMS systems). For example, as the Federal Register notice states, there are various aspects of a REMS that must be addressed including, "building and operating a centralized database or repository for patient enrollment, prescriber and pharmacy certifications, and wholesaler enrollments," as well as "host[ing] a website or web portal that participants, such as patients, prescribers, pharmacies, and wholesalers, use to enroll in the program" and "provid[ing] the technological means for pharmacies and other dispensers to perform the necessary verifications at the point of dispensing."

We agree with FDA that "[i]n many cases, therefore, the REMS administrator performs critical functions in the daily operations of a REMS which directly impact patient access to the drug." Those functions are conducted in accordance with REMS program specifications that FDA establishes in consultation with sponsors. In addition, REMS programs are subject to FDA oversight at every stage, from the earliest steps of development and throughout their operation.

C. Background on Events Leading Up to This Information Collection

In the more than fifteen (15) years that REMS have been in existence, there have been many modifications, service provider transitions, and other applicable updates to REMS programs that have proceeded without incident. Despite this, however, RIC recognizes that there have been instances where a modification caused delay in access to REMS products. FDA's current request for comments arises following a series of events that resulted in patients facing significant obstacles in accessing certain REMS drugs. In fact, the interruption in medication access prompted

FDA to announce temporary enforcement discretion with respect to certain REMS program requirements to ensure continuity of care to patients.[1]

In retrospect, the disruptions that impacted patient access were exacerbated by a relatively recent cessation of REMS-related services by a major service provider. That major service provider's unanticipated announcement of its planned departure from the REMS space compounded existing issues, ultimately prompting a significant effort to react. Although sponsors and REMS service providers undertook substantial remedial efforts for the impacted REMS programs, we can now re-examine these endeavors with the 20/20 clarity that hindsight offers. In doing so, it is evident there was a lack of sufficient time, flexibility, or safeguards to achieve uninterrupted patient access to certain medicines.

In theory, there are many reasons why an extraordinary challenge arose for some of the REMS programs that were impacted. Historically, few REMS service providers have been capable of full REMS administration. This led to main service providers shouldering responsibility for the establishment and administration of numerous REMS programs, including multiple shared system REMS programs involving multiple brand and generic sponsors (which are inevitably more complex). Past providers have acted as a *de facto* "control center" for a multitude of interconnecting systems within each REMS programs that they managed.

In prior years, unforeseen circumstances have proved to be highly disruptive, particularly where the timeframe for change is brief. For example, when sponsors are given a short, one-time contract extension, that timeframe places an incredible burden on the sponsors and other stakeholders to transition to comparable service providers. Overall, collective efforts undertaken to respond to previous disruptions have fallen short of what was needed for a seamless transition.

When transitioning any REMS program to a new service provider, there are many moving parts that must be addressed. For example, there are many parties involved in each REMS program (especially in shared system programs). Those parties must work to reach consensus as they establish and execute on a new plan of action to effectuate and operationalize the REMS program transition.

The service providers (both the incoming service provider and the exiting service provider) also must establish new protocols and procedures. In addition, new work instructions are needed for all the entities that will need to interface with that replacement service provider (such as patients, pharmacies, prescribers (and potentially other healthcare providers such as hospitals or infusion centers and distributors)).

This is particularly intricate and complex with respect to shared systems. All participants involved in the administration and management of a REMS program - including all participating brand and generic sponsors for shared systems - must agree to a cohesive, tightly controlled, and effective plan of action for the transition. At the same time there must be continued attention to

[1] E.g. U.S. FOOD & DRUG ADMIN., *FDA Is Temporarily Exercising Enforcement Discretion with Respect to Certain Clozapine REMS Program Requirements to Ensure Continuity of Care for Patients Taking Clozapine*, https://www.fda.gov/drugs/drug-safety-and-availability/fda-temporarily-exercising-enforcement-discretion-respect-certain-clozapine-rems-program (last updated Nov. 2, 2022).

the on-going operations of the existing REMS program while simultaneous plans are made to transition to the new service provider.

As the effort to on-board new service providers was undertaken, many factors came into play, including but not limited to the following:

Limited Service Provider Options - There were only a limited number of REMS program service providers that possessed knowledge, technology and know-how to quickly substitute in for the exiting service provider. It remains unclear why so few service providers provide comprehensive REMS services; recent mergers are certainly one reason why the REMS service provider pool is continuing to shrink. In addition, even companies that do offer REMS services may have limited staffing and technology capabilities to deliver on REMS required operations that FDA has mandated. With these and other factors contributing to a limited REMS service provider pool already in play, sponsors and the service provider market generally were not ready for a disruption like a REMS program service provider's exit.

Exclusive Technology Capability of Exiting Service Provider - Some service providers may possess certain exclusive technological capabilities that FDA requires for particular REMS programs. Differences in available service providers' technological capabilities (at the time that the major REMS service provider was exiting the REMS space) made the transitions that much more difficult.

Past limitations and differences in other available service provider capabilities resulted in a need to identify, develop, and deploy alternate technology approaches to achieve each REMS program's individualized objectives. As such, prior transitions were not an "apples-to-apples" change-over. Stated another way, this meant that new service providers were, by necessity, tackling REMS program objectives in a different manner (based on their existing technological capabilities) so it was not merely a simple switchover to a new service provider utilizing the same technology solutions.

Insufficient Staffing of Experienced REMS Professionals or Time to Scale Up – Past exiting and incoming service providers have had a limited number of knowledgeable, experienced people to handle the multiple transitions that were happening all at once. (This was true also at the various interfacing entities such as pharmacies, prescribers and distributors as well.) New hiring of additional personnel did occur, but the scale-up to meet this unexpected demand simply was not accomplished fast enough. REMS program professionals across all the interconnecting aspects of REMS programs mobilized to make the necessary changes before the exiting service provider's departure, but time was not on anyone's side.

In sum, past withdrawals from REMS programs by major service providers have offered us important lessons for managing disruptions. In recent history, numerous independent but highly interconnected factors converged to create a "perfect storm." There were multiple REMS programs with transitions occurring simultaneously. Limited service provider options existed to fill the void, and none offered identical technology capabilities of the exiting service provider. There were finite numbers of knowledgeable, experienced REMS service providers available to support the sponsors and programs, and the existing vendor's expiration date for exit steadily approached. In light of

these circumstances, patients were not able to access specific medicines without interruption, which is an obvious concern for healthcare providers, program sponsors, and FDA. However, in several other program transitions that followed, sponsors benefited from the lessons learned to ensure that program transitions happened relatively smoothly. Nonetheless, RIC members are working in tandem now so that this "perfect storm" will not recur. As such, it is RIC's view that these unusual events leading up to the information collection should not form the basis for new, rigid requirements applicable to all REMs. Alternatively, any new requirements should enable more flexibility based on the unique aspects of each REMS program.

D. RIC Responses to Five Questions Posed by FDA in this Information Collection

Given RIC's mission, we embrace this opportunity to study and consider ways to improve REMS service provider transitions. RIC members are fully committed to undertaking whatever measures may be warranted and to work together with service providers, FDA and the vast number of other stakeholders to avoid delays or interruptions in patient access to REMS-regulated medicines. Here are our responses to the five specific questions that FDA has posed.

1. **Comment on any stakeholder input that the applicant and/or REMS administrator should obtain prior to developing and implementing a new REMS system, including the extent and timing of stakeholder input.**

RIC recognizes the value and importance of stakeholder input throughout the lifecycle of a REMS program. This begins at the design and development stages and continues through implementation, modification (if applicable) and assessment.

This question asks about solicitation of stakeholder feedback "prior to developing and implementing a REMS system, including the extent and timing of stakeholder input" (emphasis added). While stakeholder feedback can be extremely valuable in certain circumstances, RIC strongly discourages a new requirement that would mandate stakeholder feedback before each REMS system is developed or implemented. A formal collection of stakeholder feedback should be undertaken (in advance of a REMS system update taking effect) only when it is justified because meaningful input is expected on one or more key areas of inquiries.

It is important to emphasize that FDA, together with sponsors, synthesize and assess vast amounts of data and experiences about the drug, the drug class, and its relevant therapeutic areas. All of that data and experience guides FDA's REMS program decisions. Stakeholder feedback (whether solicited or unsolicited) can serve as an important additional factor for consideration and assessment. Ultimately, however, flexibility remains a paramount value for nearly all aspects of REMS program development and management. We view that as especially true regarding whether, when, and how stakeholder feedback should be collected.

There are certainly circumstances when stakeholder feedback could be valuable with respect to a particular aspect of, for example, a planned substitution of service providers. But whether a formal solicitation of that feedback is warranted depends on whether there is an identified, *bona fide* value in formal collection of stakeholder input on particular topics in advance

of a REMS program update. In contrast, an omnibus requirement that would mandate soliciting feedback every time a new REMS program is approved, or a service provider substitution occurs is not justified.

Stakeholder feedback can at times be one of the most important and integral sources of ideas for how best to enable fulfillment of REMS objectives of prompt and safe patient access to medicines. It is important to also remember, however, that final authority for what actions, if any, should be taken with respect to REMS and stakeholder feedback rests ultimately with the FDA. FDA, in consultation with sponsors, must base such decisions on the wide universe of data sources that help inform REMS program-related decisions.

Without a doubt, stakeholder input has been, and will continue to be, an intrinsic part of every REMS program. By way of example, under current practices, stakeholder input is gathered through multiple approaches, such as Knowledge, Attitude, and Behavior (KAB) surveys, as well as direct feedback from sponsor field representatives, patients, and healthcare provider advisory boards. In addition, sponsors may also utilize various market research methodologies to inform how they manage their REMS programs.

RIC members recognize the various perspectives that different stakeholders can offer for REMS programs, and we value engagement with, and feedback from, stakeholders (whether sponsor- or stakeholder-initiated). However, flexibility should remain a key factor so that sponsors have discretion to determine when, whether, and how such feedback is solicited. The ultimate objective is to achieve as much value as possible from such inquiries while avoiding feedback fatigue that can arise when the same stakeholders are called upon too often and without a compelling need to drive such outreach.

2. **Comment on whether the sponsor and/or REMS administrator should conduct testing of the changes to the operation of the REMS system prior to full implementation including: user acceptance testing with stakeholders and evaluation of any unexpected impact on stakeholder workflow; and an assessment of REMS data flows, including whether REMS data from the existing REMS system can be timely and successfully transferred to a new REMS system.**

This question asks, "whether the sponsor and/or REMS administrator should conduct testing of the changes to the operation of the REMS system prior to full implementation" and names particular tests about which FDA seeks feedback. Again, the most valuable outcome here is for sponsors to have the flexibility they need to conduct the testing that makes sense for each particular circumstance.

Various factors play a role in what types of testing might occur before full implementation of a REMS. This is again not an instance where a "one size fits all" approach to how a REMS program (or a modification) should be tested or assessed before its launch makes sense.

An array of tests, assessment tools and approaches exist for sponsors and their third-party service providers to utilize. At its core, sponsors and third-party service providers must comply

with all applicable aspects of 21 CFR Part 11, which addresses in detail an extensive array of quality requirements that must be met.

RIC agrees that at times there may, indeed, be a value to conducting user acceptance testing with stakeholders – but there may not be a *bona fide* benefit in every instance of a REMS program creation or modification. The nature and extent of each REMS modification needs to inform whether particular tests or assessments will be valuable.

Likewise, there are various approaches – test case simulation scenarios, or pilot program roll-out, to name a few – that can be effective in aiding sponsors, in consultation with FDA, to ensure that any updates to a REMS program will work as intended.

We recognize and agree that changes to the operations of a REMS system that is undergoing a service provider transition, or is otherwise undergoing modification, must be handled with the utmost care and vigilance. It is also of the utmost importance for sponsors to have flexibility to engage with the right expertise and undertake the best approach to identify and address major pitfalls before full implementation of an updated REMS program occurs.

At the end, stakeholders exist along every step of the healthcare system and are vested in a REMS system that operates efficiently. Sponsors, and their service providers alike, need to undertake the steps necessary to ensure that updates to an existing REMS program are well-vetted before proceeding to implementation, utilizing whatever tools are most suited to achieve the particular circumstances that a new situation presents.

Importantly, in fact, sponsors do routinely undertake risk assessments before transition work begins or is implemented. They also routinely prioritize independent quality oversight by the service providers (in consultation with, and at the direction of, the sponsors). Ultimately, sponsors share with FDA the significant responsibility to undertake essential steps to prevent interruption in access to REMS medicines, while mitigating (as much as possible) safety risks to optimize patient outcomes to the farthest extent possible.

All this is to say that mandating one type of testing for every circumstance is not the answer. Already, sponsors are faced with compressed timelines (sometimes due to involuntary substitutions of service providers (as was the case in 2021-2022)). In other instances, compressed timelines may result from FDA-defined priorities or preferences. Steps taken should therefore always be reasonably likely to yield actionable information or feedback to guide an expeditious roll-out of the new REMS (or REMS update).

As stated elsewhere in this submission, ultimately FDA and sponsors have the primary responsibility to undertake a thoughtful, well-reasoned and "right-sized" approach for each REMS program and any modifications or updates that may be needed. Testing and assessments, as well as stakeholder input addressed in Question #1, may have a role, but sponsors should have flexibility to work with FDA to land on the right approach for what is needed for each particular REMS program.

Each REMS program is unique. Each may include components that may be similar (or even identical) to other REMS program components, but ultimately the REMS program in its entirety is "one of a kind" and a "one of a kind" approach is what is warranted.

With that said, RIC recognizes that there can also be tremendous value in standardization and uniformity, where appropriate. That is why the RIC Best Practices Working Group is now working on identifying ways that sponsors, service providers and others can work together to achieve a common and unified approach to particular aspects of REMS. Ultimately, rigid standardization and uniformity in approach is not the answer. We need to strive for intelligent, thoughtful, well-reasoned approaches, and in the end, consistency and standardization should be embraced when, and only when, the objectives of safe, prompt access to REMS products is specifically and meaningfully advanced.

3. **Comment on the amount of time needed to transition stakeholders from one REMS system to another REMS system (e.g., enrollment or recertification), and the factors that go into that time frame.**

It is difficult to ascertain the amount of time that may be needed to transition stakeholders in any given circumstance because there are so many factors that may impact the answer to that question. In addition, in many instances, the amount of time needed will not be fully appreciated until the process has begun and sponsors, service providers, and others begin to work through the various steps to achieve that transition.

The safeguards needed, and how to implement those safeguards, can vary significantly from one product to the next as well – even when products pose similar safety concerns. This is because various criteria may impact the REMS program and how it operates – including such criteria as the age and maturity of typical patients who utilize the drug, the frequency of use of the product, and the incidence of the safety concerns at issue, to name a few.

Ultimately, with regard to what amount of timing is sufficient, "when you have seen one REMS, you have seen one REMS." Stated simply, there can be no "one size fits all" approach in REMS and this is especially true when factoring in a transition of service providers, especially for an already operational REMS program. Because a limited pool of service providers typically handles much of the work needed for REMS to run smoothly, but how much any one particular service provider does varies widely from one REMS program to the next.

Likewise, it is essential to ensure ample opportunity for sponsors to have the time before (and potentially also during) implementation (such as by permitting a phased roll-out, or a pilot program for a particular region), to allow for the opportunity to address any issues before a REMS program in its entirety is transitioned completely to a new service provider. Such an approach enables sponsors and their service providers to take actions that will meaningfully improve processes, and expedite patient access, in a safe and effective manner.

In terms of overall timelines, RIC invites FDA to engage frequently with sponsors early in the launch timeline of a new REMS or of a significant REMS modification (or transition to a new service provider or transition to a shared system REMS). Sponsors should also be provided the

opportunity to request regular meetings, which should, when needed, occur promptly for the Agency to, for example, review launch timelines and preparedness well before final REMS approval is due.

RIC also strongly encourages FDA to keep the lines of communication open and to refrain from last-minute requests for changes or unexpected new requirements that are introduced late in the REMS modification development process. Indeed, last-minute requests or requirements often directly threaten a sponsor's ability to execute (or to effectuate a seamless transition to a new service provider). For these reasons, we encourage FDA to prioritize feedback early in the timeline as this will help to enable adequate lead time to address FDA feedback effectively. Feedback early in the process also helps ensure that there will be sufficient time for testing (when a particular type of testing is viewed as a valuable step in REMS program readiness).

Moreover, RIC recognizes and encourages FDA to continue their efforts on REMS integration and innovation (e.g., FDA's work with MITRE Corporation, through the CodeX initiative, to integrate health data standards into clinical workflows). Appropriate standardization – particularly when it is focused on open standards and implemented at a high level so as not to mandate particular technology or a single path to achieve that standard – will be extremely beneficial to all involved stakeholders.

FDA, RIC members, and various other stakeholders should also consider together how best to address the limited number of companies that have the knowledge, experience, and technical capabilities to serve as REMS service providers. The limited vendor pool is a major factor that directly impacts the ability of sponsors to ensure that REMS programs are not negatively impacted, especially at times of service provider transitions.

With this objective in mind, sponsors and FDA will need to work together to ensure that REMS program requirements are not tied to one specific or proprietary technology solution – particularly one that may be available from only one or two service providers. The service provider who pulled out of the REMS services market in 2021 utilized technology capabilities that were, by the time of that service provider's exit, possessed solely by that service provider alone. As a result, sponsors were unable to secure that exact technology capability from any other service providers. We welcome FDA joining with the RIC to consider how best to foster a robust marketplace of service providers when identifying requirements for particular REMS programs.

Finally, RIC welcomes FDA's help in encouraging additional service providers to pursue open innovation in REMS technology solutions. We are open to FDA's thoughts in this regard. As a starting point, we think tactics could include FDA communicating its commitment to flexibility for addressing how different technologies may be leveraged so long as REMS program objectives are met. These types of communications that emphasize flexibility and acceptance will, we think, help to spur technology innovation and advancement to benefit REMS.

Technology solutions are continuing to evolve, and we see FDA as having an important role as being the bellwether of embracing those new technologies and encouraging investment of time and money by both existing and new companies to develop capabilities to optimize REMS operations. It is essential that we create a climate of receptivity to technology innovation, as well

as an "open door" policy for inexperienced REMS providers to adapt their "technology know-how" to REMS program challenges and for RIC members and FDA to work side-by-side with them to guide them to success in navigating the ins-and-outs of REMS program operations. These are some ways that may be effective to encourage existing REMS service providers to expand their willingness and ability to meet REMS needs, and for new service providers to choose to participate, in providing REMS-related services.

Were FDA to accept this approach of embracing the expansion of the REMS service provider community, there will be times when a course-correction will be needed, and imperfections may occur as service providers expand their offerings and new service providers emerge to help with REMS. RIC commits to working diligently to minimize any disruptions in patient access to their medicines in such circumstances. A welcoming approach is needed if existing service providers (as well as new service providers who have the technological know-how to adapt their expertise to meet REMS needs) are to invest their time in money in solving REMS program needs. Service providers will make such investments if there is awareness of the opportunity, coupled with some level of certainty that there is no significant barrier to entry – such as a lack of, or limited experience, that will serve as a block to being selected as a REMS service provider.

Ultimately if we establish the right climate for investment, then the limited service provider pool will see expansion, leading to easier service provider transitions. In addition, innovation can be expected to prosper, as more service providers dedicate their time and effort to REMS.

4. **Comment on whether the sponsor and/or the REMS administrator should conduct a failure modes and effects analysis to identify and plan for system failures. This includes providing for adequate support services in the event that the system fails to work as intended following full implementation of the new REMS system.**

RIC member companies undertake a wide array of measures to prepare for the roll-out of an existing or updated REMS program. The question of whether a failure modes and effects analysis ("FMEA") may be warranted depends on a variety of factors such as the complexity of the particular REMS program being implemented and the nature of the services that a transition provider will be expected to provide. As each REMS program's requirements are unique, some REMS programs may warrant a FMEA, while others may not.

Ultimately, the conduct of any analysis should be based on the identified risk and assessment of applicable quality standards. It will naturally often be dependent on evaluation of past performance as well as any lessons learned (e.g., by the sponsor, the service provider, or the industry as a whole) that shed light on any expected challenges or pitfalls for the type of REMS-related action or service provider transition that is underway.

The criticality of the particular risks identified is a central component of this assessment. Decisions are made throughout the process of REMS program design and implementation, or modification. At each step of the process for REMS program management, various factors come into play (such as a REMS program's specific components, the existing strengths and weaknesses

of past evaluations and other information generally available about the objectives to be achieved and the expected pitfalls that may arise).

Stated another way, REMS programs are typically geared to address the standards that FDA deems essential to ensure safe access to drugs that have potentially serious adverse events. The circumstances of each new REMS program, or plan for modification, will be important to consider in determining whether a FMEA is recommended and warranted.

In fact, there are numerous methodologies for conducting quality risk management and each approach has its benefits and limitations, which must be considered in reaching a determination as to which may be best suited to any particular REMS program update. Existing quality management systems and standards, and especially 21 CFR Part 11, provide important criteria that guide how implementation, management, troubleshooting, and quality control are to be handled.

5. Comment on the metrics that the sponsor should capture to evaluate whether the REMS system was successfully and efficiently implemented.

The combined efforts of all participants within each REMS program provide, and aim to ensure, safe access to certain drugs with serious risks (that would otherwise not be approved and available on the market). Therefore, in the event of the launch of, or a major modification to, a REMS program, we endorse an approach under which sponsors gather and closely monitor program-specific metrics to quickly identify and address when system functionality may adversely impact patient access to a drug. These metrics may vary widely dependent upon the REMS program and its individual components.

Indeed, there are many different key performance indicators ("KPIs"), but these vary from one REMS program to another. This is the case whether we are focused on healthcare provider, patient or other stakeholder compliance, or on the understanding each requirement of a particular REMS program.

As a result, there are many factors that contribute to building a REMS program evaluation strategy that is strategically targeted to assess the particular and unique safety and patient access objectives that each individual REMS program seeks to achieve.

E. RIC Commitment to Excellence & Looking Ahead

Over the fifteen years that REMS have existed (and over the even longer span of time with RiskMAPs (i.e., the predecessor to REMS)), countless transitions of third-party service providers have occurred, and the vast majority have not resulted in undue delay or interruption to patient access.

This has been the case whether the transition was necessitated due to a sponsor-initiated, or third-party service provider-initiated, change. This is not intended to suggest that a "vast majority" of successes is good enough because even one mishap that results in patient delays or

interruptions in obtaining their medicine is too many. But it is important to recognize that REMS program that have resulted in interruptions in patient access to their medicines is not the norm.

RIC members are dedicated to working together to improve upon past successes and to identify "lessons learned" to enable on-going improvement in the REMS space. We appreciate the value of Congress' mandate that there be a review of how service provider transitions are conducted to identify best practices and avoid past pitfalls. We look forward to the valuable information derived from this FDA request for comments, as well as what the forthcoming GAO report will uncover. RIC members will seek to leverage those findings to inform their efforts on the many REMS systems that our RIC members are continuing to design, implement, and administer.

It cannot be overemphasized that flexibility remains paramount in REMS program development and management, and the need for flexibility and "right-sizing" an approach applies across the entire REMS system – from stakeholder feedback to pre-launch testing to timelines and metrics to measure success. The adoption of new standard REMS requirements must be carefully assessed. Standardization is valuable when there is a weighing of the benefits along with associated costs to assess whether sufficient value is derived from adding more requirements to apply across all REMS programs. In the end, it is unavoidable that the overall cost of REMS programs will have a direct impact on the entry (and exit) of brand and generic drug sponsors. We are today facing major challenges in our drug supply, including shortages of some drugs that are essential to patient care, as well as the on-going need to bring costs down to enable more expansive access to patient treatments. The decisions made today will directly impact all of this and it is therefore essential to proceed with full consideration of how requirements today will likely impact the marketplace of medicines tomorrow.

RIC is open to, and encourages the exploration of, additional opportunities to engage with prescriber groups, patient advocacy groups, and other stakeholders as the industry works together to achieve an appropriate balance between patient safety and access.

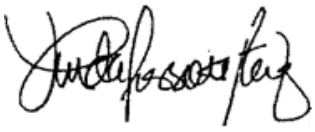
Looking ahead, it will be valuable if FDA prioritizes the importance of feasible timelines that allow for adequate time for sponsors (and their service providers) to take all necessary actions. We also encourage FDA whenever possible to avoid imposing additional, last-minute requirements or revisions for REMS (which we understand at times may be unavoidable and of course, we accept that this will sometimes be the case). When such last-minute requirements are unavoidable, these unanticipated developments can make it extremely difficult for sponsors to ensure that transitions occur without incident or delay. Whenever possible, it will be extremely helpful for there to be additional time allotted for sponsors to work with their service providers to undertake and execute on those newly added requirements.

Importantly, the actual time needed for REMS program establishment or updates, or for a service provider transition, may only reach clarity as efforts begin to undertake that transition. Flexibility is essential. It is critical that there be flexibility so that as new information comes to light or unexpected developments occur (such as with the control center technology underlying the REMS system, or with the many interfaces that must be made) there is the ability to pivot and time to execute a new approach to overcome any newly identified hurdles to success.

CONCLUSION

It remains the primary and central focus of RIC to support our members' development and delivery of medicines to patients who need them in an efficient, prompt, and safe manner. We are prepared to work with FDA, and with the many stakeholders who interact with REMS, to do whatever we can to learn from our past experiences and move forward with best practices that enable REMS programs to achieve their objectives. When a replacement service provider must be on-boarded, we are likewise committed to taking reasonable, targeted steps to achieve a smooth and seamless transition. In the end, it is of paramount importance, and it is what our most valued stakeholders – including patients, caregivers, physicians, pharmacies, and other healthcare providers – deserve.

Respectfully submitted,



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