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RE: Waivers of the Single, Shared System Risk Evaluation and Mitigation Strategy Requirement; Draft Guidance for Industry Dkt. No. FDA–2018–D–1043, 83 Fed. Reg. 25465 (June 1, 2018)

Dear Ms. Lippmann and Mr. Ripley:

The Leukemia & Lymphoma Society (LLS) appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) on the agency’s Draft Guidance for Industry, *Waivers of the Single, Shared System Risk Evaluation and Mitigation Strategy Requirement*, 83 Fed. Reg. 25465 (June 1, 2018) (Draft Guidance or Draft Waiver Guidance). As the world’s largest voluntary organization dedicated to the needs of blood cancer patients, LLS supports efforts to strengthen the healthcare system by breaking down barriers that stand between patients and their care. LLS serves the needs of blood cancer patients by working to find cures for leukemia, lymphoma, Hodgkin’s disease, and multiple myeloma, and by ensuring that blood cancer patients have sustainable access to quality, affordable, coordinated healthcare.

LLS Support for REMS and the Draft Guidance

LLS strongly supports the use of Risk Evaluation Mitigation Strategies (REMS), including those with Elements to Assure Safe Use (ETASU). Without such conditions, a product may not otherwise be available to patients due to its overall risk profile. A REMS with ETASU shifts the calculus so that the benefit of a product outweighs its risks, and allows for safer administration of products to the patients who need them most. Numerous products crucial to the treatment of blood cancers are subject to REMS or REMS with ETASUs.

LLS is deeply committed to assuring that blood cancer patients have access to innovative, high quality, and affordable care. To further that goal, balances must be struck between innovation and accessibility. FDA approval of new, efficacious drugs and biologics is critical; assurance that these novel, branded products will eventually be subject to robust, meaningful competition by generics and biosimilars is equally crucial. LLS believes that availability of generics and biosimilars that are equivalent to brand products at lower cost is vital to ensuring patients' access to lifesaving therapies. To that end, we are deeply concerned when REMS with ETASUs become barriers to patient access. Such burdens upon patients, as well as Abbreviated New Drug Application (ANDA) and § 351(k) applicants, run counter to Congress's intent to speed safe and effective generics and biosimilars to the public.

Section 505-1(i)(1)(B) of the Federal Food, Drug and Cosmetic Act (FDC Act or Act), 21 U.S.C. 355-1, requires that the ANDA holder use a Single Shared System (SSS) with the reference listed drug (RLD) for any ETASU. (Draft Guidance at Lines 63-64.) Though not provided for in the FDC Act, FDA similarly encourages applicants for a drug product submitted under § 505(b)(2) of the Act or a biosimilar product submitted under § 351(k) of the Public Health Service Act to work with the applicant for the product they are referencing to establish a SSS REMS with ETASU. See *Draft Guidance for Industry, Development of a Shared System REMS*, Lines 106-116 (June 2018) (Development REMS Draft Guidance). LLS strongly supports a SSS REMS between the ANDA or other license or application holder(s) and the application or license holder of the product referenced. A SSS will generally be more efficient to administer and erects only a single obstacle that patients and their healthcare providers must navigate.

Experience has shown, however, that some RLD application holders have stymied negotiations over development of an SSS with their would-be generic competitors, thereby delaying the introduction of the lower cost, equivalent products into the marketplace. LLS strongly opposes such conduct as it artificially maintains high costs to the detriment of patients and the healthcare system and impedes patient access to lifesaving therapies.

LLS believes that FDA should grant waivers from ANDA applicant participation in an SSS with ETASU where appropriate under § 505-1(i)(1)(B). Where FDA is able to work with ANDA applicants to develop a new REMS with measures comparable to those in the RLD's ETASU, we believe patients and the healthcare system are far better off with access to the generic drug or biosimilar. In a choice between a single drug with a single REMS or multiple, competing drugs under two comparable REMS, LLS strongly supports a competitive marketplace and multiple REMS.

The Draft Guidance aligns with § 505-1(i)(1)(B) and sets forth a reasonable and practical waiver process that properly balances burdens and benefits to application holders, patients, and healthcare providers while protecting patient health. In these comments, we offer suggestions for where the Draft Guidance might be expanded and/or clarified when finalized, particularly with regard to the FDA taking a more proactive role in initial SSS negotiations, and in the content of waiver requests under § 505-1(i)(1)(B)(ii).

Clear guidance is particularly important as negotiating an SSS can be burdensome. The process and standards set out in the Draft Guidance will profoundly affect resource decisions by companies, not only in the short-term, but for product development that may not reach the

agency for many years. We conclude these comments with a discussion of where further reforms may be needed to address abusive and anticompetitive practices that are harming patients' access to lower cost generic drugs that are as safe and effective as the RLD.

Section III, Benefits and Burdens of A SSS

LLS supports FDA's proposed factors to consider in weighing a waiver of the SSS requirement. (Draft Guidance at Lines 106-144.) We do believe, however, that the Draft Guidance could be strengthened where it addresses the burdens of creating an SSS that may be borne by healthcare providers and patients. FDA explains, correctly, that providers and patients "may be disadvantaged to the extent that access to a generic version of the drug is delayed pending the formation of a SSS REMS." (Draft Guidance at Lines 142-144.) We suggest adding language to indicate that if generic versions of a drug are not able to enter the market, patients and health care providers may bear higher costs, and that waiver applicants may therefore include information on these higher costs and other burdens in their waiver requests. For instance, information on the RLD's history of price increases should be considered by FDA when weighing the burdens to patients and healthcare providers when there is only one approved drug and a single REMS.

Section IV, Timing and Process for FDA Consideration of a Waiver

We commend FDA for summarizing the process of beginning negotiations for a SSS (Draft Guidance at Lines 147-153.), and addressing this issue in more detail in the Development REMS Draft Guidance. LLS believes that FDA should take a more proactive and visible role in the SSS negotiation process than described in the Draft Guidance. We suggest that FDA initiate the REMS negotiation process upon submission of an ANDA and not wait until it has been received for review. We also recommend that the agency set a clear timeline, with milestones and firm deadlines that the FDA expects the parties to meet. We ask that the agency commit to hosting regular teleconferences and in-person meetings where necessary. We believe that SSS negotiations are more likely to proceed smoothly and swiftly where FDA participates early, actively, and visibly. When finalizing this Draft Guidance and the Development REMS Draft Guidance, we suggest the agency adopt this more assertive and proactive stance.

The Draft Guidance provides that FDA will consider a waiver at any time, either upon the request of an applicant or on the Agency's own initiative. (Draft Guidance at Lines 157-160.) LLS strongly supports this flexibility. The Draft Guidance also establishes reasonable, flexible, and clear provisions on how to submit a waiver request and what information that request should include. The process, in our view, meets the standards of § 505-1(i)(1)(B)(i). However, we defer to the views of generic drug stakeholders on this issue.

The Draft Guidance states that FDA will determine whether a waiver is appropriate by analyzing whether the burden of forming a SSS outweighs the benefits of a SSS, taking into account the impact on healthcare providers, patients, the ANDA applicant(s), and the RLD application holder. (Draft Guidance at Lines 89-92.) This consideration and weighing of the relative benefits and burdens appears to align with § 505-1(i)(1)(B)(i) and LLS supports this articulation in the Draft Guidance. We note, however, that benefits to efficiency, simplicity, and cost sharing that may result from a SSS are unlikely to materialize if the parties cannot agree to SSS REMS terms. (See

April 13, 2015 Memorandum From Dale Conner, Pharm. D. Regarding Shared REMS Waiver Decision For Alosetron Hydrochloride and February 19, 2015 Memorandum From John R. Peters Regarding Shared REMS Waiver Extension For Buprenorphine-Containing Transmucosal Products.) Where a therapeutically equivalent generic drug would be available but for a SSS, we believe patients are better served with access to that generic even if there must be two comparable REMS. Accordingly, LLS recommends that the burdens and costs of no agreement on SSS REMS terms be specifically recognized in the Draft Guidance.

The Draft Guidance Should Address Waivers Under § 505-1(i)(1)(B)(ii)

Section 505-1(i)(1)(B) sets out two bases for a waiver request – under (i) as discussed above, where the burden of creating a SSS outweighs its benefits and under (ii) where an aspect of the ETASU for the RLD is claimed by a patent or trade secret and the ANDA applicant has been unable to obtain a license from the RLD application holder. The Draft Guidance acknowledges that it is primarily focused upon (i) waiver requests, not requests under (ii). (Draft Guidance at Lines 95-96.) As discussed above, LLS in significant part supports the Draft Guidance’s process for requests for waivers from SSS requirements under § 505-1(i)(1)(B)(i).

We respectfully submit that the Draft Guidance should provide a similar “roadmap” for seeking a waiver under § 505-1(i)(1)(B)(ii). The Draft Guidance addresses § 505-1(i)(1)(B)(ii) only within the context of a larger discussion of the content of the ANDA applicant’s waiver submission:

If applicable, discussion of the attempts made by the ANDA applicant to obtain a license to an aspect of the ETASU that is protected by an unexpired patent or, alternatively is a method or process that, as a trade secret, is entitled to protection. (Draft Guidance at Lines 213-215.)

We believe that providing additional guidance to stakeholders on the process for seeking waivers from ETASUs protected by patent or trade secrets would be very useful as we have seen, in our experience, increasing instances of RLD holders successfully using their ETASU-related patents to harass and delay generic competitors and thwart patient access to generic drugs.

We suggest expanding the Final Guidance to expressly address a (ii) waiver request. Among other things:

- The applicant’s request for a waiver should clearly identify in the cover letter and submission whether the waiver is being sought under § 505-1(i)(1)(B)(i) or § 505-1(i)(1)(B)(ii), or both.
- Section 505-1(i)(1)(B)(ii) requires the applicant for the SSS waiver to “certify” that it has sought and been unable to obtain a license for use of the protected or patented aspect or aspects of the ETASU for the applicable drug. To provide clarity for waiver applicants, we recommend that FDA provide an example of the contents of an adequate certification that is modeled upon other certifications the agency requires and the

language of (ii). For example, the final Guidance could suggest submission of a certification modeled upon the following:

I certify that, to my best knowledge and belief, (a) an aspect or aspects of the elements to assure safe use for [name of applicable listed drug] is subject to a patent that has not expired or is a method or process that is asserted by [name of applicable listed drug application holder] as a trade secret entitled to protection, and (b) I have sought and been unable to obtain a license for use of the aspect or aspects of the elements to assure safe use for [name of applicable listed drug].

- From the January 17, 2017 Memorandum From Trueman Sharp Regarding Waiver Of The SSS REMS For Xyrem (Sodium Oxybate Oral Solution) (Sodium Oxybate SSS Waiver Memo), it is clear that the ANDA applicant included information regarding its failed attempts to obtain a license from the RLD application holder. It is equally clear that § 505-1(i)(1)(B)(ii) does not require the submission of anything other than a certification. However, particularly in cases where FDA has not been actively involved in the failed SSS negotiations, LLS believes that it would be useful to the expeditious consideration of the waiver request and a demonstration of the RLD application holder's delaying conduct, if the ANDA applicant seeking a SSS waiver provided a timeline of its efforts to obtain a license and relevant correspondence. We recommend that FDA make this suggestion to ANDA waiver applicants in the final Guidance.

The Sodium Oxybate Waiver Memo contains an important concept that we believe should be included in the final Guidance. On page 20, in describing the licensing dispute between the RLD application holder, Jazz, and the ANDA applicant(s) seeking the waiver from the SSS requirement, the agency states:

As with the shared REMS negotiations, the patent license negotiations seem to be described differently by Jazz and the ANDA [redacted]. It would be difficult for FDA to assess the merits of these respective positions, but the statute does not require us to do so. Under [§ 505-1(i)(1)(B)(ii)], the Agency may waive the SSS requirement if (1) an aspect of the ETASU for the applicable listed drug is claimed by a patent that has not expired; and (2) an ANDA applicant certifies that it has sought a license for use of an aspect of the ETASU and that it was unable to obtain a license. Both criteria are satisfied here. Sodium Oxybate Waiver Memo at 20 (footnotes omitted).

We recommend that FDA be equally clear in the Final Guidance that these are the sole criteria for the grant of a waiver from the SSS requirement pursuant to § 505-1(i)(1)(B)(ii).

Lastly, in footnote 61 of the Sodium Oxybate Waiver Memo, FDA addresses the argument that the agency should have sought to negotiate a voluntary agreement with the patent holder upon receiving a waiver request from the ANDA applicant under § 505-1(i)(1)(B)(ii). The agency disagrees, characterizing its authority as not one it is obligated to exercise, stating "The authority to negotiate a voluntary agreement with the patent owner is discretionary, and given the longstanding disagreement between the parties over the SSS REMS and related patent issues, FDA declines to invoke this discretionary authority here." As discussed above, LLS

supports FDA taking an active, aggressive, and early role in the SSS negotiations between an ANDA applicant and the RLD application holder to encourage a swift resolution. Nevertheless, we also agree that the agency's decision to not participate in the negotiation in no way impacts the ability of an ANDA applicant to seek and obtain a waiver from the SSS requirement pursuant to § 505-1(i)(1)(B)(ii). We recommend that FDA make this point explicit in the Final Guidance.

Section V. Comparability of Separate REMS

The FDC Act authorizes FDA to waive the SSS requirement under either (i) or (ii) of § 505-1(i)(1)(B) and permit the ANDA applicant “to use a different, comparable aspect” of the ETASU. § 505-1(i)(1)(B). The Draft Guidance incorporates a rubric for evaluating comparability between the ANDA applicant's proposed REMS and the one covering the RLD, stating “[A] separate system for ETASU with a waiver of the SSS requirement must include the same ETASU as described in the statute.” (Draft Guidance at Lines 224-226.) The Draft Guidance provides the example that if the RLD's ETASU consists of prescriber certification and dispensing only in certain healthcare settings, “the ANDA's separate REMS must include those elements as well.” (Draft Guidance at Lines 226-229.)

Although we are concerned by FDA's statement that the ANDA's separate REMS must include the “same ETASU” as the RLD's ETASU, our concerns are ameliorated by the agency's interpretation of the term “different, comparable aspect” of the ETASU under § 505-1(i)(1)(B). LLS is pleased that the Draft Guidance permits “a separate REMS for ANDA applicants to use different methods or operational means to effectuate a REMS requirements, provided the program achieve the same level of safety.” We believe this standard will substantially ease the development of REMS that are the subject of a § 505-1(i)(1)(B) SSS waiver, thereby speeding the introduction of generic competition, while ensuring the same level of patient safety achieved under the RLD's ETASU.

LLS Supports Greater Authority For FDA And Legislation To Prevent Abuse

Holders of approved applications must not use any ETASU to block or delay approval of another application. (§ 505-1(f)(8); Draft Guidance at Lines 169-175.) Nevertheless, LLS continues to observe anticompetitive conduct by RLD application holders that hinders the entry of generic competitors into the market, resulting in higher costs for patients, payers, and the healthcare system. While we fully support both the Draft Development Guidance and the Draft Waiver Guidance, these guidances cannot change FDA's current authority. FDA can encourage and support SSS negotiations and shame companies that engage in blocking and delaying tactics, but the agency's statutory authority remains unchanged and limited. We are particularly concerned that even where FDA waives the SSS requirement, the presence of patents on the ETASU for the RLD will continue to chill and threaten generic competition if the ANDA applicant believes it cannot avoid infringement.

Accordingly, LLS encourages FDA to work with Congress to pursue patent reforms that will reduce the risk of infringement that ANDA applicants confront from REMS-related patents. Congress could consider deeming REMS methods or systems patents as within the “prior art,” thereby limiting patent claims that branded companies have used to delay generic competition on REMS products. We suggest also that FDA consider re-examining its policy on listing REMS-



related patents in the Orange Book and consider delisting the REMS-related patents listed there. Taken together, these actions would speed patient access to generic alternatives to costly branded medications, while maintaining the public safety protections that have proven so beneficial to patients who rely on drugs that would not receive FDA approval except under a REMS program.

LLS thanks FDA for the opportunity to provide comments and suggestions on FDA's Draft Guidance. If you have any questions, please contact me at Bernadette.Odonoghue@lls.org or Liza Holder, Director, Policy, at Liza.Holder@lls.org.

Sincerely,

A handwritten signature in black ink that reads "Bernadette O'Donoghue".

Bernadette O'Donoghue
Vice President, Office of Public Policy
The Leukemia & Lymphoma Society