HORSESHOE CRAB RECOVERY COALITION

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RE: PF 46(6) [Nov.-Dec. 2020]

On behalf of the Horseshoe Crab Recovery Coalition, we are writing in response to your Request for Input to the "General Chapter Prospectus: Use of Recombinant Reagents in Bacterial Endotoxins Test"[1] regarding your plan to develop a new informational chapter <1085.1> regulating use of recombinant reagents in the bacterial endotoxins test, instead of proceeding with your original plan of revising USP Bacterial Endotoxins Test General Chapter <85> to include recombinant Factor C (rFC) as an equivalent alternative to biologically-sourced tests derived from Limulus Amebocyte Lysate (LAL).

As we shall explain in this letter, we are requesting that USP do the following:

1. Move as quickly as possible to expand adoption of rFC with the fewest barriers for drug manufacturers.
2. Based on your commitment to transparency and public disclosure[2], make publicly available for further discussion and debate:
   a. the "stakeholder input" that drove this policy change, and
   b. minutes of the Microbiology Expert Committee meeting where this change was decided
3. Specify the criteria, including the "real world data[3]" that you believe is missing from the published literature and necessary for your endorsement of rFC for endotoxin testing.[4]

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[1] https://www.uspnf.com/notices/bacterial-endotoxins-gc-prospectus-20200529

[2] https://www.usp.org/legal-notices/document-disclosure-policy

[3] https://in.reuters.com/article/lonza-crabs/drugs-standards-group-nixes-plan-to-kick-pharmas-crab-blood-habit-idINKBN23702I

[4] https://doi.org/10.1371/journal.pbio.2006607

As fellow organizations that serve the public interest, we recognize and support the primary mission of USP in ensuring patient safety. As science-based, data-driven organizations we are equally compelled to evaluate policy using established empirical tools.

With the assistance of experts in microbiology we have evaluated the published, peer-reviewed data comparing rFC and LAL, using a wide range of "real-world" samples from diverse pharmaceutical product manufacturing processes. We understand there have been over 200 pharmaceutical products studied using rFC – providing significant real-world data with biologics such as vaccines and antibodies, a range of raw materials, active pharmaceutical ingredients, clinical trial samples, and small molecule drug products.

Thus, we are dismayed that USP and the Microbiology Expert Committee did not arrive at the same conclusion as the European Pharmacopeia – that rFC, with the same enzymatic mechanism of detection as LAL, is an equally valid method for detecting bacterial endotoxins, and should be interchangeable with assays based on LAL. Indeed, by lagging behind the policy updates of peer Pharmacopeias, the USP is delaying global harmonization, thus adding complexity and cost to biopharma industry stakeholders.

It is critical for companies to have the option of using synthetic rFC kits to test for endotoxin in their products, without having to go through burdensome and expensive re-validation of their processes. Particularly in the era of COVID-19, there is a need to remove all unnecessary barriers that could potentially hamper scale-up of promising vaccines and therapeutics. While the LAL producers claim that there is no limit to the supply of their tests, the Atlantic horseshoe crab is, in essence, a sole source for endotoxin assays, and USP should agree that for critical quality reagents, multiple sources – not just multiple manufacturers dependent on the same sole source – are essential. Horseshoe crab populations have been under threat for decades, and their availability for biomedical supply cannot be viewed as sustainable.

Given USP's "commitment to seeking alternatives to animal-based products wherever possible," there is a compelling argument for moving more quickly toward adoption of a synthetic alternative. Notwithstanding the claims of the LAL manufacturers – unsupported by either transparency or independently reviewed data, hundreds of thousands of crabs are subjected each year to capture, extended time out of water in harsh conditions, bleeding, and return to waters different from where they were caught, with a substantial impact on viability and breeding potential. As you know, this has a knock-on effect to the populations of many species that depend on the horseshoe crabs, especially migratory shorebirds.

We believe that the literature, independent expert opinion, the policy decisions of peer Pharmacopeias, and the commitment of several biopharma manufacturers to convert to rFC with no diminution of patient safety together provide compelling support for affirming the rFC tests as functionally equivalent in their ability to ensure safety and sterility of injectable drugs. The problems of sustainable supply, animal welfare, and environmental conservation will be solved if industry can convert freely to synthetic rFC products that offer equivalent or greater performance, and limitless supply.

Moreover, we believe that on a topic that affects so many issues and stakeholders, transparency is absolutely essential to a coherent process that reflects the integrity and values of your organization. In the interest of open scientific decision-making, we urge you to open your

process to share the data, influencers, rationales and decisions that have led to your current position. We stand ready to engage in dialogue with the USP on this matter at any time.

Sincerely yours,

Members of The Horseshoe Crab Recovery Coalition including:

American Littoral Society

Anglers Conservation Network

Audubon Connecticut

Audubon Maryland-DC

Audubon New York

Audubon South Carolina

Maryland Ornithological Society

National Audubon Society

National Wildlife Federation

New Jersey Audubon

New York City Audubon

North Carolina Wildlife Federation

Revive and Restore

The Charleston Audubon and Natural History Society

Wildlife Restoration Partnerships