

September 24, 2020

Steven Hahn  
Commissioner  
Food and Drug Administration  
10903 New Hampshire Ave  
Silver Spring, MD 20993-0002

**Comment Regarding the Citizen Petition from bioMerieux: FDA-2020-P-1405-0001**

Dear Commissioner Hahn:

On behalf of the undersigned groups in Atlantic Coastal States and beyond who care about birds, we write to support bioMerieux's Food and Drug Administration (FDA) Citizen Petition, calling on the FDA to recognize the synthetic alternative to horseshoe crab blood for biomedical use.

For the past 40 years, proteins in horseshoe crab blood have contributed to ensuring safe vaccines and medications. Horseshoe crab blood contains a unique type of blood cell that is made into an aqueous extract called Limulus ameocyte lysate (LAL), which is sensitive to endotoxins. LAL is used for endotoxin detection in biopharmaceutical products. LAL is produced through the process of bleeding horseshoe crabs, and leaves thousands of crabs dead every year. According to the Atlantic States Marine Fisheries Commission (ASMFC), "a 15% mortality rate is assumed for all crabs that are released."<sup>1</sup> In 2018, about half a million crabs were harvested and bled, with ASMFC's estimated mortality, 75,000 died after being released back into the wild.<sup>2</sup> This process is unsustainable not only for the horseshoe crabs, but the shorebirds and other wildlife that depend on horseshoe crab eggs for food.

Horseshoe crab eggs are the primary food source for and vital to the survival of Atlantic Coast shorebirds, fish, and other marine organisms. In the late spring and early summer, thousands of horseshoe crabs lay their eggs on Atlantic Coast beaches. At the same time, shorebirds on their northbound migrations, many going to Arctic breeding areas, arrive on Atlantic Coast beaches to replenish their energy for the next leg of migration. Their migrations are timed to coincide with the abundance of horseshoe crab eggs on beaches. Without this important food, shorebirds may perish during migration or may arrive in the Arctic in a condition too poor to breed successfully.<sup>3</sup>

For example, the federally threatened Red Knot relies on horseshoe crab eggs for survival. Every spring, Red Knots travel over 9,000 miles from the tip of South America to Arctic Canada. During this journey, they stop at key refueling spots, usually in Brazil and along the U.S. Atlantic Coast. Places like coastal Georgia, South Carolina, and Delaware Bay are critical stopover

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<sup>1</sup> Schmidtke, Dr. Mike, Eyler, Sheila, Michels, Stewart, Wright, Chris, Ebbin, Dr. Syma. 2018 Review of the Atlantic States Marine Fisheries Commission Fishery Management Plan for Horseshoe Crab. Atlantic States Marine Fisheries Commission. 2018. <http://www.asmfmc.org/files/Meetings/77AnnualMeeting/HorseshoeCrabBoardSupplemental.pdf>

<sup>2</sup> Schmidtke, Dr. Mike, Eyler, Sheila, Michels, Stewart, Wright, Chris, Ebbin, Dr. Syma. 2019 Review of the Atlantic States Marine Fisheries Commission Fishery Management Plan for Horseshoe Crab. Atlantic States Marine Fisheries Commission. Oct. 2019. [http://www.asmfmc.org/uploads/file/5e0fa319HSC\\_FMPReview\\_2019.pdf](http://www.asmfmc.org/uploads/file/5e0fa319HSC_FMPReview_2019.pdf)

<sup>3</sup> The Horseshoe Crab. U.S. Fish and Wildlife Service Northeast Region. Aug. 2006. <https://www.fws.gov/northeast/pdf/horseshoe.fs.pdf>

areas. Red Knots need a lot of food—specifically horseshoe crab eggs—to complete their long journey. Horseshoe crab populations collapsed in the 1990s as unregulated crab harvests grew from about 100,000 to 2.5 million per year by 1998. This loss of crabs and the eggs that are vital for Red Knots is a top reason that from 2000 to 2016, Red Knot populations declined by 75 percent at key stopovers and could face extinction.<sup>4</sup> When Red Knots and other shorebirds don't eat enough eggs, they take longer to get to their final nesting grounds and, once there, they may not be able to breed.<sup>5</sup>

Fortunately, science has shown there is a viable, more effective, and synthetic alternative to LAL and if implemented, would save thousands of horseshoe crabs from dying every year.<sup>6</sup> The synthetic alternative is called recombinant Factor C (rFC) and was produced in a lab by the National University of Singapore and Lonza (a chemicals and biotechnology company) by cloning from horseshoe crab blood, which produces the same results as LAL. rFC has been widely recognized and used as a viable alternative to LAL. The European Directorate for the Quality of Medicines announced that companies can begin using rFC for bacterial endotoxin testing.<sup>7</sup> Additionally, Japan and China have approved rFC as an alternative to LAL.<sup>8,9</sup> Over 200 pharmaceutical products have been reported as using rFC in a wide array of categories including active pharmaceutical ingredients, vaccine development, excipients and raw materials, clinical trial samples and others.<sup>10,11</sup> For example, pharmaceutical company Eli Lilly has committed to transitioning 90 percent of their tests from processes that rely on horseshoe crab bleeding to using rFC.<sup>12</sup> As a result of the transition, two of their products are now using rFC - Emgality® and Lyumjev™.

The production of a COVID-19 vaccine requires a plethora of endotoxin-free biopharmaceutical materials. Recognizing rFC as an equivalent to LAL is essential to the successful testing, production, and rollout of a COVID-19 vaccine, because it is more consistent and reliable.<sup>13</sup> In turn, manufacturing and testing processes are easier to control and access and are more sustainable. If we continue to rely on LAL for vaccine production, the instability of the horseshoe crab population could potentially put any progress toward a COVID-19 vaccine in jeopardy. Protecting horseshoe crabs can also boost coastal economies. Coastal communities benefit from leaving horseshoe crabs in the water, as their eggs serve as the base of the ocean food chain for a variety of wildlife, including shorebirds, fish, and other marine species. These larger

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<sup>4</sup> Rufa Red Knot. [U.S. Fish and Wildlife Service Northeast Region. Sept. 2019. https://fws.gov/northeast/red-knot/](https://fws.gov/northeast/red-knot/)

<sup>5</sup> Duijns, Sjoerd, Niles Lawrence J., Dey Amanda, Aubry Yves, Friss Christian, Koch Stephanie, Anderson Alexandria M. and Smith Paul A.. 2017 Body condition explains migratory performance of a long-distance migrant. *Proc. R. Soc. B.* **284**: 20171374 <https://royalsocietypublishing.org/doi/full/10.1098/rspb.2017.1374>

<sup>6</sup> Maloney T, Phelan R, Simmons N (2018) Saving the horseshoe crab: A synthetic alternative to horseshoe crab blood for endotoxin detection. *PLoS Biol* 16(10): e2006607. <https://doi.org/10.1371/journal.pbio.2006607>

<sup>7</sup> Reich, Johannes, Deutschmann, Sven. General chapter on the rFC test adopted by the European Pharmacopoeia Commission. *BioMerieux*. Feb. 2020. <https://www.europeanpharmaceuticalreview.com/article/113332/general-chapter-on-the-rfc-test-adopted-by-the-european-pharmacopoeia-commission/>

<sup>8</sup> Japanese Pharmacopoeia - Draft Chapter of alternative Endotoxin Testing. ECA Foundation, Mannheim. 2019. <https://www.gmp-compliance.org/gmp-news/japanese-pharmacopoeia-draft-chapter-of-alternative-endotoxin-testing>

<sup>9</sup> The pharmacopoeia rFC Guidelines Chapters 1143 and 9251. 2020.

<sup>10</sup> An Interview with Ryan Phelan: Using Biotechnology to Revive Endangered Species and Restore Damaged Ecosystems. *Revive & Restore*. July 2020. <https://reviverestore.org/an-interview-with-ryan-phelan/>

<sup>11</sup> Bolden, Jay, Smith, Kelly. Application of recombinant Factor C reagent for the detection of bacterial endotoxins in pharmaceutical products. *PDA Journal of Pharmaceutical Science and Technology* 74(4). July 2017. <https://journal.pda.org/content/early/2017/07/17/pdaipst.2017.007849>

<sup>12</sup> Environmental Sustainability. Eli Lilly. <https://www.lilly.com/operating-responsibly/environment-sustainability>

<sup>13</sup> Piehler, Maike, Roeder, Ruth, Blessing, Sina, Reich, Johannes. Comparison of LAL and rFC Assays—Participation in a Proficiency Test Program between 2014 and 2019. *Microorganisms*. 8(3): 418. March 2020. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7143553/>

species in turn support many of the ecotourism businesses on the Atlantic Coast, from dolphin cruises to charter fishing. For example, throughout the Delaware Bay, horseshoe crab-dependent ecotourism generates up to \$34 million in spending.<sup>14,15</sup> In Cape May, New Jersey alone, this ecotourism generated \$7-10 million in spending and 120-180 jobs per year.<sup>16</sup> Switching to the synthetic alternative benefits the pharmaceutical industry. One pint of horseshoe crab blood is estimated to be worth \$15,000.<sup>17</sup> By using the synthetic alternative, ending the reliance of available horseshoe crabs and the physical process of bleeding horseshoe crabs, pharmaceutical companies may decrease costs while achieving the same results.

Despite successful use in the biomedical field and science showing rFC is viable and more effective, the US Pharmacopeia, the decision-making body that must approve biomedical processes, has not accepted rFC as an equivalent to LAL. The undersigned groups urge the FDA to review existing regulations and guidance to identify opportunities to recognize rFC as an equivalent to LAL. By doing this, thousands of horseshoe crabs, birds, and other marine wildlife will benefit.

Sincerely,

#### **California**

California Academy of Sciences  
Endangered Habitats League  
Environmental Protection Information  
Center  
Revive & Restore  
Scripps Research  
University of California, Merced

#### **Connecticut**

Audubon Connecticut  
Connecticut Audubon Society  
Connecticut Ornithological Association  
Litchfield Hills Audubon Society  
Mattabesock Audubon  
Menunkatuck Audubon Society  
Quinnipiac Valley Audubon Society

#### **Delaware**

BioFeyn  
Christian Council of Delmarva  
Delaware Audubon Society

#### **Florida**

Apalachee Audubon Society  
Audubon Everglades  
Audubon Florida  
Audubon of Martin County  
Audubon of Southwest Florida  
Audubon of the Western Everglades  
Choctawhatchee Audubon Society  
Clearwater Audubon Society  
Duval Audubon Society  
Four Rivers Audubon Society  
Francis M Weston Audubon Society  
Hendry-Glades Audubon Society  
Hernando Audubon Society  
Kissimmee Valley Audubon Society  
Marine Resources Council  
Marion Audubon Society  
Oklawaha Valley Audubon Society  
Orange Audubon Society  
Peace River Audubon Society  
Pelican Island Audubon Society  
Sanibel-Captiva Audubon Society

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<sup>14</sup> Niles, Lawrence J. et al. Effects of Horseshoe Crab Harvest in Delaware Bay on Red Knots: Are Harvest Restrictions Working? *BioScience*. 59(2): 153-164. Feb. 2009. <https://academic.oup.com/bioscience/article/59/2/153/228348>

<sup>15</sup> Eubanks, Ted; Stoll, Paul Kerlinger. 2000 "Wildlife-associated Recreation on the New Jersey-Delaware Bayshore, The Economic Impact of Tourism Based on the Horseshoe Crab-Shorebird Migration in New Jersey". 16 February 2000. Prepared for the NJ Dept of Environmental Protection.

<sup>16</sup> Walls, Berkson & Smith, The Horseshoe Crab, *Limulus Polyphemus*: 200 Million Years of Existence, 100 Years of Study, Reviews in Fisheries Science, 2002.

<sup>17</sup> Nature PBS Special. 2008. Crash: A Tale of Two Species

Santa Fe Audubon Society  
Sarasota Audubon Society  
Seminole Audubon Society  
South Florida Audubon Society  
Space Coast Audubon Society  
St Lucie Audubon Society  
St. Johns County Audubon Society  
Tampa Audubon Society  
Tropical Audubon Society  
University of Miami  
West Pasco Audubon  
West Volusia Audubon

### **Georgia**

Altamaha Coastkeeper  
Coastal Georgia Audubon Society  
Georgia Audubon  
Georgia Shorebird Alliance  
Ogeechee Riverkeeper  
One Hundred Miles

### **Hawaii**

Conservation Council For Hawaii

### **Indiana**

Indiana Audubon

### **Maryland**

Audubon Maryland-DC  
Audubon Society of Central Maryland  
Chesapeake Audubon Society  
Maryland Bird Conservation Partnership  
Maryland Ornithological Society  
Southern Maryland Audubon Society

### **Massachusetts**

Manomet, Inc.  
Mass Audubon  
MIT Media Lab

### **Michigan**

Michigan Audubon

### **New Jersey**

American Littoral Society  
Flying Fish Brewing Co.  
New Jersey Audubon

ReTurn the Favor, NJ  
The Wetlands Institute  
Unexpected Wildlife Refuge  
Wildlife Restoration Partnerships

### **New York**

Audubon New York  
Bedford Audubon Society  
Bronx River - Sound Shore Audubon Society  
Central Westchester Audubon Society  
Delaware-Otsego Audubon Society  
Eastern Long Island Audubon Society  
Four Harbors Audubon Society  
Genesee Valley Audubon Society  
Hudson River Audubon Society of Westchester  
Huntington-Oyster Bay Audubon Society  
New York City Audubon Society  
North Shore Audubon Society  
Northern Catskills Audubon Society, Inc.  
Northern New York Audubon  
Onondaga Audubon Society  
Orange County Audubon Society  
Saw Mill River Audubon Society  
South Shore Audubon Society  
SUNY-ESF

### **North Dakota**

Dakota College at Bottineau

### **North Carolina**

Audubon North Carolina  
Blue Ridge Audubon Chapter  
Blue Ridge Audubon Society  
Cape Fear Audubon Society  
Mecklenburg Audubon Society  
New Hope Audubon Society  
North Carolina State University  
North Carolina Wildlife Federation  
Piedmont Bird Club  
T. Gilbert Pearson Audubon Society  
Transylvania County Bird Club  
Wake Audubon Society

**Pennsylvania**

Allegheny Plateau Audubon Society  
Audubon Pennsylvania  
Audubon Society of Western PA  
Bucks County Audubon Society  
Conococheague Audubon Society  
Lehigh Valley Audubon Society  
Presque Isle Audubon Society  
Quittapahilla Audubon Society  
Seven Mountains Audubon  
South Mountain Audubon Society  
Valley Forge Audubon Society  
Wyncote Audubon Society

**South Carolina**

Audubon South Carolina  
Charleston Audubon and Natural History  
Society  
Columbia Audubon Society of South  
Carolina

South Carolina Wildlife Federation  
Sun City Hilton Head Bird Club  
Waccamaw Audubon Society

**Virginia**

Audubon Society of Northern Virginia  
Cape Henry Audubon Society

**Washington**

Pembient

**Washington, D.C.**

DC Audubon Society

**National/International**

bioMerieux  
Endangered Species Coalition  
National University of Singapore  
University of New South Wales