

Nature action case study

Horseshoe crabs

At AstraZeneca, we are following the science to minimise our impacts and sustainably manage our dependencies on nature.

For decades, the pharmaceutical sector has been dependent on the blood of horseshoe crabs, a key ingredient needed for bacterial endotoxin testing (BET). BET is a regulatory requirement for testing a subset of pharmaceuticals and medical devices. The test uses Tachypleus or Limulus Amoebocyte Lysate (TAL and LAL), extracts from the blood of horseshoe crabs from Asia and North America to ensure that injectable medicines are safe for patient use. Historically, horseshoe crabs have been the only available source of TAL and LAL.

We aim to responsibly manage this dependency on nature, balancing the importance of patient safety and compliance with regulatory requirements and the critical role that horseshoe crabs play within their ecosystems, which are under pressure.

Our sector's reliance on horseshoe crabs

Horseshoe crab blood has a unique coagulative property that detects endotoxins. This has been used to provide the reagent used for the testing of vaccines, injectable medicines, and medical devices.¹ Management of horseshoe crabs in the US is under the oversight of the Atlantic States Marine Fisheries Commission, who reported that, in 2022, approximately 911,826 *Limulus polyphemus* were collected for LAL production, with an estimated mortality rate of 15%.²

Background on the testing requirements

Our medicines are manufactured under strictly controlled conditions requiring measures to prevent and minimise the possibility of endotoxin contamination. Endotoxins are resistant to sterilisation techniques used in manufacturing and pose a high risk to patient health if they enter the bloodstream. Quality control testing is therefore critical to ensure patient safety. Testing is performed throughout the manufacturing process:

Water systems

- Validated process taken at manufacturing sites to ensure water systems are performing properly and remain free of contamination

Raw materials and critical components

- Many ingredients in our medicines are tested for endotoxin prior to use

Product samples

- Samples are taken at various points during the manufacturing process, including a final sample for safe release of each batch

Regulatory requirements

The US Pharmacopeia, which provides quality standards for our sector in the US, now includes the use of a synthetic alternative for BET in USP <86>, which became available for early adoption in November 2024. This enables the transition away from the use of horseshoe crab blood. As a highly regulated industry, the processes to make this transition are complex and extensive. For existing products, the transition to a synthetic alternative will have to be assessed and deemed suitable, after which regulatory filing must be completed in all markets where each individual medicine is approved. There may be some products where synthetic alternatives are not suitable, requiring the continued use of horseshoe crab reagents.

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7612741>

2. Atlantic States Marine Fisheries Commission. (2024). Horseshoe crab stock assessment update. Atlantic States Marine Fisheries Commission. <https://asmfc.org/resources/science/stock-assessment/horseshoe-crab-stock-assessment-update-2024/>

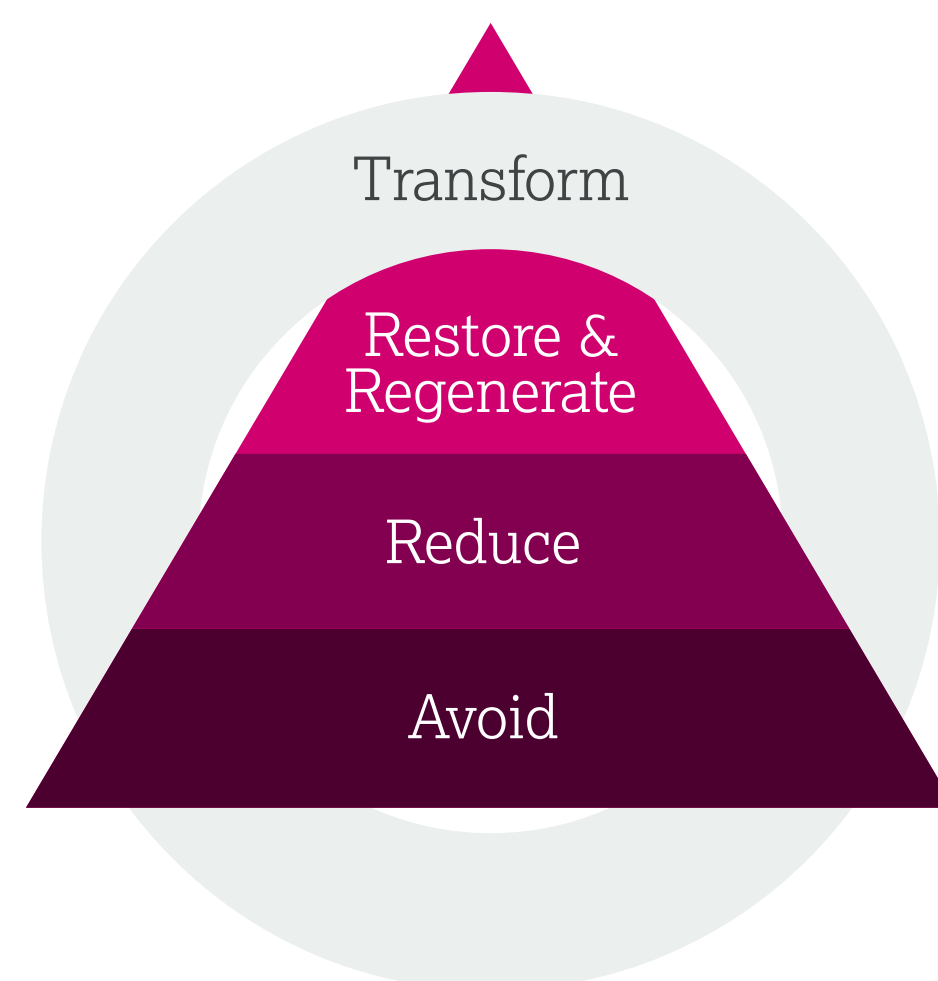
Horseshoe crabs and their ecosystems

There are four surviving species of horseshoe crabs. The Atlantic species is found along the East Coast of North America and the other three (tri-spine, coastal and mangrove) are found in South and Southeast Asia. While the North American horseshoe crab population is managed, the Asian species are endangered and threatened with extinction. All species are under pressure for reasons beyond the use of their blood within the pharmaceutical sector, including loss of habitats from coastal development, extreme storms, pollution, and use from other sectors such as fisheries also contributing to their decline.

Horseshoe crabs have been referred to as a “keystone species”, as their removal from the ecosystem would impact other species. There is increasing public awareness around the relationship between horseshoe crabs and migratory shorebirds. The horseshoe crab mating season aligns with the timing of the birds’ migration through the region. The spawning of horseshoe crabs on the beaches provides eggs that are a critical food supply for migrating bird species including the rufa red knot in the Americas and other sandpiper species in both the Americas and Asia. Many of these birds are also listed within the International Union of Conservation (IUCN) red list, in part because of declining horseshoe crab populations.^{3, 4, 5, 6}

Taking Action

We are following the Science Based Targets for Nature AR3T framework – Avoid, Reduce, Restore, Regenerate, and Transform – to guide us in identifying opportunities to make a positive impact on the ecosystems that we depend on and contribute toward efforts to halt and reverse the decline of horseshoe crab populations.



Avoid and Reduce:

In 2022, we published our short, mid- and long-term [strategy](#), outlining actions needed to optimise endotoxin testing in order to minimise our dependence on horseshoe crab blood.

Key actions include:

Completed and ongoing	Implementation started	Plans in progress
<ul style="list-style-type: none"> We have implemented the use of microfluidic technology as our standard for water testing, which reduces the horseshoe crab lysate used by over 90% compared to testing methods that were replaced, in-line with the 3Rs principles (Replacement, Reduction and Refinement) and our Values. We are working to align with the Principles of the Pharmaceutical Supply Chain Initiative (PSCI). The Use of Horseshoe Crabs in the Pharmaceutical Sector position paper, including no use of TAL for our direct operations and our tier 1 suppliers. 	<ul style="list-style-type: none"> We are progressing plans to transition to synthetic alternatives. In 2024, we evaluated several available synthetic options and identified the most suitable options for water testing. We are looking to transition all of our current quality control labs to a synthetic reagent for water testing in the near-to-mid term. 	<ul style="list-style-type: none"> We aim to launch all new products with synthetic endotoxin testing alternatives as an option in regulatory submissions. We are identifying the medicines in our existing portfolio that are most suitable for transition to synthetic alternatives as well as developing a plan for regulatory submission.

3. <https://blog.nwf.org/2022/06/synchronous-survival-red-knots-and-horseshoe-crabs/>
 4. https://link.springer.com/chapter/10.1007/978-0-387-89959-6_4
 5. <https://esajournals.onlinelibrary.wiley.com/doi/full/10.1002/fee.2738>
 6. <https://awsq.org.au/wp-content/uploads/2020/11/Stilt-32.pdf#page=18>

Restore and Regenerate:

We are investing in nature and water stewardship projects tied to our value chain. Given our dependence on horseshoe crabs, we identified two suitable opportunities to restore and regenerate horseshoe crab populations through partnership with the National Fish and Wildlife Foundation (NFWF). NFWF is a leading conservation organisation dedicated to fostering sustainable and impactful conservation solutions so that people and nature thrive together. NFWF's long-standing Delaware River Program works with organisations ranging from local conservation nonprofits to state and local governments to restore fish and wildlife habitat and improve the water quality of the Delaware River and its tributaries. As part of its objectives, the programme funds efforts to restore habitat for horseshoe crabs and migratory shorebirds.

In August 2024, NFWF awarded funds to two projects within the Delaware Bay to support ongoing conservation work that benefits horseshoe crabs and migrating shorebirds in the region:

1. Monitoring shorebird and horseshoe crab populations in Delaware Bay (NJ)

Grantee: New Jersey Audubon Society

Aim: Monitor shorebird and horseshoe crab populations to inform disturbance protection and recovery efforts in the Delaware Bay stopover. The project will support the maintenance of effective, established, volunteer-based population satellite tagging and monitoring programmes in the region, providing data critical to recovery of red knots, other shorebird species and horseshoe crabs.

2. Restoring horseshoe crab and shorebird habitat at Thompsons Beach (NJ)

Grantee: American Littoral Society

Aim: Restore crucial beach habitat for horseshoe crabs, red knots and other shorebirds at Thompsons Beach in the Delaware Bay. The project will place up to 45,000 cubic yards of sand to stabilise the shoreline, extend suitability for stopover migration and increase stewardship within the Bayshore Region through presentations and large-scale community engagement events.

Thompsons Beach is located within the Delaware Bay along the western shores of New Jersey, US. It is a sensitive area rich in biodiversity with many protected areas.

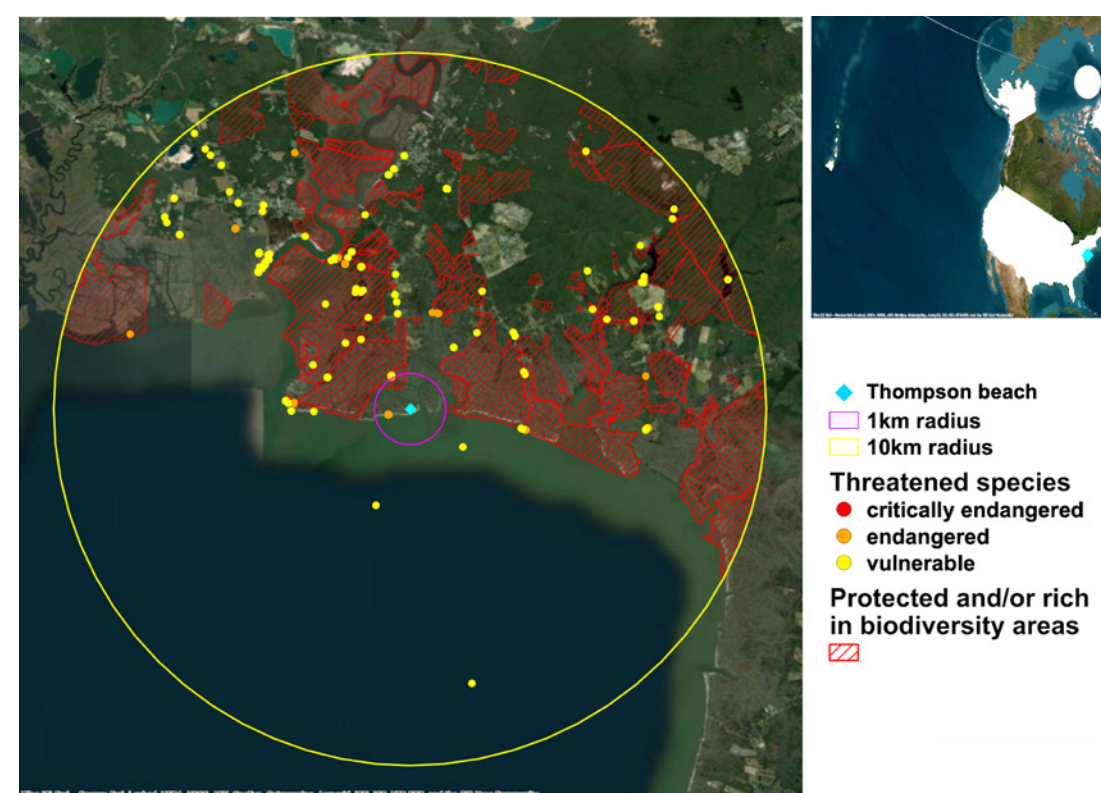


Figure 1: Overview of threatened species observations and protected areas around Thompsons Beach (sources AXA Climate, threatened species records from GBIF)

The Delaware Bay is also strategically relevant to our sector as a major source of biomedical harvesting of horseshoe crabs. While the Atlantic States Marine Fisheries Commission (ASMFC) has maintained a ban on the bait harvest of female horseshoe crabs through 2025 to protect migratory shorebirds like the red knot, this restriction does not extend to biomedical harvesting.

Horseshoe crab populations depend on the stability and quality of their ecosystems, especially shorelines which provide the right conditions for them to spawn and protection from disruption. Pollution from agriculture, industry, and urbanisation harms water quality, while erosion and land use changes degrade egg-laying environments. The proximity of Thompsons beach to other protected and biodiversity rich areas guards against these pressures.

We determined that Thompsons beach is a resilient area that is well suited to support the protection of horseshoe crabs and the wider ecosystem.

Transform

We are engaging with our stakeholders, including our sector's regulatory agencies and our peers through ongoing PSCI led efforts, to accelerate the transition to the synthetic alternative to horseshoe crab reagent and reduce our sector's reliance on wild populations.

We look forward to continuing our partnership with others to help protect the species that has protected our patients for decades.

Contributions from

