PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

The use of Horseshoe Crabs in the Pharmaceutical Sector

A position paper from the PSCI

22 May 2023

Context and background

Blood products derived from Horseshoe Crabs are used in the process of pharmaceutical development and manufacturing as endotoxin testing reagents; materials which indicate the presence of certain bacterial toxins when applied to a sample. Testing for contaminants is a crucial part of ensuring safety in drug products.

There are three affected species of Horseshoe Crabs: *Limulus polyphemus* found on the East Coast of the US, and the Indo-Pacific and Tri-spine Horseshoe crabs (*Tachypleus gigas* and *Tachypleus tridentatus*) found in Asia. These are used to produce Limulus Amebocyte Lysate (LAL) and Tachypleus Amebocyte Lysate (TAL) respectively, both being extracted from the animals' blood. This does not require the death of the animal; they are typically collected, a measured amount of blood extracted, and released back into the wild.

Nonetheless, there are potentially animal welfare and sustainability impacts from the collection of these materials from populations of wild crabs, with concerns that the process may increase mortality and lead to population decline among the crabs and related species (birds and sport fish). *Tachypleus tridentatus* is listed as endangered[1] (with concerns over the other Asian species, where the data is deficient).

Change within the pharmaceutical industry must be carefully managed to ensure products are safe and to secure regulatory approval, however there are opportunities for progress. Good laboratory practices (automation, sample grouping, waste management) provide ways to reduce consumption. Microfluidics test technology offers accurate, reproducible tests using only a tiny fraction (as little as 5%) of the volume of LAL when compared to the traditional LAL test, dramatically reducing the demand for animal-derived product.

There are alternative technologies available in certain applications which do not require LAL or TAL at all. Recombinant Factor C (rFC) assay is an alternative to endotoxin testing using LAL/TAL. Regulators have approved rFC in some contexts; the FDA guidelines in 2012 allow for the consideration of rFC "if appropriately validated" and there is a guidance compendial test chapter in Europe. First regulatory approval using rFC for the approval of a medicine was in 2018 and this product has been approved in over 60 markets. At least seven products to date have global regulatory approvals using an alternative test reagent. Other LAL-like reagents, including a recombinant LAL, are also being introduced to the market.

[1] IUCN Red List

The PSCI's Position

Against this backdrop, the PSCI – representing 74 of the world's largest pharmaceutical companies and their suppliers – is pleased to affirm the following elements of good practice, and to encourage their adoption by all members:

Protect all endangered species – no further collection of TAL. The PSCI's members will end commercial pressure on the populations of *Tachypleus gigas* and *Tachypleus tridentatus*, by committing to no further collections from these species. PSCI members and first tier suppliers will no longer use TAL after existing supplies have been exhausted.

Minimize the requirements for naturally-derived testing materials. The PSCI recognizes that members will potentially require a range of endotoxin testing techniques, and the availability of rFC, other recombinant reagents, and microfluidics offers members a route to dramatically reduce the demand for LAL. Members are encouraged to explore and adopt alternatives, setting themselves internal goals to minimize the volume of LAL used in their own operations and first tier suppliers.

Understand the animal welfare and conservation position. For the residual use of LAL, members are encouraged to take an active and intentional approach to sourcing, to understand where the material derives from and the animal welfare and biodiversity considerations that may result. Members are encouraged to co-operate and share data on traceability, populations and conservation status of *Limulus polyphemus.*

Governance and monitoring

This is a PSCI position paper, but it is not a formal membership requirement of PSCI; the organization believes it to be good practice and a progressive approach to be widely adopted.

Members are encouraged to adopt positions as set out in this paper and to promote their adoption throughout the supply chain.

The PSCI in turn commits to:

- monitor and review our members' approach on this and report it on an anonymized basis
- engage with others to learn and develop particularly on the US conservation position
- prepare guidance, materials, and support to members and suppliers to implement the good practice elements of this statement