PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Building responsible supply chains

The use of Horseshoe Crab Blood for Endotoxin Testing in the Pharmaceutical Industry

April 2025

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→ This report sets out the context and complexities in its use and explores a pathway for better practices in the pharmaceutical industry

About the horseshoe crab, and PSCI's work on this topic

The horseshoe crab's bright blue blood is vital to human medicine. This report sets out the context and complexities in its use and explores a pathway for better practices in the pharmaceutical industry.

The Pharmaceutical Supply Chain Initiative (PSCI) is a group of over 80 pharmaceutical companies working collectively to drive excellence in responsible supply chains. The PSCI works across the industry to define common best practices and drive progress against our Responsible Supply Chain Principles, the 'PSCI Principles'. We are a non-profit membership organization registered in the US with members in Europe, North America and Asia.

This report represents a brief summary and analysis of the environmental and ethical issues around endotoxin testing in relation to the horseshoe crab population and related risks for the Pharmaceutical industry.

About the horseshoe crab

Most closely related to arachnids, the blood of the horseshoe 'crab' contains an enzyme that have made it vital to modern day human healthcare. The blood contains a protein called Factor C that detects bacterial endotoxins, which can cause sickness or even death in humans. As such, pharmaceutical companies use this Amebocyte lysate to test parenteral or implantable medicines and vaccines for safety as well as medical devices, water and other equipment. As an example of the ubiquity of this test, anyone who has received a Covid-19 vaccination has benefited from endotoxin testing.

The amebocytes of three species are used in the testing for biologics and medical devices quality control – The Atlantic Horseshoe Crab (*Limulus polyphemus*) found on the East Coast of the US and Mexico, and the Indo-Pacific and Tri-spine Horseshoe crabs (*Tachypleus gigas* and *Tachypleus tridentatus*) found in Asia.

In recent years, several new testing methods have been launched onto the market, meaning it's possible to carry out the test using less horseshoe crab blood. Most suppliers of endotoxin testing now offer methods that reduce the amount of horseshoe crab blood needed for the test (microfluidics etc). Additionally, two alternatives (rFC and rCR) have been developed and one (rFC) has been approved for use across most major markets. In practical terms, this means that a drug can be guaranteed as safe for use in humans without the need for any horseshoe crab blood.

What do the PSCI Principles say?

PSCI members commit to upholding the PSCI's Principles for Responsible Supply Chain Management. These set out responsible practices across five pillars: Ethics, Environment, Health & Safety, Human Rights & Labor and, underpinning these, Management Systems. Under each pillar, specific topics are defined as sub-Principles.

Two sub-Principles are relevant to endotoxin testing:

Environment Pillar

Biodiversity conservation:

> **Suppliers shall understand their impacts on biodiversity, reducing and mitigating their footprint wherever possible.**

Ethics Pillar

Animal Welfare:

> **Animals shall be treated humanely with pain and stress minimized. Animal testing should be performed after consideration to replace animals, to reduce the numbers of animals used, or to refine procedures to minimize distress. Alternatives should be used wherever these are scientifically valid and acceptable to regulators.**

PSCI's work on endotoxin testing

PSCI has engaged with its members on this topic via a working group and in 2023, published a position paper to articulate the issues around horseshoe crab blood use and set a progressive position. The paper encourages companies to minimize their use of the horseshoe crabs and to seek out safe alternatives for their supply chains.

This report has been prepared with inputs from PSCI members, predominantly based in Europe and North America, but does not represent any company's individual view or position.

The PSCI Position Paper

The PSCI Position Paper on the Use of Horseshoe Crabs outlines good practices and encourages members to adopt these, specifically:

- Protect all endangered species and cease further collection from the Asian horseshoe crab population,
- Minimize the use of horseshoe crab blood in the endotoxin testing process, whether through minimization techniques or through the use of synthetic alternatives,
- Understand the animal welfare and conservation position, taking an active and intentional approach to sourcing, knowing where their endotoxin tests come from and the conservation and biodiversity considerations that may result.

In turn PSCI itself is committed to:

- Monitor and review 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 in the position paper.

The PSCI Position Paper

The conservation context for horseshoe crabs

The impact of the amebocyte collection process on the crabs, and what should be done about it, is contested. Here we outline the main challenges and complexities:

1 Asian horseshoe crab population: Endangered

The tri-spine horseshoe crab, from which Tachypleus Amebocyte lysate (TAL) is derived, is a registered endangered species. According to the IUCN, *"Asian horseshoe crabs are legally protected in Mainland China, India, Bangladesh, Vietnam, Singapore, and several regions of Japan, although the effectiveness of enforcement is largely unknown"*. The IUCN points to lack of baseline population data as a major impediment to species conservation.[1] The PSCI's Position Paper, 2023, set out that the sector should procure no more stocks, and cease use of TAL once existing stocks are run down. TAL is used primarily in China.

2 Mortality rate from amebocyte collection: Contested data

Data from the Atlantic States Marine Fisheries Commission (ASMFC), synthesizing scientific studies purported to imitate LAL manufacturing processes at key North American Atlantic horseshoe crab locations, suggests that approximately 1 in 7 horseshoe crabs die due to amebocyte collection for biomedical purposes,[2] with the remainder released. In Asia, the mortality rate is reported to be 100%, with crabs used for bait or food after amebocyte collection.[3]

3 Lifecycles, spawning seasons and egg quality: Impact of amebocyte collection on eggs

Practices used to gather amebocytes from the crabs vary. In North America, responsible practices have been deployed by companies like Charles River Labs (CRL), Lonza, Associates of Cape Cod, Inc. (ACC) and Wako; for example, careful hand collection of the crabs, limited collection (CRL commits to collecting no more than 30% of a crabs' total blood), and release back to the wild within 36 hours. Since 2013, the Atlantic States Marine Fisheries Commission (ASMFC) has restricted harvests of the female Atlantic horseshoe crabs for bait purposes in order to support spawning populations. These practices offer some protection to the crabs. We know little about the subtler impacts of amebocyte collection on horseshoe crabs' normal behavior and spawning patterns, egg quantity and weight. *Note: In 2024, a petition was launched to list the North American horseshoe crab as endangered.*[4]

→ **CRL commits to collecting no more than 30% of a crabs' total blood**

[1] https://iucn.org/news/species-survival-commission/202104/a-program-implementing-effective-regional-conservation-actions-asian-horseshoe-crabs
[2] http://www.asmfc.org/species/horseshoe-crab
[3] https://therevelator.org/asian-horseshoe-crabs/
[4] https://www.fisheries.noaa.gov/s3/2024-03/American-horseshoe-crab-petition-2-27-24-508.pdf

4 Red knots and other migratory coastal birds: Dependent on horseshoe crab eggs

As with any species, there is ecological concern over interdependencies. In the case of horseshoe crabs, in particular that a decline in eggs will negatively impact the population of creatures which consume them, including migratory and coastal birds, turtles and finfish. Perhaps best documented are the threatened sub-species of red knots which each year fly 9,000 miles from southernmost South America to the Arctic, stopping over in the Delaware Bay area and other areas in the Eastern United States, the foremost laying site for the North American horseshoe crab.

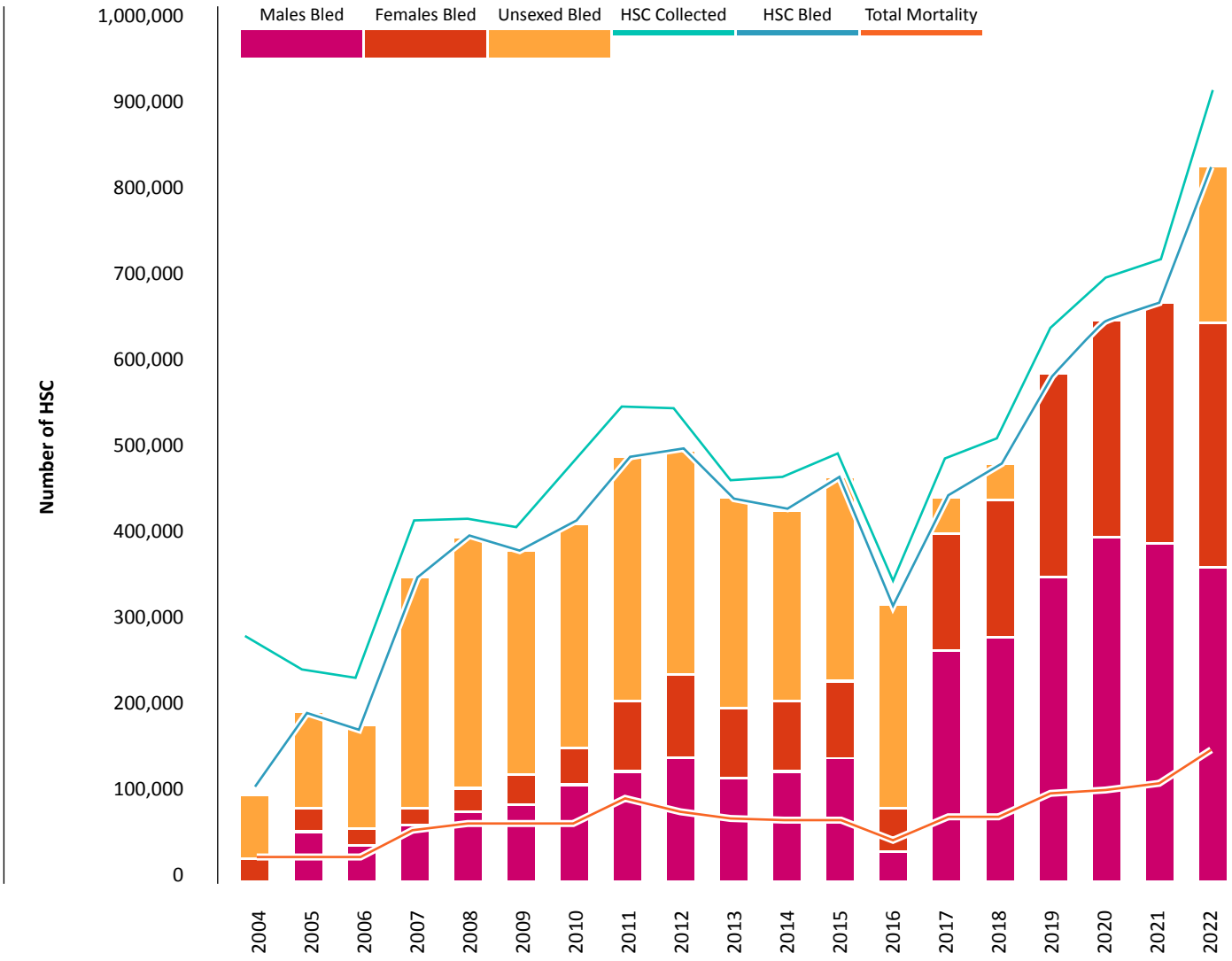
→ As with any species, there is ecological concern over interdependencies

5 Special protections for the Atlantic horseshoe crabs: Positive impacts of biomedicine on horseshoe crab populations

With human health reliant on the success of this species, there have been some special protections afforded to the Atlantic horseshoe crab. Some Pharmaceutical companies in North America lead initiatives which support populations of horseshoe crabs.[5] As a case in point, amongst many others, the industry has helped to prevent the crab's use as bait through both legal protections and supporting viable alternatives such as synthetic baits, and bait bags to minimize waste. Importantly, not all of these responsible practices have been employed everywhere, notably in Asia where the horseshoe crab is endangered.

Finally, this report does not consider the impacts of climate change and weather events on the horseshoe crab, nor is there a wealth of research on this topic. Presumably this is another important factor in the species' success.

Data from Atlantic Sea Fisheries Marine Council on horseshoe crabs caught and bled for Pharma purposes in the USA, including mortality rates, 2024; ASMFC Report

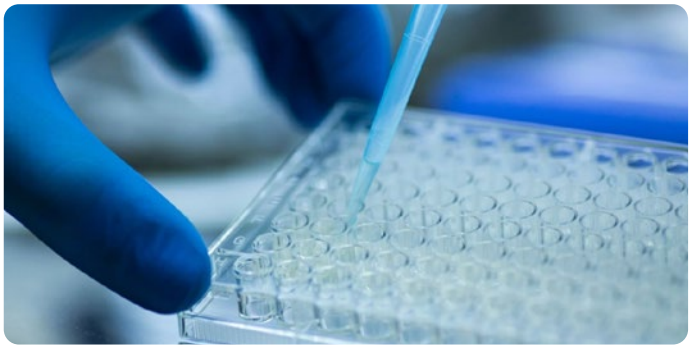


[5] https://www.acciusa.com/assets/files/pdf/Horseshoe_Crab_Sustainability-PressRelease_MKT_21-110.pdf

A brief history of endotoxin testing

Endotoxin testing was introduced to ensure parenteral solutions and medical devices did not cause fever when administered. Methods have evolved significantly over the last century. The first, the Rabbit Pyrogen Test (RPT), was developed in the early 20th century, which involved injecting test samples into rabbits and detecting fever responses.[6] The test was standardized and included in the United States Pharmacopeia (USP) from 1942. RPT was critical for medicinal product development and was the sole method used for endotoxin testing for 40 years, however it outputs qualitative results, has low sensitivity and brings ethical concerns.[7] In June 2025, the European Commission will remove the RPT from the European Pharmacopeia (EP).[8]

RPT was slowly phased out after the discovery that horseshoe crab blood clots in the presence of bacterial endotoxins in the 1960s, which led to the development of the Limulus Amebocyte Lysate (LAL) test.[6] The test was reported to be cost-effective and have a higher sensitivity, and was approved by the US Food and Drug Administration (FDA) in 1977.[9] LAL is primarily used for endotoxin testing globally. The Tachypleus Amebocyte Lysate (TAL) test works in the same way, is derived from the Asian horseshoe crab and primarily used in Asia. The high sensitivity of these amebocyte lysate tests ensure pharmaceutical products and medical devices are safe for human use, especially to vulnerable patients who would be particularly impacted by a pyrogenic response.



With medical advances, the demand for endotoxin testing continues to increase. Synthetic alternatives are growing in availability and popularity, driven in part by ethical and environmental concerns about pharmaceutical supply chains. Recombinant proteins have been developed and are being used as a replacement to naturally sourced LAL and TAL. The methods based on recombinant Factor C (rFC) and Recombinant Cascade Reagent (rCR) (containing rFC, rFB and rPCE) maintain the high standards for endotoxin testing while removing the need for horseshoe crab blood.

What is the Pharma industry doing to reduce risks?

Good laboratory practices

Good laboratory practices to reduce consumption:

- **Replace:** More use of recombinants.
- **Reduce:** Microfluidics test technology offers accurate, reproducible tests using only c. 5% of the volume of LAL traditionally used.
- **Refine:** Optimizing processes, for example sample grouping.

Sievers Eclipse Bacterial Endotoxins Testing (BET) Platform. Source: Veolia

Example of a Kinetic Chromogenic LAL or rCR Cartridge. Source: Charles River Laboratories

Alternative technologies

Often referred to as 'synthetic alternatives', for example rFC and rCR which do not require LAL or TAL.

Reactor holding cell culture for manufacturing recombinant proteins such as rFC.

Source: Ecological Research & Development Group

[6] Jianning T, Bill T. 10.15406/jabb.2024.11.00351

[7] Dubczazk, J. https://www.americanpharmaceuticalreview.com/Featured-Articles/571720-Past-Present-and-Future-of-Endotoxin-Testing/

[8] European Directorate for the Quality of Medicines & Healthcare. https://www.edqm.eu/en/-/ph.-eur.-bids-adieu-to-rabbit-pyrogen-test-in-its-monographs

[9] U.S. Food and Drug Administration. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-technical-guides/bacterial-endotoxinspyrogens

The context within key regions

As the number of endotoxin tests continues to increase - and with it, the use of horseshoe crab-derived amebocyte lysate - the most effective supply chain strategy for pharmaceutical companies is to explore the adoption of recombinant alternatives. However, challenges vary regionally in terms of regulation, environmental impact, cost and accessibility.

USA

In the US, the widely used LAL test is derived from the amebocytes of the Atlantic horseshoe crab. The numbers of crabs collected for LAL manufacture, known as 'biomedical' by the Atlantic States Marine Fisheries Commission (ASMFC), is approaching one million annually. In 2022, approximately two thirds of crabs captured in Delaware Bay, US were used for bait (100% mortality) rather than for biomedical use.[10] Their continued and increased use is prompting questions around animal welfare and biodiversity impacts, especially for red knot birds, whose populations are estimated to have declined by as much as 94% over the past 40 years.[11] Horseshoe crabs are also an important source of bait for commercial eel and conch fisheries along the coast. The Delaware Bay region holds most of the crab harvest, followed by New York, New England, and the Southeast regions.

LAL testing has been accepted globally for over 40 years and is outlined in USP Chapter <85> for Bacterial Endotoxins Testing (BET). In 2024, the USP Chapter <86> which outlines the use of synthetic alternatives (Recombinant Reagents, rCR and rFC) was approved. It is currently available for early adoption and will be officially implemented in May 2025, demonstrating that synthetic alternatives can be recognized as standard approaches where sample type and validation allow.

Europe

There are no populations of horseshoe crabs in Europe. Popularity of the synthetic alternative test appears to be growing across the region. The European Pharmacopeia Commission's Chapter 2.6.32 describes the methods of analysis for bacterial endotoxins using recombinant factor C (rFC). This became effective on January 1st 2021, making its implementation relatively straightforward for drug manufacturers who cite the chapter.

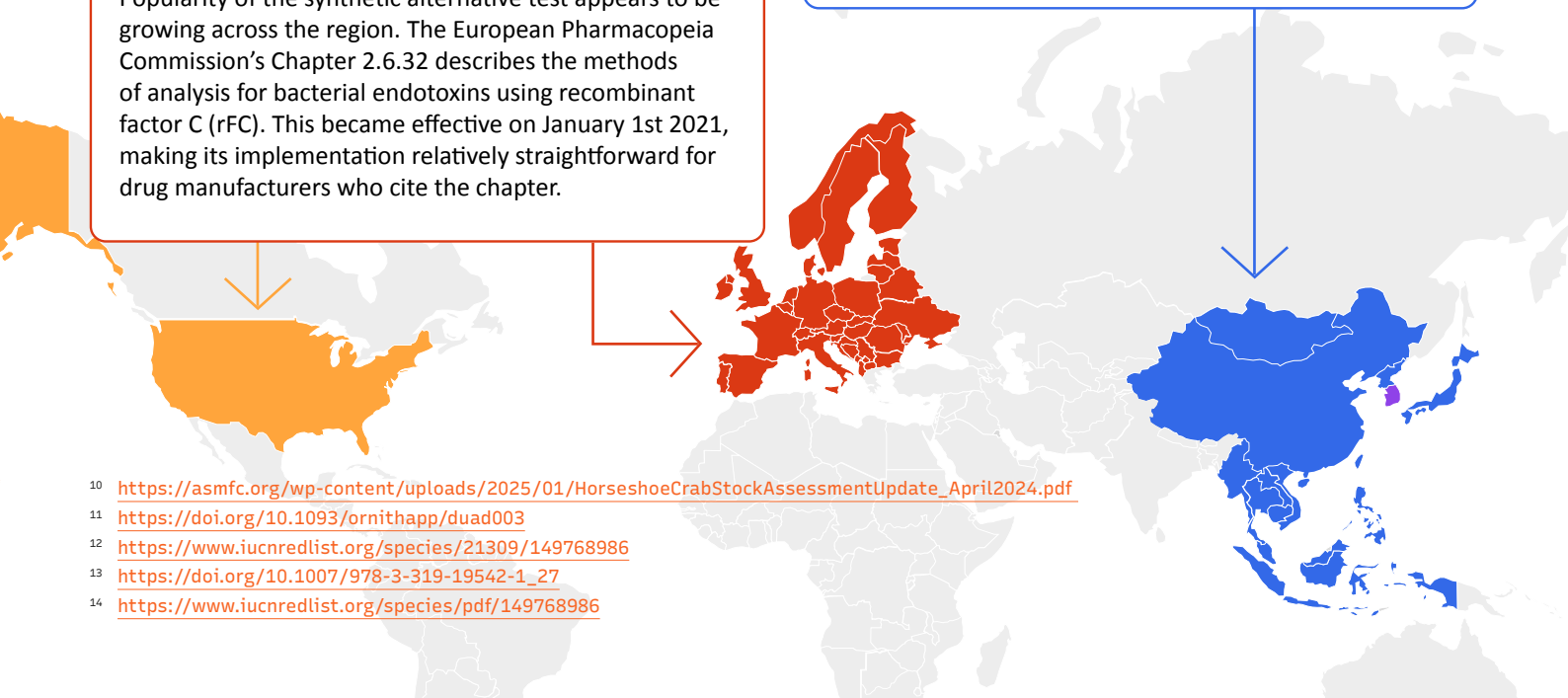
Asia

One of the Asian species of the horseshoe crab (*Tachypleus tridentatus*) is considered endangered and is legally protected in parts of Asia. Besides their use in biomedicine and as bait, in many South and Southeast Asian countries, horseshoe crabs are consumed as food. Along with habitat degradation, these factors are contributing to their population decline.[12]

In China, use of horseshoe crabs for the biomedical industry and human consumption results in 100% mortality of the animal.[13] China is also the largest consumer and primary supplier of TAL and there is little effective regulation or monitoring on the harvesting of these horseshoe crabs. The rFC method has been recognized as an alternative method through Guideline <9251> since 2020. Advocacy is currently ongoing to implement rFC as compendial test in China. For the past two years, manufacturers of rFC reagents have been operating in China.

The Japanese Pharmacopeia's approach aligns with that of the US and Europe; however horseshoe crabs have been critically endangered in Japan since 2006[14], therefore Japan and the rest of the Asia-Pacific region largely relies on LAL imports. The rFC method has been recognized as an alternative method through Guide <G4-4-180> since June, 2021, as part of the 18th edition of the Japanese Pharmacopeia.

Recombinant bacterial endotoxin test chapters are described in the respective pharmacopoeias in Japan, China and Korea.



10 https://asmfc.org/wp-content/uploads/2025/01/HorseshoeCrabStockAssessmentUpdate_April2024.pdf
11 https://doi.org/10.1093/ornithapp/duad003
12 https://www.iucnredlist.org/species/21309/149768986
13 https://doi.org/10.1007/978-3-319-19542-1_27
14 https://www.iucnredlist.org/species/pdf/149768986

The role of global pharmacopoeias and health authorities

Global pharmacopoeias establish pharmaceutical quality standards, and in most countries are a direct extension of the country's health authority. A published, consistent test method standard benefits all stakeholders, including health authorities, pharmaceutical manufacturers as end users, and patients. The bacterial endotoxins test using LAL was first published in the USP in 1980 and harmonized with the European and Japanese Pharmacopoeias in the early 2000s, providing a common set of expectations across major global health markets and lowering the regulatory effort needed per pharmaceutical product. However, the harmonized test chapters specify the use of LAL and TAL and harmonization took more than 20 years to achieve, which illustrates the complexity involved.

The pharmacopoeias do not approve pharmaceutical products; rather, the health authority does. An end user submits which test method they intend to use to test their product and the health authority reviews and potentially approves it. The end user does not have to use a pharmacopoeia method but there are advantages to doing so. To date, synthetic alternative tests have been approved by at least 65 different health authorities for at least 13 different products. Several companies are also known to be using alternatives to test water in pharmaceutical production, which constitutes a large percentage of total sample numbers.

65 **different health authorities have approved synthetic alternative tests to date**

Pharmacopoeias influence on testing in different regions

Pharmacopoeias set quality standards and testing procedures for medicines, ensuring their safety, efficacy, and consistency. Regulatory authorities protect public health by enforcing these standards, approving new medicines and monitoring the safety of both new and existing medicines.

The endotoxin test is internationally accepted, described in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, and harmonized in many pharmacopoeias including Europe, the US, China, Japan and others. Specifically:

Europe The rFC is considered equivalent to LAL in the EP Chapters 2.6.14 and 2.6.32, and is included in the water monograph.

USA The USP has published Chapter 86 describing the use of recombinant alternatives to horseshoe crab blood-based testing. This will be effective from May 2025. As in the EP, the USP does not require a comparison to LAL for new product launches. However, unlike the EP, no comparison to LAL is required for new launches. Unlike the EP, a comparison to LAL is required for lifecycle changes.

China The Chinese Pharmacopoeia has two chapters noteworthy in this context: 1143 Bacterial Endotoxins Test and 9251 which is a Guideline for BET Application and where rFC is listed as a supplemental method.

Japan The Japanese Pharmacopoeia Chapter 4.01 is harmonized with the European Chapter 2.6.14, describing Recombinant Protein-reagents for Endotoxin Assays in G4.4.180, 'Bacterial Endotoxins Test & Alternative Methods'. It is not specified which recombinant technology can be used.

The global market for endotoxin testing

With growth in biomedicines, the demand for endotoxin testing is increasing and forecast to continue doing so, with a direct impact on the horseshoe crab. Here we outline the scale and distribution of the endotoxin market to indicate the scale of the issue and where focus is best placed.

Today, it is estimated that around 90-100 million endotoxin tests are currently sold annually.[15] This covers several markets including:

- **Testing water** - To ascertain fitness for parenteral manufacturing. This is the largest market for endotoxin testing.
- **Pharmaceuticals** - Typically delivered either as parenterals (injectables) including intravenous, biologics and sterile pharma, and devices including hard (stents, catheters, scalpels) and soft (cell culture media).
- **Dialysis** - Relating to a relatively small number of patients but requiring a high intensity of tests and high accuracy.
- **Cell and gene therapy** - This represents a small but rising share of the market.
- **Animal health** - This concerns Pharmaceuticals for use in animal care.
- **Medical devices** and/or implants.

Within the Pharmaceutical sector, customers are predominantly: Pharmaceutical and biomedical companies, contract research organizations (CROs) and medical device manufacturers.

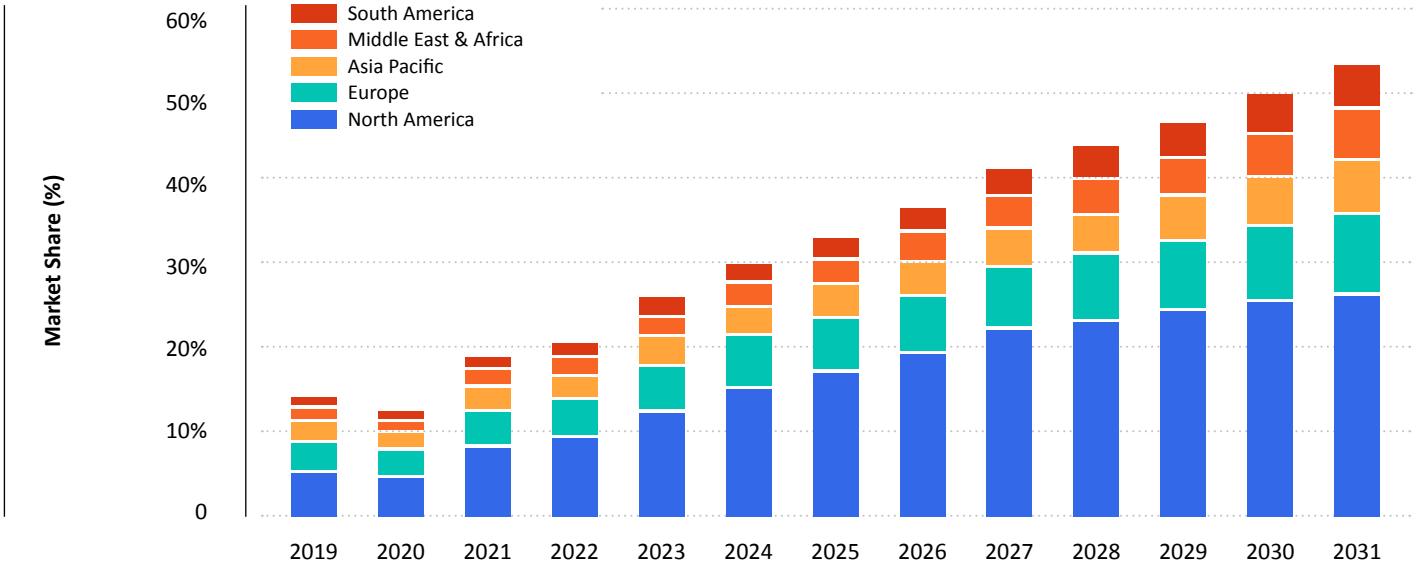
Getting a sense of scale

According to publicly available market data, North America represents approximately 40% of global demand, with Europe at around 30% and Asia at 20-25%. Small markets (1-5% each) exist in Latin America, Middle East and Africa.[16]

Despite concerns over crab populations, there is currently no indication of consumption decline, with trends for significant growth in the Asian market.[17,12] It is unclear what portion of collected TAL is serving markets outside of Asia; responses to our survey suggest that demand from European buyers is declining due to concerns over crab populations, which would logically increase demand for LAL and synthetic alternatives.

Endotoxin Testing Market Share (%) by Region (2019 - 2031)

Chart from 'Endotoxin Testing Market Report 2025', Cognitive Market Research



[15] Bob Ferguson, Strategic Consulting, author of IMMR report

[16] https://www.cognitivemarketresearch.com/endotoxin-testing-market-report

[17] https://doi.org/10.1007/978-3-030-82315-3_21

Test type

Pharmaceutical companies themselves have limited visibility on how much horseshoe crab blood is used in their endotoxin testing programs. They likely keep records on the number of tests or 'kits' purchased, but have no access to the detail on how much TAL or LAL was used for each by the company supplying the test. The volumes per test is subject to a host of factors including:

- Intensity of the test type (see page 12) including minimization techniques or the potential use of a synthetic alternative.
- Number of tests needed to ascertain safety of the drug / treatment in question, which is influenced by the patient's vulnerability level and the stage(s) in the process where testing must occur.
- Need for controls, standard curve, confirming label claim, number of re-tests needed and other efficiency factors.
- The need to meet approval requirements in different markets.

What is clear, is that switching to lower intensity methods and adopting minimization techniques –such as microfluidics–or including synthetic alternatives where possible can considerably reduce TAL and LAL volumes required and improves end user supply chain positions. In addition, avoiding use of the Asian horseshoe crabs preserves the most endangered populations.

A list of endotoxin suppliers and their offerings

	LAL	RFC	RCR
Associates of Cape Cod	✓	✗	✓
Biomerieux	✗	✓	✗
Charles River Labs	✓	✗	✓
Fuji Wako	✓	✗	✓
Lonza	✓	✓	✗
Xiamen Bioendo	?	✓	✓

The market for synthetics

According to a recent market assessment, global demand for rFC was valued at USD 0.15 billion in 2022 and is forecast to rise to USD 0.3 billion by 2030.[18] Regional demand follows a similar pattern to overall demand for endotoxin tests.

> **"Through our engagement, we have discerned three distinct ways companies can - and are - replacing TAL and LAL with synthetics. The easiest usage to address is testing lab water. As this testing accounts for around 80-90% of use, starting here is a massive win, whether by moving to synthetics or using micro-fludics that use much less LAL than previous technologies. The next step is moving to testing all NEW products with synthetics. The hardest challenge is legacy products because they were originally registered with authorities around the world based on TAL/LAL tests. Companies tell us it would be prohibitively costly to resubmit that documentation and go through the whole registration process again having retested these products using synthetics."**
>
> **Adam Kanzer**
> **Head of Stewardship, Americas, BNP Paribas Asset Management**

Barriers to reduction

Switching to lower intensity methods is not always straightforward and some of the reported barriers include:

- The time to receive regulatory approvals to change existing licenses, if required.
- Knowledge and experience among testers, and availability of equipment; for example, *"gel clot requires less equipment and is easier than other test methods".*[19]
- Synthetic tests are perceived to be more expensive when compared to gel clot methods.
- Lack of a local pharmacopoeia method or lack of pharmacopoeia harmonization.

[18] Recombinant Factor C (rFC) Market Size, Assessment, Growth & Forecast 2032

[19] Interview – Representative for an Endotoxin test supplier to the industry

PSCI member companies and use of horseshoe crab blood

A survey of PSCI members was conducted between May-November 2024, intending to take the pulse of member companies which carry out or commission endotoxin tests, establishing their corporate policies and plans for TAL and LAL usage, as well as their current practices.

20 members responded to the survey, providing information on their positions and practices, including:

- Actions or plans to reduce or eliminate usage of TAL and LAL.
- Agreed corporate positions or commitments.
- LAL usage data including the number of tests performed and any business continuity or supply chain resiliency planning undertaken.

Members also shared and discussed ideas for advancing progress towards the commitments laid out in the position paper, including:

- Ways in which PSCI could further progress, in particular through building understanding and capabilities amongst both suppliers and members.
- Further steps the industry should take, collectively.

A summary of the findings are provided below.

Corporate policies and positions

As expected given the endangered status of the Asian horseshoe crab species and responses coming predominantly from Europe and USA, nearly all (18 of 20) had stopped using TAL in their own operations. Two respondents were still using TAL, due to either local market regulations requiring TAL or phasing-out in progress.

No respondents have made public commitments on TAL.

For LAL, all respondents were working on reduction or elimination; or were among four not using LAL at all. Two had made public policy statements or commitments on their LAL usage, Eli Lilly[20] and Roche.[21]

Supply chain engagement

We asked respondents whether and how they have engaged with relevant suppliers conducting tests for them, likely to be predominantly direct suppliers in the form of contract research organizations (CROs) and contract development and manufacturing organizations (CDMOs). A minority (six of 20) respondents have checked with relevant suppliers to ensure no TAL is used. None had checked or audited their entire supply chain for TAL usage.

On LAL, even fewer (four of 20) had actively engaged with their supply chain on the topic.

Furthermore supply chain resiliency, in terms of dependency on TAL or LAL and the ensuing risk, is not well understood at this stage, with only three firms having conducted any formal planning or costing to quantify the risk.

90%

members surveyed (18 of 20) had stopped using TAL in their own operations

[20] https://sustainability.lilly.com/environmental/biodiversity

[21] https://www.europeanpharmaceuticalreview.com/article/175455/pharmas-green-mission-trends-in-bacterial-endotoxin-testing/

In practice – member use of LAL

Most respondents (16 out of 20), primarily based in North America and Europe, were able to provide data on their annual testing volumes. They reported carrying out a total of just under 0.7m tests, based on annual data. **This is a small fraction of the total tests conducted by the industry.**

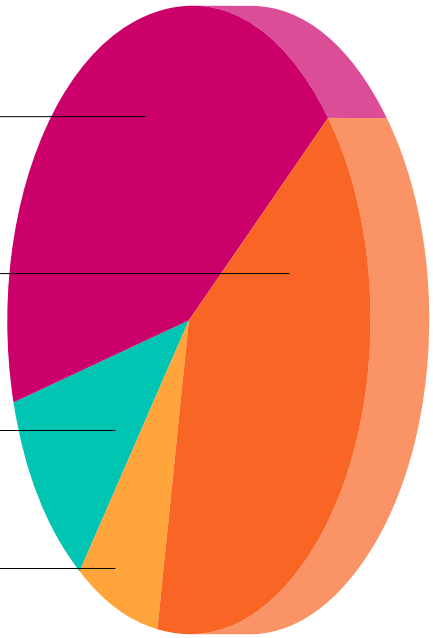
For three companies, these figures included tests carried out by their CROs and CDMOs: direct suppliers carrying out tests on their behalf. The remaining companies could not provide this data.

Kinetic chromogenic ("chromo") and Kinetic turbidimetric ("turb") are the dominant methods globally, aligning with our survey responses.

Gel clot tests made up a tiny fraction of tests reported by our members, but is widely used in the Latin American, African and Asian markets, due largely to the simplicity and lower cost of this method versus others.[18]

Although representing the smallest portion of the tests reported by respondents, we believe that the synthetic alternative (recombinant) is over-represented in our survey versus global testing, due to its more recent market entry.

Member survey respondents: Total tests conducted, by test type



0.7m tests reported

Choice of test method

↓

impact on horseshoe crabs

Different testing methods use different amounts of horseshoe crab blood. Data published by Charles River Labs show the gel clot and turb methods as the most intensive in terms of their use of LAL. Also available are the chromogenic method and several other 'minimization techniques' which use existing methods but adapted to reduce intensity, such as microfluidics cartridge technology. These offer lower intensity versus gel clot and turb*.

Several other factors will influence the choice of test method. A primary factor is cost, as well as inclusion by the relevant pharmacopeia and acceptance by health authorities. Other factors include the availability of equipment and skills, the levels of sophistication at the testing site and the need for simplicity.

* It is worth noting that real-world efficiencies are affected by a number of practical factors in the labs such as the necessity for re-tests.

Planning for resilience in the supply chain

Few cases of supply chain security can be deemed more important than that of pharmaceuticals. Dependable access to quality medicine is something that most of us consider an essential. For resilient supply, crucial inputs (such as ingredients, administering technologies, safety tests) must be carefully monitored, with contingency plans in place where supply disruption is foreseeable.

In the case of any natural material, supply can be hard to effectively predict or control over the long term, particularly in the context of the external supply chain pressures described in this report. In parallel, a responsible pharmaceutical company may decide to reduce or eliminate their TAL and/or LAL usage in order to meet either internally-set ethical and environmental goals or external expectations, as Eli Lilly has been doing since 2016.[22] Given the scrutiny and attention given to the *Tachypleus* horseshoe crabs, and their endangered status in Asia, planning for such scenarios ought to form part of a well-governed company's risk management and planning.

With companies phasing out TAL and increasing demand for LAL and synthetic alternatives, a well governed business should be planning for the resilience of its supply. Only six respondents to our survey have begun this journey so far; either actively ensuring supply chain security, including conducting resilience planning and understanding held stocks and cost of replacement, or working towards this. We would expect to see more undertake this work following the publication of this Report.

[22] https://www.lilly.com/news/stories/horseshoe-crabs

These response excerpts from our member responses provide further insight:

> **"LAL is flagged as high-risk material [and] we have started to evaluate the replacement. The cost depends on several factors such as purchasing and validating a new equipment and eventually software, validating the supplier of the recombinant reagent, replacing life cycle methods or non-registered tests, having one or several health authority consultations, validating the methods including potential comparability studies, writing the variation to change and potential submission fees. This can easily reach an investment of >$0.5m to replace LAL for a registered life cycle product. An evaluation for zero use on several sites is expected to leverage from the pilot work but can be multiple times the cost."**

> **"Cost of replacing LAL with rFC in the global network initially assessed for capital and operational expenses."**

> **"Working towards a plan. Business continuity plans currently based on alternate LAL vendors. Will be designed to be backed up by recombinant once qualified."**

> **"Due to long delivery times, our laboratory keeps own LAL-reagent stock to mitigate potential manufacturing problems at the supplier. We lack data on stock levels within the supply chain, but there are indications that stocks may be kept at a very low level. We have not explored the costs of replacement."**

→ Dependable access to quality medicine is something that most of us consider an essential

Questions raised, and next steps

This report offers a brief view into a complex issue and raises a number of questions, as well as highlighting opportunities for the industry to improve. Here we outline some key findings from our analysis, and suggest potential areas for further action—both for the PSCI and for others operating within this ecosystem.

Key findings

Putting together an analysis of the market and the positions and plans of PSCI member companies (as disclosed in our member survey), PSCI has identified several key findings:

1 Responses to our survey indicate that PSCI member companies are phasing out the use of TAL, from Asian horseshoe crabs. This is likely contributing to growth in demand for LAL and for synthetic alternatives. With global medicines dependent on the American horseshoe crab population, a well governed business should be planning for the resilience of its supply. Only a few respondents to our survey have done this so far; we would expect to see more undertake this work following the publication of this Report.

2 Many companies are developing positions and setting targets around TAL and LAL reduction, with a few being made publicly. We expect more companies to develop roadmaps towards reduction and even elimination, with these being put into the public domain. This will become mandatory for those in scope for the EU Corporate Sustainability Reporting Directive (CSRD).[23]

3 Test type is closely linked with horseshoe crab blood intensity. Besides cost, an important barrier to flexibility of test choice is efficiency of regulatory approval, so the local agencies and pharmacopoeias play a key role. The industry operating across global markets can move no faster than they allow. An acknowledgment of the issue and creation of innovative regulatory pathways is needed.

PSCI is a mission-driven organization and works collectively across the industry to drive progress against our Responsible Supply Chain Principles. In the interest of advancing progress, here we point to several actions that we believe can advance progress towards the commitments laid out in our Position Paper.

→ An acknowledgment of the issue and creation of innovative regulatory pathways is needed

[23] https://xbrl.efrag.org/e-esrs/esrs-set1-2023.html#d1e134-3-1

Practical steps for PSCI

These are steps that PSCI will take:

- Develop informational resources for companies procuring and/or conducting endotoxin tests. These resources will help build knowledge and support holistic, sustainable choices around key factors such as responsible sourcing and choice of test method.
- Develop a corporate-level roadmap for LAL and TAL reduction, setting out the steps towards upholding the commitments in the PSCI Position Paper.
- Provide tools to support companies in LAL reduction and TAL elimination, such as a roadmap to reduction, template wording for corporate policies and/or supplier codes, and a responsible sourcing guide.
- Launch a second member survey and progress report to show change over time, likely to be published in 2027.

Collaborative opportunities for the industry

The PSCI will need to partner in order to realize the following:

- In Asia, ensure a rapid and complete elimination of TAL usage for the pharmaceutical industry, and protect the Asian horseshoe crab population. This could include greater transparency around usage amongst Asian companies, as well as encouraging pharmacopoeia acceptance of alternatives–particularly in China.
- In cost-sensitive markets, work alongside industry, regulators and local pharmacopoeias to accelerate the transition to lower intensity and alternative test methods. At present, PSCI has the most knowledge, reach and influence in Europe, North America and parts of Asia. How could we extend out influence to Latin America and elsewhere?
- Define the industry-wide average for LAL and TAL intensity by test type. CRL has published a helpful explainer, but this reflects their own processes and technologies. Some variation is expected per test supplier and geography. What would an industry agreed view look like?
- Globally, enable transparency through regular reporting of industry progress on the issue, starting with PSCI members. Acknowledging the reporting burden on companies, can we build on our member survey to form a useful, voluntary reporting tool within the PSCI structure?
- Support useful data and supply chain resiliency planning across the sector, establishing the level of risk and making it easier for companies to make their own business continuity plans. This could include independent data on stock levels, as well as forecast usage and other key factors.

→ **At present, PSCI has the most knowledge, reach and influence in Europe, North America and parts of Asia. How could we extend out influence to Latin America and elsewhere?**

PSCI welcomes the opportunity to collaborate with partners who share our mission.

For those who can help and work alongside us in this endeavor, please contact Rosie.Towe@SLRConsulting.com.

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