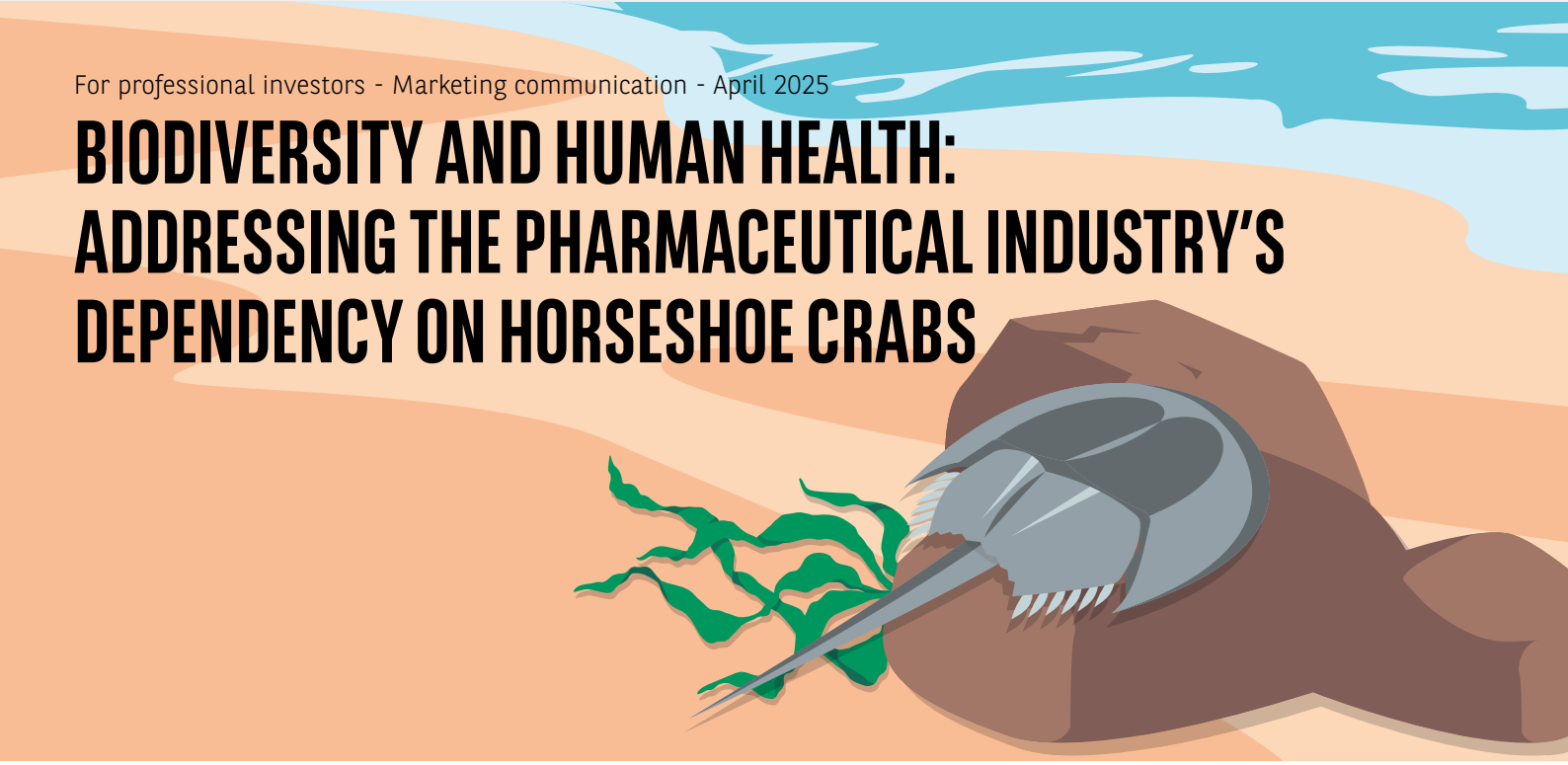
For professional investors - Marketing communication - April 2025

BIODIVERSITY AND HUMAN HEALTH: ADDRESSING THE PHARMACEUTICAL INDUSTRY'S DEPENDENCY ON HORSESHOE CRABS



INTRODUCTION

Every vaccine, injectable drug and medical device implanted in the human body must first be tested for potentially deadly endotoxin contamination. The standard test relies on a component of the blood of the horseshoe crab. However, the three principal horseshoe crab populations (two in Asia, one in the US) are declining, in part because they are harvested for this purpose. If these populations cannot be sustained, both human health and pharmaceutical companies' profitability are at risk, as are other species that depend on these crabs for their survival.

Thankfully, there is a synthetic alternative that should ultimately render the horseshoe crab-based test obsolete, but industry adoption has been slow. We have therefore been engaging with companies in the pharmaceutical sector for several years to address the substantial and clear risk to their businesses due to their dependency on this one sea creature. We provide a summary of our engagement on this issue in our 2023 and 2024 Sustainability Reports; this article is intended to provide a fuller account of our work and our progress.

LAYING THE GROUNDWORK

We first approached selected pharmaceutical companies on this topic towards the end of 2021 but received few responses to our initial inquiries. We therefore changed tack and approached the Pharmaceutical Supply Chain Initiative (PSCI) in 2022, which works with 80 companies in the sector, to ask whether it would be willing to facilitate an industry-wide approach to addressing this challenge.

In response to our outreach, PSCI established a working group and in May 2023 published a set of good practices for the use of horseshoe crab-derived reagents:

I. An immediate end to the use of the blood of two species of the Asian horseshoe crab considered endangered
II. Minimise the use of horseshoe crab blood in endotoxin testing techniques worldwide, including by using synthetic alternatives
III. Share data on the health of the horseshoe crab populations, to better understand population health and the impact of industry use.

The goal of our engagement is for all companies to adopt these practices and to disclose their progress in doing so.

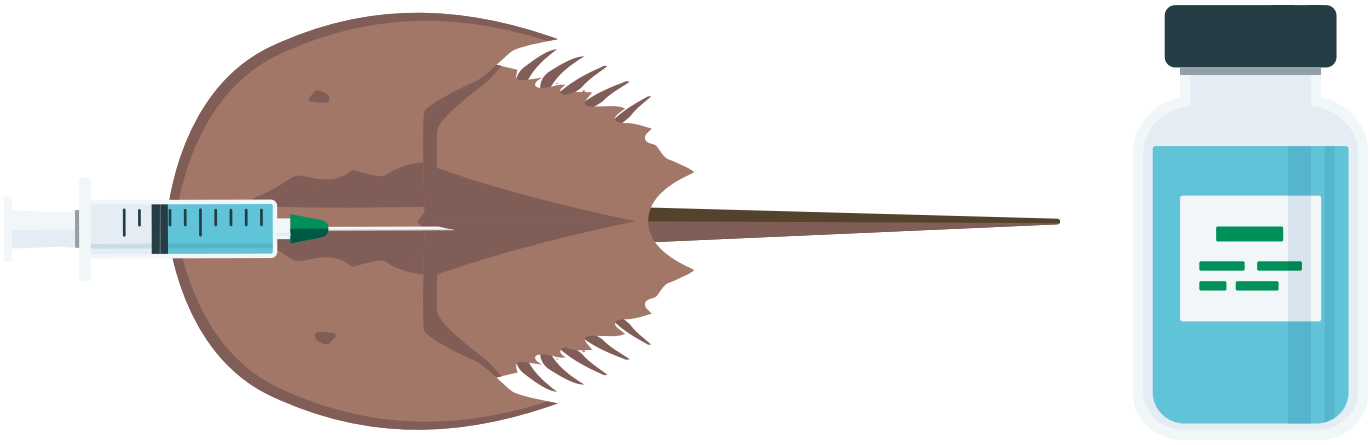
In terms of the regulatory landscape, while synthetic alternatives were approved in Europe and the US Food & Drug Administration had approved drugs tested with synthetics, they were not widely used. Eli Lilly and Company was the only company we identified that had made the switch for some products, blazing the trail for other companies to follow.

Nevertheless, the pharmaceutical firms we spoke to indicated that to do more on this issue, they needed greater clarity and alignment among regional and national regulators, and a globally consistent formulary.

In a crucial development towards the end of 2024, the US Pharmacopeia (USP), the body that develops and disseminates public compendial quality standards for medicines, published a new chapter which confirmed the suitability of synthetic alternatives for endotoxin testing and set out protocols which come into force in May 2025.

Further, several synthetic alternatives are now available, and for those tests that still contain horseshoe crab-derived reagents, technologies have recently been developed to substantially reduce the volume of both TAL and LAL (the acronym used for the component of Asian and North American horseshoe crab species, respectively) used in standard industry testing kits – both for products, but also – crucially – for testing lab water which accounts for the vast majority of use.

The regulatory and technological groundwork has therefore been laid, paving the way for an industry phaseout of horseshoe crab-derived reagents.



CORPORATE ENGAGEMENT DURING 2024

In total, in 2024, we had 104 interactions with 28 European and US-based companies. On the question of not continuing to use TAL, most companies we raised this with confirmed they no longer use it, or are phasing out its use in their own testing labs and/or also in third-party suppliers' labs. Other companies have committed to replacing TAL with LAL as an interim step; while welcome, this will temporarily increase demand for LAL, which is a concern.

With respect to minimising the requirements for naturally derived testing materials and phasing out LAL, companies are at different stages. Some are still exploring how to replace LAL while others are implementing a plan. Examples of particularly good progress include:

- **Novo Nordisk A/S** was the first company to have disclosed to us a comprehensive time-bound plan for the phase out of LAL, a very welcome development
- **AstraZeneca** plc is working on setting internal targets for its raw materials and responsible sourcing, which will include horseshoe crab lysate. It has also made progress through switching to microfluidic technology in its water testing, which has reduced its consumption of horseshoe crab lysate by over 90%, in line with the company's commitment to the 3Rs principles (Replacement, Reduction and Refinement) and its values. The company has also begun the process of transitioning all locations that perform water testing onto recombinant alternatives. Finally, it aims to begin proposing recombinant endotoxin testing alternatives as an option for all regulatory submissions post-2025
- **Bristol Myers Squibb** has begun the process of developing the method to transition water testing at its manufacturing sites, which is a large percentage of LAL testing, to synthetic reagents. It is also in the process of actively testing synthetic alternatives for some products. It included a new section in its ESG (Environmental, Social and Governance) report disclosing a commitment to use 'synthetic alternatives to LAL reagents for new medicines in our development pipeline'
- **Orion Oyj** has had discussions with its contract research agencies and included alternative testing methods within relevant investment consideration processes. It confirmed that it plans to include commentary on both its impact and related actions regarding horseshoe crabs under the 'E4 biodiversity section' of its 2025 CSRD statement – something we have urged all companies that need to report under CSRD to do
- **Amgen Inc**: In response to our engagement, Amgen has begun publishing progress reports on its efforts to phase out the use of horseshoe crab-derived reagents in favour of synthetic alternatives. The first report, published in December, states that the company anticipates completion of global validation to enable use of recombinant cascade reagent (rCR) for water testing, which can represent upwards of 80% of a company's use of LAL, in 2025. Amgen has committed to providing periodic public updates until it has completed the transition for water testing and new product approvals. Amgen's report also links to an update of its biodiversity statement, which notes its work to align with the recommendations of the Taskforce on Nature-related Financial Disclosures (TNFD).

On the broader question of efforts to understand the animal welfare and conservation position of horseshoe crabs, several companies provided particularly good responses.

Orion Oyj is developing a biodiversity action plan which involves assessing its strategic resilience against biodiversity loss and identifying associated risks. One issue of particular focus is any use of endangered species, to gain a deeper understanding of the current baseline before establishing milestones and targets.

GSK plc, in the context of its overarching biodiversity commitments designed to align with the post-2020 Global Biodiversity Framework to halt and reverse biodiversity loss by 2030, is implementing its Sustainable Marine Sourcing standards, developed in 2022. The standard sets requirements across eight impact categories, including greenhouse gas (GHG) emissions, biodiversity, waste, labour rights and animal welfare. In 2023, GSK audited its main third-party horseshoe crab blood facilities against such standards but did not identify any major findings. It expects to revisit the facilities in 2024.

Novartis AG said it will 'put actions in place to promote conservation efforts.' It is the only company to date to take this kind of step – that we know of.

WIDER ENGAGEMENT TO AMPLIFY OUR MESSAGE AND STAKEHOLDER ACTION

To strengthen our message to companies, investors and suppliers of endotoxin testing, we also took part in the following meetings and calls during the year:

PSCI annual meeting: We delivered the keynote speech to the PSCI's 80 members at its annual meeting in New York. Several pharmaceutical companies within scope of the Nature Action 100 initiative were in the audience, providing a good opportunity to introduce the investor perspective on nature loss generally, and the use of horseshoe crabs, specifically

NA100 pharmaceutical sector educational webinar for investors: We were pleased to partner on this webinar for NA100 investor participants on this issue, urging them to cover endotoxin testing in their NA100 engagements

New York State Senate Bill: We also engaged with two US companies with operations in New York state on their positions on a proposed bill to ban the in-state horseshoe crab (HSC) harvest until the end of 2028. Unfortunately, the NY Governor vetoed the bill, but we hope it will return in future legislative sessions at which point we will urge the relevant companies to support it

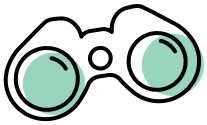
Biopharma Roundtable: We attended a workshop of the Biopharma Roundtable, hosted by the New York Stock Exchange. Five corporations participated, as did other investors. We discussed the evolution of pharmaceutical industry ESG disclosures and practices and highlighted the use of horseshoe crab blood, which has not generally been disclosed in investor-facing reports

Endotoxin suppliers' open letter: In the early summer we also had a call with the key suppliers of LAL reagents, **Charles River Laboratories International Inc, Lonza AG, bioMerieux SA and Associates of Cape Cod, Inc** to discuss and help finalise a public statement that these companies were preparing to demonstrate their united position on the desirability, equivalence and feasibility of switching to synthetic endotoxin testing. The group's statement, released in July, features our engagement on the issue, which the suppliers believe has helped to increase interest in their synthetic products

BNPP AM Cape May event: Working with Physicians Committee for Responsible Medicine, Eli Lilly and Company, and other members of the Horseshoe Crab Recovery Coalition, we hosted an event in Cape May, New Jersey, to witness the annual horseshoe crab spawn and red knot migration. Eli Lilly and Company, GlaxoSmithKline plc (GSK), AstraZeneca plc and Regeneron

Pharmaceuticals Inc attended the event. There were several presentations on various aspects of the topic, which led to an active and engaging discussion among the companies about how to address the remaining regulatory obstacles to synthetic adoption. Participants also went to the beach to see the horseshoe crabs at first hand. They learned how local scientists, supported by a network of volunteers, are tracking the health of the local horseshoe crab population. Following the event, we, and several other corporate representatives, participated in a red knot trapping exercise where we tagged and measured 100 birds to provide data to evaluate the health of this year's migration. We are currently planning a larger event for 2025

At the end of the year, Revive & Restore, the Horseshoe Crab Recovery Coalition and the Center for Biological Diversity launched a new industry scorecard to measure progress towards adoption of synthetic alternatives. We were pleased to have provided guidance on it. We look forward to seeing the first ratings during 2025.

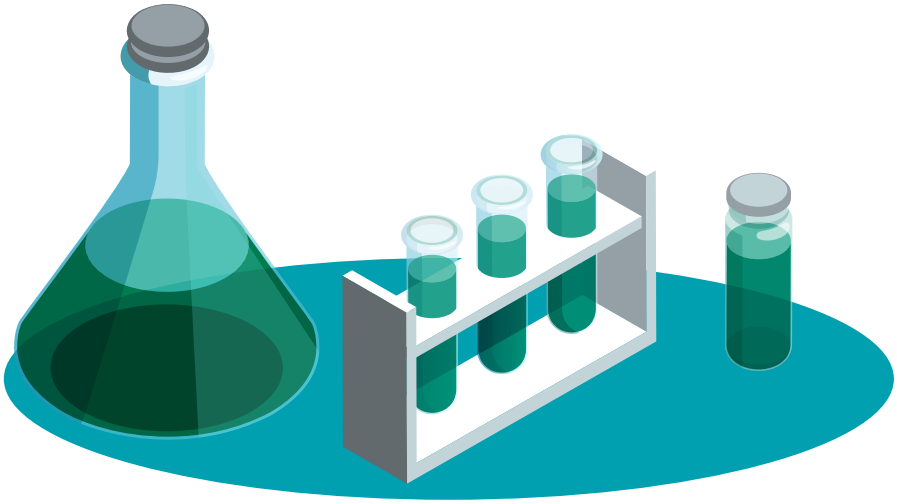


CONCLUSION

Our engagement continues to show progress across the industry. Companies are at various stages of exploring the equivalence of synthetic alternatives to horseshoe crab-based tests and/or actually switching to alternatives, usually starting with lab water and looking at how to make a similar move for new product testing.

We are pleased to have heard from various sources that our work has raised awareness and is generating discussion among industry players.

Source: BNPP AM



The securities mentioned are for illustrative purposes only; they are not intended as solicitation of the purchase of such securities, and do not constitute any investment advice or recommendation.

While we set out changes to company practice and disclosure that were in line with our expectations and / or recommendations, we acknowledge that these changes in many cases may not have resulted from our engagement alone, as companies take input from many other investors and stakeholders.

All information referred to in the present document is available on www.bnpparibas-am.com

VIEWPOINT

April 2025 - Design: Creative Services BNPP AM - P2504062

BNP PARIBAS
ASSET MANAGEMENT

The sustainable investor for a changing world