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A NEW TECHNOLOGY TO SOLVE **the peptide API supply challenge**

The market opportunity and the manufacturing challenge

Two years ago, Croda announced that we had a technology to solve the peptide active pharmaceutical ingredient (API) supply challenge.

Now, we have the data to prove it.

The world has now firmly entered the peptide therapeutics era. Demand for incretin-based peptide agonists continues to accelerate as **glucagon-like peptide-1 (GLP-1)** and **glucose-dependent insulinotropic polypeptide (GIP)** therapies expand rapidly across diabetes, obesity, cardiovascular disease, and broader metabolic health applications.

Although drugs in this class were first discovered decades ago, the clinical and commercial impact of the recent iterations has transformed the market. Public awareness of products such as semaglutide and tirzepatide has driven unprecedented global demand, while the next generation of peptide therapeutics is already advancing through development pipelines.

At the same time, the market itself is evolving rapidly. Semaglutide is now generic in countries including India and Canada, increasing affordability and patient uptake. Oral peptide formulations are also moving closer to widespread adoption.

While these formulations offer major patient advantages, they dramatically increase API requirements compared with injectable products. Novo Nordisk's oral semaglutide formulation, for example, requires approximately 70 times more API than its injectable equivalent.

The consequence is clear: global peptide demand is accelerating far faster than existing manufacturing technologies can scale to meet it.

Unfortunately, the current peptide production infrastructure was never designed for the volumes now required. Existing technologies remain expensive, difficult to scale, resource intensive, and environmentally burdensome at the production levels future peptide therapeutics will demand.

Global patient penetration remains relatively low despite the enormous market attention surrounding GLP-1 therapies. According to research by JP Morgan, diabetes penetration is still estimated at only around 7%, while obesity penetration remains close to 2%. In other words, the overwhelming majority of potential patients worldwide still cannot access these therapies. By addressing the manufacturing bottleneck, supply can increase to meet demand, thereby driving down price, and helping these therapies become more accessible.

In this article, we examine the limitations of existing peptide manufacturing technologies, explore why current approaches are struggling to keep pace with demand, and present the latest data from Croda's Group Assisted Peptide Production (GAPP™) technology.

The evidence now demonstrates that GAPP™ is capable of delivering what the industry has long required: a cleaner, scalable path to high purity complex peptide manufacturing.

GLP-1 demand continues to accelerate

- In 2025, the WHO added GLP-1 therapies to its Essential Medicines List for managing type 2 diabetes in high-risk groups.
- According to KFF Health Tracking Poll data, approximately one in eight U.S. adults has now used a GLP-1 therapy.
- Oral peptide formulations are expected to significantly increase API requirements, compared with injectable formulations.
- Novo Nordisk's oral semaglutide formulation requires approximately 70 times more API than the injectable equivalent.
- Some global GLP-1 market forecasts now exceed $180 billion by 2033.

Why existing peptide manufacturing technologies are struggling

The peptide industry today relies primarily on two established manufacturing approaches: **Solid Phase Peptide Synthesis (SPPS)** and **Liquid Phase Peptide Synthesis (LPPS)**. And more recently, various forms of Tag-Assisted Peptide Synthesis (TAPS) have emerged to bridge the gap between them.

Each approach offers certain advantages. However, none has fully solved the central challenge facing the peptide industry today: how to manufacture highly complex peptide therapeutics at the scale, speed, cost profile, and sustainability level now required.

Solid Phase Peptide Synthesis (SPPS)

Highly capable but increasingly difficult to scale sustainably or economically

SPPS remains the dominant manufacturing approach for complex peptides and historically has been the only chemical synthesis technology capable of reliably producing GLP-1 therapeutics. However, it relies on specialised resins, leading to repeated filtration and solvent washing cycles. This makes large-scale SPPS manufacturing expensive, resource intensive, and difficult to scale efficiently at the volumes now required.

SPPS also requires specialised peptide-only infrastructure and generates significant solvent waste - often between 10 and 20 kilotons per ton of peptide API produced.

Ergo, SPPS remains highly capable, but increasingly difficult to justify economically or sustainably at the production volumes future peptide therapeutics will require. There is simply not enough available SPPS reactor capacity around the world to meet the forward demand for GLP-1 peptides.

Liquid Phase Peptide Synthesis (LPPS)

Scalable and efficient but fundamentally limited in capability

LPPS offers important scalability and sustainability advantages because reactions occur entirely within a homogeneous liquid solution using conventional reactor infrastructure.

However, peptide solubility becomes increasingly difficult to control as peptide chains grow longer and more complex. In practice, a conventional LPPS workflow becomes untenable for fragments larger than 3 – 5 amino acids. Complicating this further, assembly of larger fragments from 3 – 5 mer pieces requires fragment activation during the fragment condensation steps, which leads to significant complications, including epimerisation, purification, and solubility control (operability) as the pieces eventually grow larger. Given that most modern GLP-1 therapeutics require around 40 amino acids, plus conjugation of a complex lipid side chain, LPPS capability is simply not suitable for these APIs.

LPPS therefore offers sustainability and scalability, but is simply incapable of producing many next-generation peptide APIs.

Tag-Assisted Peptide Synthesis (TAPS)

Incremental improvements, but still constrained by trade-offs

Over the last decade, growing interest has emerged around Tag-Assisted Peptide Synthesis technologies, often referred to as TAPS or TA-LPPS. These approaches attempt to bridge the gap between SPPS capability and LPPS scalability by using lipid tails or related tags to facilitate peptide purification during solution-phase synthesis.

While these technologies can improve certain aspects of LPPS operability, most existing systems still suffer from limited solubility control. In practice, many conventional tag technologies begin losing reliable process control between approximately 5–10 amino acids. An improvement over LPPS, but still far below the complexity required for many GLP-1 therapeutics. This lack of control leads to several technical difficulties:

1. Reliance on co-solvents, like dimethyl sulfoxide (DMSO) or dimethylformamide (DMF), to maintain control. DMF is a sustainability and regulatory issue, and DMSO will cause increased levels of insertion and epimerisation, creating close-eluting impurities that increase purification burden, reduce API yield, and increase cost.
2. Reliance on precipitation / filtration / washing every cycle, while more consistent than standard LPPS, still leads to long cycle times and high solvent use.
3. If a true one-pot extraction process, reliance on solvents such as methylene chloride or chloroform, which are a sustainability and regulatory nightmare.
4. If a true one-pot extraction process, stability issues of C-terminal Tag esters in wet solvent, leading to unacceptable levels of hydrolysis or time-consuming drying steps at every cycle.

The above limitations lead more to trade-offs than to a true solution to the problem. For example, a developer may find that going from an LPPS to a TAPS process allows them to make slightly more complex peptide fragments, but that this will certainly increase their costs, along with solvent and material usage. And they still may not be able to make their complex fragment or target with acceptable economics.

In addition to the technical limitations, many existing TAPS systems also operate within highly restrictive commercial models that create significant vendor lock-in for pharmaceutical innovators.

As a result of these technical and commercial limitations, most current TAPS technologies still represent a compromise between capability and scalability, rather than a complete solution to the peptide manufacturing challenge.

The ideal peptide manufacturing platform would be more capable, scalable and sustainable

To meet the future demands of peptide therapeutics, the industry requires a manufacturing technology capable of combining the strengths of SPPS and LPPS while avoiding their limitations.

Any technology to tackle the GLP-1 challenge must be **capable** enough to synthesise complex molecules and complex APIs. An ideal solution would combine all solid phase's capabilities (ie. unit operations that are rapid, simple and consistent for complex molecules) but be able to apply them to a solution phase, which is more efficient and sustainable.

For the huge, growing peptide demand, the technology needs to be rapidly **scalable**, preferably within existing infrastructure, to decrease the need for further CapEx by utilising existing reactor capacity.

And, because of this huge demand and the huge waste profile associated with peptide manufacturing, the technology must be environmentally **sustainable**.

Croda has now proven its GAPP™ technology can deliver all of this.



GAPP™: A technology to solve the peptide API supply challenge

Group Assisted Peptide Production (GAPP™) is Croda's next-generation TAPS platform. The technology has been under development for more than 12 years and represents a fundamentally different approach to solution-phase peptide manufacturing.

How it works: Anchoring for solubility control

Unlike conventional tag-assisted systems, GAPP™ introduces a proprietary solvent anchor alongside a smaller lipid tail. This Anchor provides the precise solubility control required to synthesise highly complex peptide sequences fully in solution.

The Anchor (lipid + linker + solvent anchor) performs three critical functions simultaneously.

- First, the lipid prevents peptide loss during aqueous workup by maintaining low water solubility, enabling rapid water-wash purification without sacrificing yield. This allows GAPP™ to replace many solvent-intensive SPPS wash cycles with water-based operations, dramatically improving sustainability performance.
- Second, proprietary Linker technology stabilises the C-terminal ester, where the Anchor attaches to the peptide, stabilising the ester to the rapid water wash protocol while maintaining yield and purity. This Linker also allows for soft cleavage, or removal of the Anchor, while maintaining side chain protection.
- Third - and most importantly - the solvent anchor actively controls and enhances peptide solubility within the organic reaction phase. This is critical for maintaining process-relevant concentrations during scale-up. It also enables the synthesis of much longer peptide sequences than conventional LPPS or many existing TAPS systems can reliably support.

Precise control of solubility enables fast, predictable extraction workflows that remain consistent - from one peptide sequence to the next.

This creates several major advantages simultaneously. Processes can operate at higher concentrations, reactor volumes can be reduced, extraction performance is excellent and highly consistent, development timelines become significantly shorter, and manufacturing cycles can be completed more rapidly and consistently.

Most importantly, GAPP™ enables access to highly complex peptide synthesis fully in solution. This combines SPPS-like capability and operability with the scalability and process economy of LPPS chemistry.

The Tirzepatide proof of concept

The data speaks for itself

Croda has successfully synthesised all four Tirzepatide (TZP) fragments using GAPP™, providing the clearest demonstration yet of the platform's capability.

As one of the most commercially important and technically demanding GLP-1 therapeutics currently on the market, Tirzepatide represents a significant challenge for peptide manufacturing. The molecule contains 39 amino acids, alongside a complex lipid conjugation. This places it well beyond the practical limits of conventional LPPS workflows and many existing tag-assisted technologies.

To evaluate the performance of GAPP™, each fragment was synthesised using Croda's solvent anchor approach. Development was carried out by one chemist per fragment, over the course of a few weeks:

The resulting data demonstrated consistently high yield and purity, alongside strong process economy, rapid cycle times, robust scalability characteristics, and exceptional solubility control throughout the syntheses.

Importantly, GAPP™ successfully produced peptide fragments that would traditionally have required solid-phase synthesis due to their complexity and length. This marks a major milestone for the technology. It demonstrates not only that GAPP™ has overcome the long-standing limitations of conventional liquid-phase approaches, but that it can function as a practical, scalable alternative to solid-phase synthesis for complex peptide manufacturing.

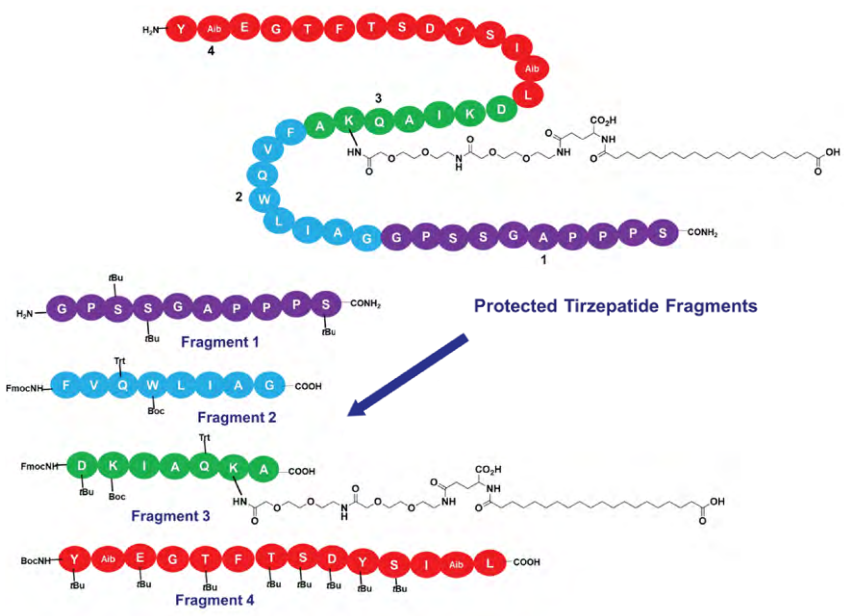


Figure 1. Tirzepatide fragments as examples

Fragment number	Sequence	Development resource	Development Time
1	GPSSGAPPPS	One Chemist	8 weeks
2	FVQWLIAG	One Chemist	2 weeks
3	DKIAQK(Lipid)KA	One Chemist	12 weeks
4	Y-Aib-EGTFTSDYSI-Aib-L	One Chemist	16 weeks

Table 1. Development time

Purity and yield data for all fragments

Fragment name	Percentage yield (from anchor)	Crude purity
Frag 1 (TZP 30-39)	93%	95%
Frag 2 (TZP 22-29)	93%	93%
Frag 3 (TZP 15-21 + lipid)	90%	92%
Frag 4 (TZP 1-14)	98%	86%

Table 2. Purity and yield data for all fragments

Soft cleavage of frag 3 (TZP 15 – 21 + Lipid)

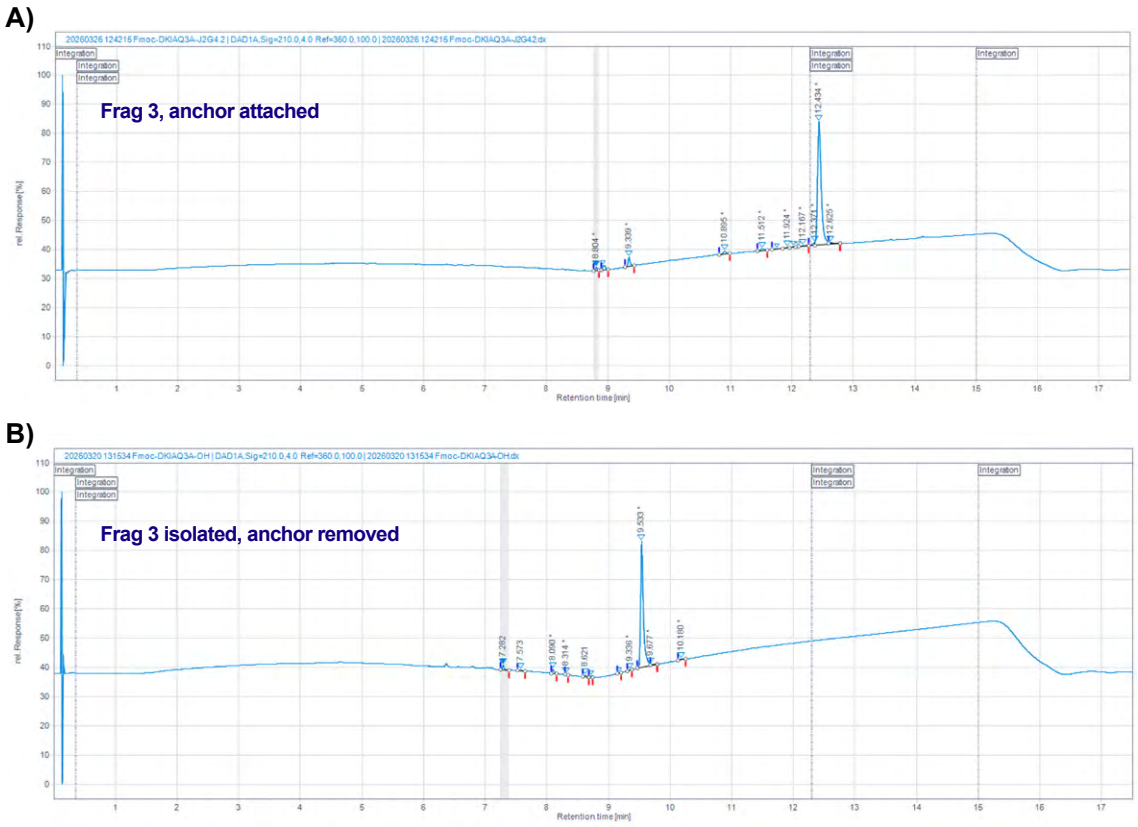


Figure 2. Soft Cleavage of Frag 3 (TZP 15 – 21 + Lipid)

HPLC data shows Anchor can be soft cleaved to prepare a fragment for condensation, then easily removed via a single precipitation step, even for lipidated Frag 3.

Images of isolated TZP fragments from GAPP™



Image 1. Isolated TZP Fragments from GAPP™

Synthesising peptide fragment 1

Fragment name	GAPP™	LPPS	SPPS
Relative Material Cost per Kg **[Ratio]**	1.00[1]	0.54	1.54
Product yield per 2KL batch **[Kg]**	73[2]	101	73
Total Plant Hours per 2KL batch **[Hours]**	94	206	246[3]
Plant Days per 2KL batch **[Days]**	3.90	8.59	10.26
Plant Hours per Kg **[Hours / Kg]**	1.29	2.05	3.38
Avg. Monthly Product Output per 2KL Kit **[Kg]**	467	293	177

Table 3. Fragment one would be particularly challenging with other tag technologies, due to its high percentage of Gly and Pro, which are very difficult to consistently keep in solution. With GAPP™, no issues with control were encountered, projecting a process time of only 3.9 days per 2 KL batch.

Synthesising peptide fragment 4

Fragment name	GAPP™	LPPS	SPPS
Relative Material Cost per Kg **[Ratio]**	1.00[1]	N/A	1.29
Product yield per 2KL batch **[Kg]**	106	N/A	104
Total Plant Hours per 2KL batch **[Hours]**	223	N/A	280[2]
Plant Days per 2KL batch **[Days]**	9.28	N/A	11.66
Plant Hours per Kg **[Hours / Kg]**	2.10	N/A	2.69
Avg. Monthly Product Output per 2KL Kit **[Kg]**	286	N/A	223

Table 4. Fragment 4 contained 14 amino acids, well beyond what LPPS or another tag technology can do. And GAPP™ outperformed SPPS on all key metrics.

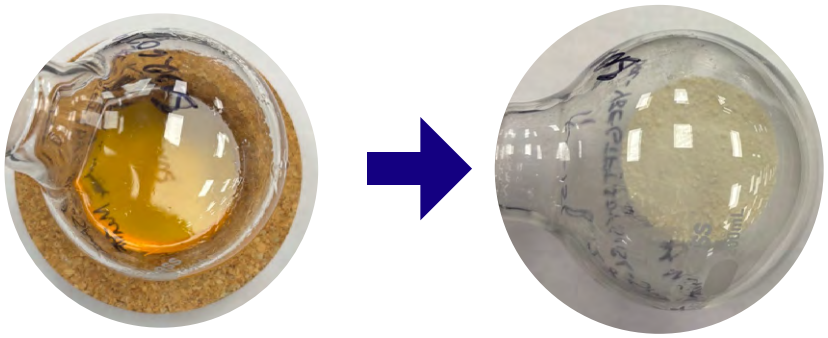
Process Mass Intensity Fragments 1 and 4

FRAGMENT 1 (TZP 30-39)	GAPP™	LPPS	SPPS
PMI **(Kg/Kg)** water not included	188	183	1422
Petrochemical **(Kg/Kg)**	151	116	1422

FRAGMENT 4 (TZP 1-14)	GAPP™	LPPS	SPPS
PMI **(Kg/Kg)** water not included	239	N/A	971
Petrochemical **(Kg/Kg)**	149	N/A	971

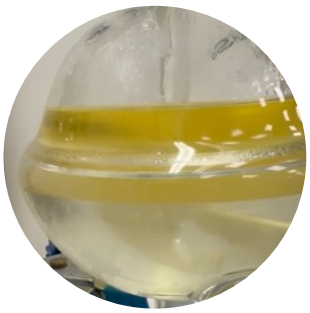
Table 5. GAPP™ is competitive on sustainability and also capable of producing fragments that some other methods cannot.

Boc-TzpFrag4-Anchor in solution **Boc-TzpFrag4-Anchor precipitated**



- TZP 1-14 fully soluble at 376 g / Kg of solution
- Only 1.66 g of solvent per gram of 14-mer peptide

Image 2. We achieved high yield and high purity for each TZP fragment, with minimal amounts of solvent needed per gram of product.



GAPP™ Anchored

TZP 1-14 Y-Aib-EGTFTSDYSI-Aib-L

No optimisation (1 FTE x 1 wk) Single Fragment, 130 mg / mL

Now up to 200 mg / mL with optimisation (67 mmol / L)



GAPP™ Anchored

TZP 30 – 39 GPSSGAPPPS-amide

No optimisation (1 FTE x 1 wk) Made using Suberol-GAPP™ Anchor Single Fragment, 110 mg / mL

Now up to 160 mg / mL with optimisation (80 mmol / L)



2,000 L Vessel

All phase splits consistent

All splits < 10 min

Image 3. Note the consistent, clean and rapid phase splits across each fragment.

Even at this relatively early stage of optimisation, the data demonstrates that GAPP™ already outperforms many conventional manufacturing approaches across major operational, sustainability, and scalability metrics

How to use GAPP™ for your peptide production

A simpler, more versatile, and more economical approach that avoids vendor lock-in

There are many different proprietary tag technologies that can tie a peptide producer to a single provider, preventing supply chain diversification and driving up costs.

Alternatively, this model can create the need for a producer to invest in different tag processes with different suppliers for every product, along with all the expense and complexity that entails.

Our approach is different, and our offer is simple. We manufacture the Anchor, and then help you develop a process to use it for your own peptides. This is possible because Croda is the only company in the world with a TAPS technology that is this capable, and that can be so easily and quickly adapted to different kinds of GLP-1 agonist production.

There are two ways to integrate GAPP™ into your own peptide synthesis processes. These are:

- **Option 1: Hands on experience with support**

  If you wish to get hands on experience with the technology and undertake a development project in house with Croda's help (the self directed approach), we can provide the Anchor and help with development - for example, by providing model processes to help you learn the technology.

- **Option 2: Full development and handover**

  Alternatively, if you do not want to develop your own processes, Croda can do the development in-house, before transferring that process to you. You can then use that process to manufacture the peptide yourself, or contract with the CDMO of your choice.

Please note, any and all use of Anchor or proprietary Linker materials, along with GAPP™ methodology, will require either a Material Transfer Agreement or License Agreement with Croda.

A next generation TAPS for the new peptide therapeutics era

GAPP™ is a true replacement for solid phase synthesis. It offers one-pot synthesis of peptide therapeutics, but with SPPS-like operability, capability, scalability, and process economy.

It merges the best of existing processes to make peptide production more sustainable, drastically cutting raw material and solvent use, hazardous waste, and purification steps. And, it does all this while eliminating Carcinogenic, Mutagenic, or toxic to Reproduction (CMR) substances.

This makes GAPP™ more than simply an alternative technology. It is a practical route to de-risking supply, reducing costs, and enabling wider access to GLP-1 therapies - along with all the substantial health and societal benefits that will provide.

With GAPP™, we have the technology to produce GLP-1 agonists at scale. Now we need peptide makers and drug innovators to embrace the technology in practice.

A new peptide manufacturing era begins here - will you be a part of it?

Contact us to learn how GAPP™ can help solve your peptide manufacturing challenges.

References

[1] Magalhães, P. O. et al. Methods of endotoxin removal from biological preparations: a review. J Pharm Pharmaceut Sci. 10 (3): 388-404 (2007).

[2] Kondratova, L. et al. Removal of endotoxin from rAAV samples using a simple detergent-based protocol. Mol Ther Methods Clin Dev. 15: 112-119 (2019).

[3] Pi. W. et al. Purification of plasmid DNA using anion exchange chromatography and removal of endotoxin with triton X-114 or triton X100. Chin J Chromatogr. 25: 809-813 (2007).

[4] Reichelt, P. et al. Single step protocol to purify recombinant proteins with low endotoxin contents. Protein Expr Purif. 46: 483-488 (2006).

[5] Koziel, D. et al. Broad application and optimization of a single wash-step for integrated endotoxin depletion during protein purification. J Chromatogr B. 1091 :101107(2018).

[6] Candidate list of substances of very high concern for authorisation (2012) ECHA. Available at: https://echa.europa.eu/candidate-list-table/-/dislist/details/0b0236e1807db570 (Accessed: 19 May 2023).

[7] KSubstance information ECHA. Available at: https://echa.europa.eu/substance-information/-/substanceinfo/100.123.919 (Accessed: 15 June 2023).

[8] Annex XIV Authorisation list (2022) ECHA. Available at: https://www.echa.europa.eu/authorisation-list (Accessed: 19 May 2023).

[9] Lindsay, G.K. et al. Single-step, chromogenic Limulus amebocyte lysate assay for endotoxin. J Clin Microbiol. 2(5): 947-951 (1989).

[10] Zhang, G. and S. Ghosh. Molecular mechanisms of NF-kappaB activation induced by bacterial lipopolysaccharide through Toll-like receptors. J Endotoxin Res. 6(6): 453-457 (2000).

[11] Derde, M. et al. Hen egg white lysozyme permeabilizes Escherichia coli outer and inner membranes. J Agric Food Chem. 61(41):9922-9929 (2013).

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