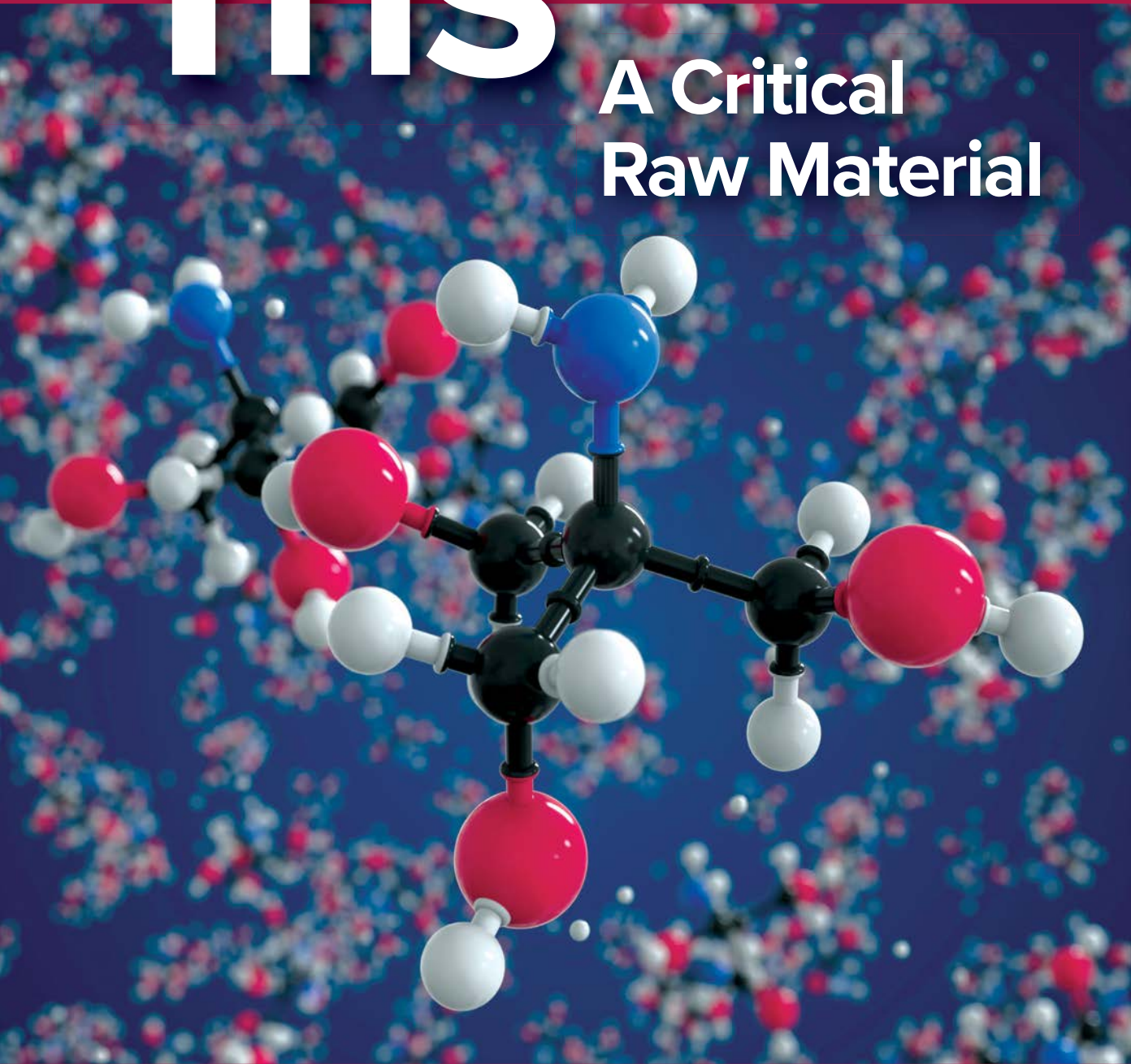


Tris

A Critical
Raw Material



**BioProcess
International**
SPECIAL REPORT

ANGUS[®]

Tris, a Critical Raw Material

Improving the Quality and Consistency of Supply

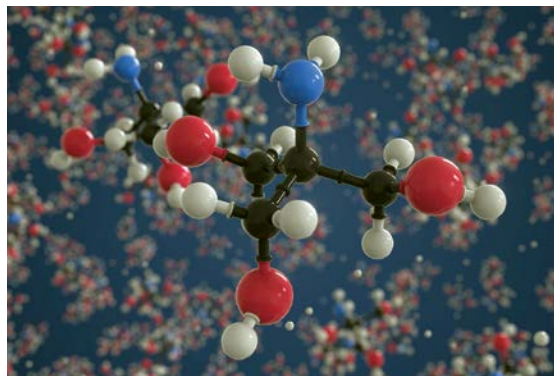
Cheryl Scott

Tris(hydroxymethyl)aminomethane — otherwise known as “tris” — is a buffer used extensively in biopharmaceutical manufacturing, including for mRNA-based vaccines that target SARS-CoV-2, and diagnostic/assay test kits. The market for this essential raw material continues to expand as a result of rapid growth in the biologics industry, the compound’s broad utility in a wide range of biological formulations and manufacturing processes, and the unprecedented global demand for COVID-19 vaccines. That increased demand shows no signs of slowing down and puts increasing pressure on the tris supply chain. ANGUS Life Sciences is helping the biopharmaceutical industry improve productivity by not only strengthening the supply chain for tris, but also reducing handling difficulties associated with its tendency to clump and cake.

ADDRESSING CAPACITY DEMAND

ANGUS Life Sciences is the world’s largest supplier of tromethamine buffers and the only manufacturer of the tris molecule based in the Western hemisphere. The company sells directly to biopharmaceutical customers and contract manufacturing organizations, as well as to reprocessors who repackage the chemical or process it into different grades and derivatives. In October 2021, ANGUS announced plans to expand its tris manufacturing footprint in the United States by adding a fourth dedicated manufacturing line to the company’s plant in Sterlington, LA. That expansion nearly doubles the company’s global production capacity. The plant also recently started commercial production of tris hydrochloride, which is used in a number of biopharmaceuticals, vaccines, and diagnostics test kits such as those for COVID-19.

High-purity, multicompendial grades of TRIS AMINO products also are made at ANGUS’s recently expanded manufacturing facility in Germany. In addition to expanding capacity for production of these essential buffers, the presence of manufacturing plants on two continents mitigates the potential risk of supply disruptions.



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ANGUS is the only fully integrated original manufacturer of tris, a fact that provides supply chain transparency, continuity, and security. The company makes the primary raw materials used for production of tris, including nitromethane, which is generated from a proprietary nitration process. The approach contrasts with that of the only other major supplier, which is based in China and relies on multiple sources for different chemistries used in tris manufacturing. Depending on additional steps in the supply chain, such as the need to purchase nitromethane on the open market, increases the risk of supply disruptions and makes batch-to-batch consistency difficult to achieve.

INCREASING PRODUCT CONSISTENCY

Along with strengthening the supply, ANGUS recently introduced TRIS AMINO AC advanced crystal buffer, a next-generation form of the tris molecule that is less prone to clumping and hardness. Because it is a hygroscopic material, tris absorbs moisture. That causes clumping and caking, the degree of which partially depend on environmental and/or storage conditions (e.g., humidity, compression, temperature cycling) and their duration. Clumping generally manifests as aggregates mixed in with the powder but also can result in formation of solid blocks. Clumping of tris buffer leads to increased operating costs and potential safety concerns as biomanufacturing

Figure 1: The unique morphology of TRIS AMINO AC buffers helps reduce cake strength, resulting in less clumping and hardness than are possible with competitive materials.

Conventional tris crystal structure



TRIS AMINO AC advanced crystals from ANGUS



operators work to declump the raw material. In addition, the time required to break apart aggregates of tris buffers manually and the associated need for prolonged mixing can delay processes, reduce productivity, and create operational bottlenecks.

TRIS AMINO AC buffers are manufactured using proprietary process technology that does not change the tris molecular structure. ANGUS's process engineers studied the mechanisms of clumping and developed a process that eliminated as many contributing factors as possible. The tendency of tris to clump thus is minimized through a proprietary approach to crystallization growth and harvesting. A precise balance of mechanical properties such as crystal size and chemical properties such as dryness provides further reduction in clumping and best-in-class process controls.

With a unique crystal morphology characterized by a larger, more rounded particle structure than traditional tris products exhibit, TRIS AMINO AC buffer typically does not form strong cakes even when subjected to packaging, shipping, and storage conditions that otherwise might affect the chemical (Figure 1). Low interparticle cohesion among the crystals makes clumps breakable with limited effort, and the spherical crystal shape provides for improved dispensing and transport through conveyors. Because fewer fine particles are present than with other tris products, dust emissions are lowered, which benefits employees handling the chemical.

TRIS AMINO AC buffers are manufactured to high purity and quality standards and contain no additives or anticlumping agents. Because of their unique physical properties, the new tris buffers provide operational benefits related to handling and preparation at bioprocessing facilities, where the ultimate impact on facility budgets can be

Because of their unique physical properties, new tris buffers provide operational **BENEFITS** related to handling and preparation at bioprocessing facilities, where the ultimate impact on facility budgets can be substantial.

substantial. This is especially important for facilities that use tris after it is subjected to long periods of shipping/storage, or humid conditions.

A CONVERSATION WITH DAVID NEUBERGER

David Neuberger is president and chief executive officer (CEO) of ANGUS Chemical Company. In November 2021, we spoke about the company's history and plans for the future.

How has ANGUS evolved over the years? The origins of our company date back to the 1930s, when chemists at Purdue University developed a novel nitroalkane chemistry platform. In the 1940s, that platform evolved into the Commercial Solvents Corporation, which provided a variety of drugs and ingredients to scientists around the world as well as the nitroalkane chemistries that we continue to benefit from today. Some assets of that corporation were sold to Alberta Natural Gas US, which is where the ANGUS acronym originated. Dow Chemical acquired ANGUS, then went through a divestiture in 2015. Under the dual ownership of Ardian and Golden Gate Capital, we could take a fresh look at the markets in which we want to invest and serve. As part of that analysis, it was clear that biological buffers were an underserved part of the industry.



We've **INVESTED** over US\$100 million . . . geared toward and supportive of the life-sciences space. That includes good manufacturing practice (GMP) compliance, regulatory resources, and the highest level of quality and purity assurance.

—David Neuberger, president and CEO,
ANGUS Chemical Company

Why was the tris market underserved? Quite a bit of rebranding and repurification occurs for life-science ingredients, particularly consumables and raw materials such as tris. Starting materials come out of the United States, Europe, and China and then are sold to intermediaries and reproducers that may choose to rebrand, reprocess, or use the materials in house. That leads to a great deal of market confusion in terms of exactly where materials are coming from. Risks for recalls and low quality become significant with long, convoluted supply chains, and we knew that people prefer to work with brands they know and trust. Given this landscape, we thought it was a unique opportunity for ANGUS to step up.

We've invested over US\$100 million to make our portfolio more specifically geared toward and supportive of the life-sciences space. At the end of the day, that includes good manufacturing practice (GMP) compliance, regulatory resources, and the highest level of quality and purity assurance.

What was the impetus for your recently announced capacity expansion? The markets for our products are strong and healthy, and there is pent-up demand. We completed our most recent major expansion in Ibbenbüren, Germany, where we had an existing site; we will be expanding in the United States with additional capacity expected to come online in 2023. Today, we have dual-source manufacturing capabilities for our highest-purity tris products out of both the United States and Germany. We are cautiously optimistic that the size and scope of our expansions should enable us to support the market over the next four or five years.

How do you ensure quality across your manufacturing locations? Tris produced at each location meets the same specifications for our highest-purity product families. Right now, we are producing TRIS AMINO AC buffers in Germany only. The chemical makeup is identical to that produced in the United States, but our innovative manufacturing process produces inherently better flow properties

than those of anything else we've seen available. We use the exact same quality procedures and backbone at both sites. We do regular testing, analysis, quality control (QC) validation, and testing validation so that we can say with complete confidence that the products coming out of both facilities are identical in purity and consistency.

The way we developed the AC product is exciting, and I know that our customers will agree. We chose not to use process aids; it would have been easy enough to add silica or some other type of inorganic ingredient as a flow aid, but we chose not to do so.

What's on the horizon for ANGUS? We have line of sight on expansions that will extend our buffer portfolio. Buffers are the real bread-and-butter offering that largely defines ANGUS today. We've publicly announced our expansion into tris hydrochloride. We are producing that with a new line at our facility in Louisiana. We also have additional buffers that will be coming online within the next year or so.

We don't have aspirations to be a contract manufacturing organization (CMO). We don't have aspirations to move directly into active pharmaceutical ingredients (APIs). We are proud of our ability to support biotechnology customers, and that's what we will continue to focus upon. I would expect our future business makeup to be a combination of organic investments and acquisitions. Given the strong organic growth and various assets we see out there today, this approach could potentially double our size in the next couple of years.

Cheryl Scott is cofounder and senior technical editor of BioProcess International, part of Informa Connect; 1-212-600-3429; cheryl.scott@informa.com. TRIS AMINO and TRIS AMINO AC are registered trademarks of ANGUS Chemical Company.