WHITEPAPER

AJINOMOTO SUSTAINABLE SOLUTIONS

RETHINKING TRADITIONAL MANUFACTURING PROCESSES TO IDENTIFY GREEN OPPORTUNITIES

SOME CALL IT MAGIC
WE CALL IT SCIENCE

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Source: Ajinomoto Sustainable solutions

Developing greener, more sustainable processes across the fine chemicals industry is critical and must be top of mind for developers and manufacturers alike. The complexities of high value batch chemistry processes produce a significant amount of waste by way of consumption, workup, and crystallization. As a result, the carbon footprint and waste-to-product ratio in the fine chemical industry is very high. To combat this, developers will need to enlist a broad array of renewable, raw material sources, green chemistry strategies, and innovative technologies. The key is identifying how best to break bad manufacturing habits, developing strategies for sustainable chemical production, and designing approaches to reach sustainability targets.

Approach Sustainable Manufacturing Strategically

Beyond responsibility to the community and our environment, sustainability is a strategic choice and differentiator in the pharmaceutical and fine chemicals field.
In our work at Ajinomoto Sustainable Solutions, we're striving to build a vision for sustainable growth that prioritizes and strengthens our core capabilities.
Our team developed the "Net Zero Strategy," which emphasizes the following targets:

- Manufacturing to ensure carbon neutral production via the electrification of our processes, i.e., replacing fossil fuels used for heating reactors with electric heating
- Purchasing from a green supply chain
- Leveraging a low footprint portfolio during R&D via biocatalysis, electrochemistry, microwave or ultrasound technology
- Maintaining and managing an overarching green strategy

If we translate these goals into targets, in combination with a portfolio growth, the footprint of our commercial processes should reduce 40% by 2030. Furthermore, in 2030, new processes ought to have a footprint that is 80% lower compared to 2019. Though these drastic changes are necessary, that doesn't make them easy to implement. The pharma industry has strict boundaries around changing chemical processes, and if they do change, they require an expensive re-registration.

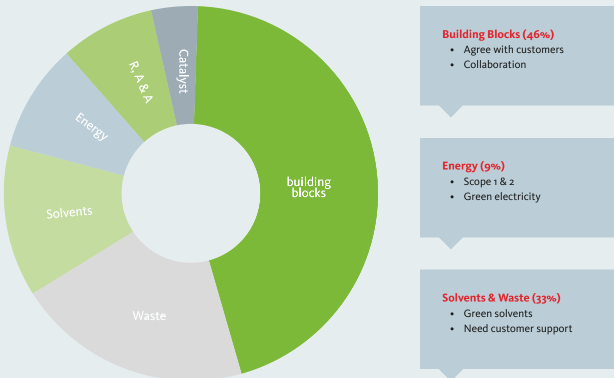

Figure 1. Visualisation of the carbon footprint distribution

As demonstrated in **Figure 1**, energy represents only 9% of our footprint. Even by electrifying and making our energy supply green, we are still a long way from our goals. Solvent and waste represent 33% of our footprint, which calls for the use of green solvents, solvent recycling, and the reduction of waste. The advanced and typically complex chemicals that are used as the basis for our processes are often known as building blocks and purchased from external suppliers. These building blocks account for 46% of our footprint. To change this, our team will need to reach agreements with our customers, and switch to suppliers with smaller footprints.

After translating this initiative into key performance indicators (KPIs), Ajinomoto Sustainable Solutions developed the "ECOpass", a calculation that combines process mass intensity (PMI) and other key aspects of our footprint. PMI represents the kilograms of raw material needed to make one kilogram of the final compound. This is combined with emission factors for materials, solvents, and building blocks. We translate all the materials that are needed into kilograms of CO_2. If you are generating a lot of waste, it's important to discern how best to handle it. For example - are you burning aqueous phases or are you able to discard the active phase into your wastewater treatment plant? Do you have to burn your solvent waste, or is it recyclable?

Figure 2. Green chemistry principles developed by Paul Anastas

Ajinomoto Sustainable Solutions shaped its R&D targets around the 12 green chemistry principles proposed by Paul Anastas in the book, Green Chemistry: Theory and Practice, published in 1998, most of which are highly important, including atom economy and the reduction of derivatives (**Figure 2**). If fewer chemical conversions are possible by working without protecting groups or by using enzymes, a drastic reduction of the footprint of a process can be achieved. Other Anastas principles, including waste prevention, design for energy efficiency, use of renewable feedstock, and catalysis, remain very relevant (**Figure 2**).

In two instances, our experts disagreed with Anastas' theories: less hazardous chemical syntheses and safer chemistry for accident prevention. Some hazardous chemical reagents are quite useful, including azides, cyanides, and oxygen. Azides and cyanides are chemicals that, when introduced in a molecule, serve as the simplest but most effective protecting groups for amines and amides. Oxygen has an explosion danger because we typically work in solvents. However, the use of oxygen as an oxidant in combination with a catalyst results in the greenest possible oxidation.

Shift Your Mindset Around Standard Process Development

Standard process development needs to drive sustainability forward. 75% of the CO2 footprint within a process, excluding building blocks, is generated by the workup. In a classical process, you carry out reactions, add solvent, do extractions, change the solvent, and conduct crystallization, which generates a lot of waste. Quelling solvent use or extractions slightly will not enact meaningful change. Therefore, the industry needs to revolutionize its approach to R&D. One option is striving for zero extractions and distillations, i.e. no workup at all. In the past, this has been done effectively by telescoping stages in which a second chemical conversion is done directly without any intermediate workup.

Another simple but underdeveloped methodology is doing slurry to slurry transformations. Ajinomoto Sustainable Solutions to slurry transformations in which the final product crystallizes at the end of reaction is to collect the product by filtration and recover the solvent. Overall, solvent usage must be readdressed. Typically, chemists follow the literature's precedent for solvent usage rather than trying aqueous chemistry. Instead, consider if the chemistry can be done in water. If that's too difficult, add a small amount of solvent. If that still doesn't address the issue, add an emulsifier or surfactant to perform micellar chemistry.

Starting a green process development revolution requires a lot of project preparation. The team must be trained, informed about new developments, and aware of green chemistry development principles. Let's consider a few examples. In **Figure 3**, (Ref. Green Chem., 2021, 23, 788-795), an example out of the pharmaceutical business. It shows six chemical stages conducted in aqueous medium and only the last stage, from API crude to pure, is still solvent. Workups can be simplified and reduced to specific stage workups if you have a good grasp on the critical impurities towards the API; you may be able to switch to less than three purifications throughout the synthetic scheme. The **Figure 3** pathway uses a few different tricks to drive sustainability. The first stage uses water while the second stage uses a tiny amount of THF in water. If one uses 15% volume of THF instead of 5 volumes or 10 volumes, that's a major improvement.

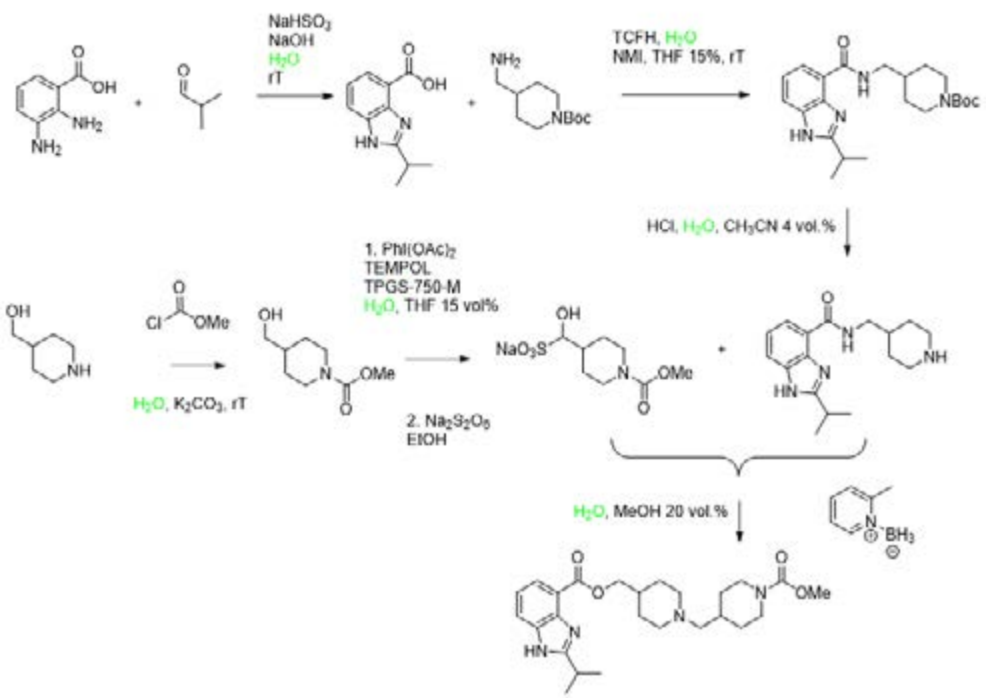

Figure 3. Ref. Green Chem., 2021, 23, 788-795

Figure 3 also exhibits an amide coupling stage using TCFH, a coupling reagent that can be used in water, which implies that even dehydration chemistry is possible in water. The only point that might be lacking in the example is an enzymatic conversion or biotransformation that also typically runs in water. **Figure 4** is an example of an Aji Bio-Pharma project[1] where we conducted phosphorylation in water using $POCl_3$. Chemists would never do $POCl_3$ chemistry in water; however, in this case, it worked perfectly fine and 98% of phosphorylation is observed versus only 2% of free phosphate forming.

[1] Aji Bio-Pharma's small molecule manufacturing is a part of the Ajinomoto Omnichem

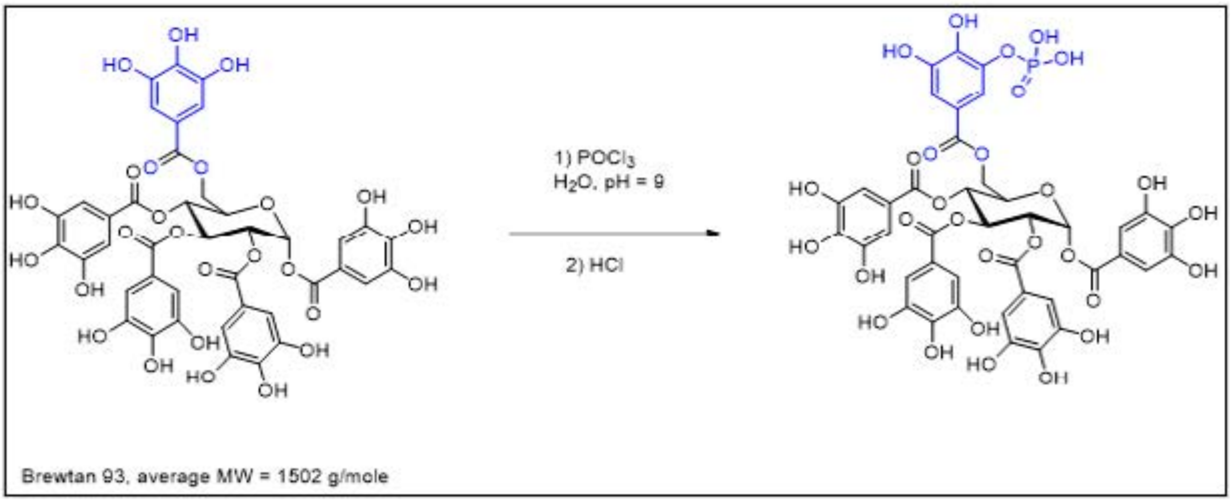

Figure 4. Aji Bio-Pharma example, 3 volumes of water, 98% yield calculated versus $POCL_3$

Another important tool to drive sustainable innovation is using enzymes from fermentation. For example, a typical chemical process to tweak sugar is to decorate the sugar with protecting groups, remove one protecting group, modify the free alcohol, and then do a general deprotection. Reducing the number of stages through a biotransformation requires metabolic engineering of enzymes to ensure that the enzyme effectively and selectively does its job and will do it in a highly concentrated medium. This enzyme can be produced through fermentation, a possible pathway offered to our customers. Third, we apply enzymatic or whole cell chemistry in practice. Our team has experience with transaminases, esterases, phospholipases, dehydrogenases, laccases, oxidoreductases, and more.

Enzymatic chemistry is another important tool to drive sustainable innovation.

If water is an ineffective replacement, green solvents are the next step. There are a number of green solvents, some of which have a high footprint on their own, and they need to be chosen carefully. Consider the following:

- Does the green solvent have a large footprint that requires a lot of stages and purification?
- Should feedstock still be used to make solvents?
- Is it wise to develop processes using a solvent that may not be acceptable 10 years from now?

The focus of renewable solvents are solvents coming from CO or CO_2. One is closing the cycle by using CO_2, and making formic acid, acetic acids, methanol, ethanol, etc. Besides biorenewable solvents, there are also new technologies becoming available. You might conduct chemistry above the boiling points of solvents rather than refluxing, which is energy consuming and demanding.

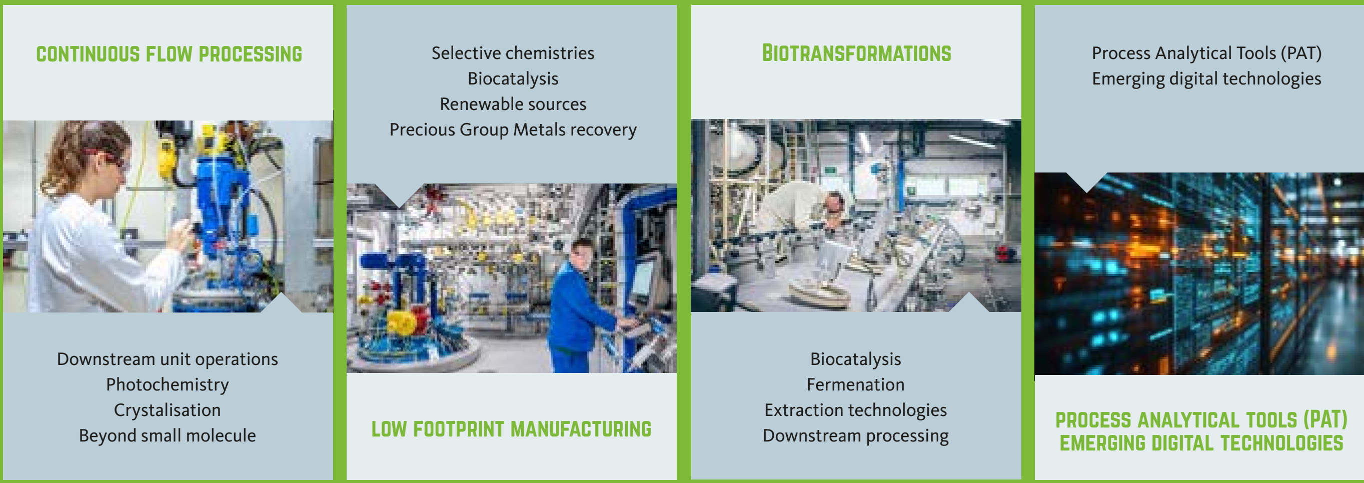

Figure 5. Ajinomoto Sustainable Solutions' strategic sustainable innovation areas

Leverage Innovation Strategically

Rather than using precious metals with massive footprints, base metals present a compelling alternative. In terms of innovation, consider continuous flow processing and low footprint manufacturing (**Figure 5**). Continuous manufacturing opens up a lot of new processing windows. A few examples include the use of photochemistry reactors to build up molecules rapidly or the use of high pressure, high temperature chemistry, and even supercritical chemistry. Dangerous conversion reactions can be done effectively and safely by continuously limiting the concentration of these dangerous reagents or their intermediates.

> **Low footprint technologies and continuous flow chemistry open up new processing windows.**

> **We are developing chemistry without solvents.**

Another tool to drive sustainability is performing gas reactions in flow. Hydrogen and oxygen are the simplest and most atom effective molecules to do hydrogen reductions and oxidations. Ajinomoto Sustainable Solutions is investigating hydrogenation inflow using static mixers. If that is combined with high pressure, this also opens up opportunities to use base methods. If aiming for solvent free chemistry, then mechanochemistry comes into the picture, which is an early-stage technology. To achieve our 2030 goals, though, we are developing a few long shots, including mechanochemistry. In this case, solid to solid conversions are targeted by working without solvents or with minimal solvents, which is then classified as paste chemistry.

Collaborate with Partners from Day 1

As of late, drug developers are increasingly interested in sustainable process development. Ultimately, the effort needs to be phase appropriate as the path from Phase 1 to market is long. Phase 2 is the critical point at which a sustainable, relatively commercial-ready process should be established. At Phase 3, final adjustments are made to optimize loss, i.e., solvent recycling and simplified unit operations.

Rather than a silver bullet, manufacturers need a diverse toolbox to build more sustainable processes. We are striving to think innovatively with a range of strategies, including continuous manufacturing, efficient synthetic routes, and simplified process stages with limited workup.

About Ajinomoto Sustainable Solutions

At Ajinomoto Sustainable Solutions, we produce green specialties in a sustainable and efficient way.

We have been specialized in green chemistry for over 75 years, and we combine our expertise in botanical extractions and access to fermentation with the latest innovative technologies in chemistry. We are a reliable partner for companies in various sectors, such as cosmetics, fragrances, food and feed. Our customes trust upon us to solve complex problems and create innovative products.

Next to our CDMO services , our customers love the power of our tannins, which have been succesfully used in food, animal feed and technical applications for decades. Our tannins are derived from natural sources and have a lower environmental impact than synthetic alternatives.

We are Ajinomoto Sustainable Solutions, your solution for a sustainable future!

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