Case Study

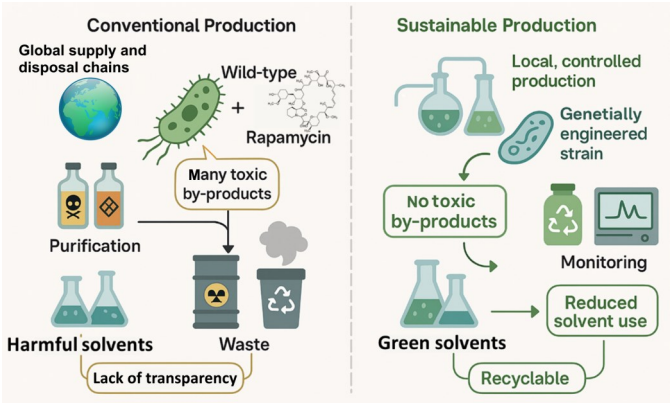
ETERNAL

SUSTAINABLE
BIOPROCESS PURIFICATION

REAL-TIME, INLINE, ON SITE

The complex global supply chains involved in drug production can be challenging to monitor and regulate, leading to potential environmental violations in less stringent regions. The chemicals that are used and generated in pharmaceutical manufacturing processes may be ecotoxic or persistent, posing risks to human health and the environment, while the volume of waste generated by drug production, including wastewater containing pharmaceutical residues, can significantly impact water quality and ecosystems.

Many of these issues can be relieved by more localised manufacturing based upon well established green chemistry principles and more efficient process design, harnessing the operational efficiencies of continuous manufacture with the control advantages of advanced in-line monitoring methods and digitalization.



Rapamycin: from problem to solution. Clean, continuous processes enabled by digitalization and green chemistry can enable producers to attain the local production and purification capabilities needed to make high quality, high demand products without all the problems of lengthy global supply and waste disposal logistics.

Context

The production and purification of high value drugs often involves lengthy global supply chains, the use of environmentally harmful chemicals, and waste flows which are imperfectly regulated and lacking in transparency.

Challenge

Large quantities of environmentally harmful chemicals are generally required to purify active ingredients produced by bio-process based routes. This case study addresses the challenge for the case of the important immunosuppressant rapamycin, which is produced by microbial fermentation.

Innovation

An innovative continuous end to end process has been developed which reduces the carbon footprint and the environmental impact of rapamycin production assessed by the toxicity of the process chemistry and products.

Next Steps

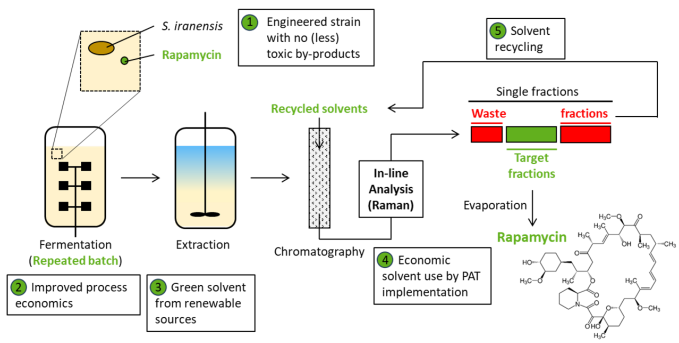
With the basic process steps established, work towards a fully integrated process demonstration is underway, with further optimization being carried out to maximize the process efficiency and scale up towards commercialization.

As an end to end provider of development and manufacturing services and innovative products for biotech and pharma, MyBiotech has been pioneering an innovative continuous downstream process for the production and purification of the prominent immunosuppressant rapamycin by microbial fermentation which reduces both the carbon footprint and the ecotoxicological impacts on the environment of this high demand drug.

Features and Advantages

MyBiotech's approach starts with waste minimization, using a metabolically engineered bacterium, which produces less toxic sides products than the conventional wild producer strain.[1] Fewer impurities upstream and less of the ones that remain mean less purification is needed downstream.

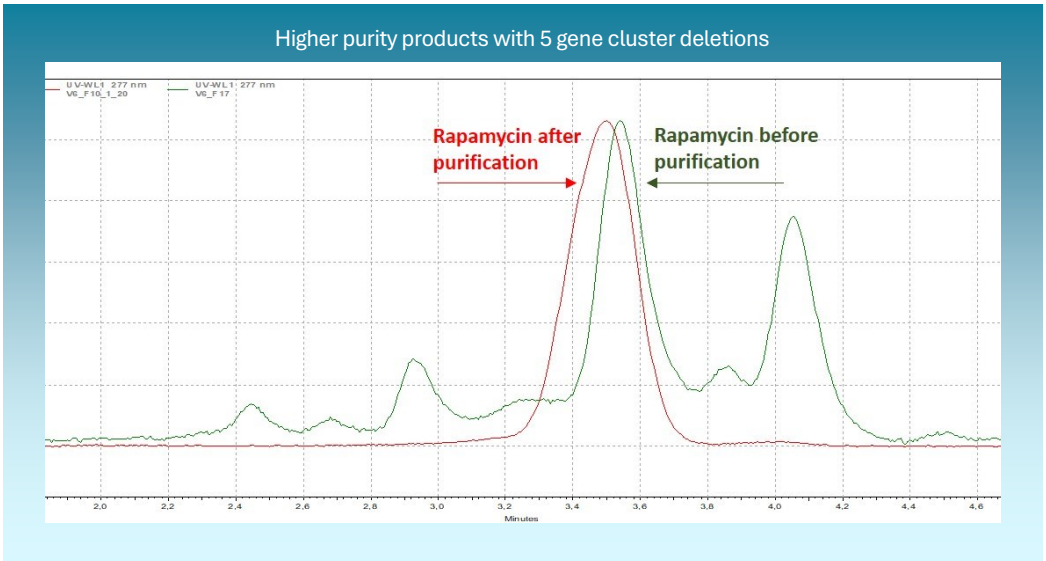
Using green and recyclable solvents from renewable sources for the post-fermentation extraction step leads to enhanced process economics. A Process Analytical Technology (PAT) solution has been successfully implemented, coupling continuous chromatographic separation with real-time, inline monitoring by Raman spectroscopy. This means that target and waste fractions in the fermentation products can be rapidly, efficiently and effectively separated from one another, facilitating both cost-effective solvent recycling and isolation of rapamycin as a high quality, high purity product.



An integrated end to end approach to safe and sustainable by design continuous bio-manufacture of a high demand active pharmaceutical ingredient (API). Operational, environmental and economic benefits are realised throughout the process.

1. Described more fully in a companion ETERNAL case study *"Strain Engineering for Better Fermentation"*

Safe and sustainable by design continuous bio-manufacture of a high demand API



Analysis of the reaction products before and after chromatographic purification shows how the impurity peaks have been eliminated without compromising the yield of rapamycin.

Results

To date, MyBiotech have already been able to produce rapamycin with a purity of >80 % in just a few process steps using solvents made exclusively from renewable raw materials. The successful PAT implementation leads to a significantly reduced solvent requirement during the purification stage of the process. With the basic process established, work towards an integrated demonstration is underway, with further optimization being carried out to maximize the process efficiency and scale up towards commercialization.

Sculpting a healthy future worth living on our planet will need holistically sustainable production processes with smart waste strategies and circular economics. Making safe and sustainable medicines available wherever there is need for them is at the heart of that vision. Global thinking however, must be matched by regional capacity and capability. Independent manufacturing value chains for drugs like rapamycin within Europe are desirable if we are to ensure security of supply to all Europe's people.

ETERNAL is contributing to the sustainable development of pharmaceutical manufacture, use and disposal, by using and promoting full life cycle approaches covering design, manufacture, use, and disposal through

- application-industry oriented R&D and scale-up;
- clear pathways to compliance;
- new scientific knowledge on the environmental fate and eco-toxicological effects of pharmaceuticals; and
- behavioural change for safe use and disposal.

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Find out more at: www.eternalproject.eu