Cutting Pharma's Carbon Footprint: Reduced Emissions through Solvent Reuse

John A. Henderson*, **Robert H. Peeling**, **Bonny Victor** (Britest Limited); **Micheál Galvin**, (Enviroeye Engineering Ltd.), **Tomasso Iaconangeli**, (Angelini Pharma)

Corresponding author, j.h@britest.co.uk

Britest Limited, Colony, 5 Piccadilly Place, Manchester, M1 3BR, United Kingdom

Key words: green chemistry, sustainability, early assessment framework, energy efficiency by design

Abstract

As an evaluation of how to embed early-stage thinking about safety and sustainability in process (re)design, the Framework for Early-Stage Sustainability Assessment (FESSA) and Energy Efficient Design (EED) methodologies have been applied to an industrial case study involving five different options for re-engineering the solvent recovery (acetone from water) duty in part of a commercial active pharmaceutical ingredient (API) manufacturing process. By systematically applying Challenge & Analyse (C&A) thinking to identify the optimal solution based upon a consistent set of decision criteria in an evaluation at the earliest stages of the project, subsequent allocation of resources could be appropriately directed towards more detailed, time and resource-intensive life cycle assessment. In the case study, the option to re-purpose an existing larger distillation column on site proved to be the most feasible solution for reasons described in more detail this paper. The early-stage assessment tool evaluated can be applied to any type of production process and to a wide range of projects aimed at manufacturing process changes and provides a written log and technical justification for any projects arising. This way of approaching improved performance can also assist in meeting the requirements of international energy performance standards such as ISO50001.

1 Introduction

In the context of the European Green Deal[1] and the ETERNAL Horizon Europe Research and Innovation Action,[2] Angelini Pharma wished to increase the overall efficiency of a process for solvent recovery by distillation to achieve environmental and economic benefits. The case study described below focuses on acetone, a solvent with an emissions intensity estimated at 2.3 kg CO_2e per kg of acetone.[3] With global production of acetone at 6-8 Mt/year that yields approximately 18.4 million tonnes CO_2e emissions annually from acetone production. Around 30% of global acetone production is estimated to be used in the manufacture of medicines and pharmaceuticals[4] giving a footprint of about 4.7 million tonnes CO_2e for acetone used in pharma.[5 a]

The European Commission's Safe and Sustainable by Design (SSbD) framework[6] requires safe and sustainable outcomes from process and product design, and any subsequent changes to these products and processes. This usually requires a life cycle analysis[7] (LCA), which is costly, time consuming and requires considerable technical expertise.[8] The FESSA[9] and EED methodologies described and utilised in this paper provide tools that can be used from project conceptualisation onwards, particularly when specific design parameters such as cost and energy consumption details are not fully known. Aspects of the product or process alternatives that are considered in the FESSA-EED study include safety, environmental impact, technical feasibility, business model, supply chain constraints and social impacts. In this way, unnecessary and costly investments pursuing unfeasible options through the exhaustive LCA process can be avoided.

[a] Few public LCA reports detail acetone's full carbon footprint as used in pharmaceutical APIs. Most existing data are aggregated industry or solvent-level estimates. LCAs are often proprietary, vary by methodology, and are not standardized enough for direct public reference or comparison.

Energy Efficiency by Design (EEbD)

The Energy Efficiency Directive 2023[10] sets revised legally binding targets for the EU to achieve a 11.7% reduction in energy consumption by 2030, compared to the 2020 reference scenario. The European Green Deal has an impact upon global climate policy through trade and commerce, and EU member states are required to implement measures to increase energy efficiency across all sectors, including industry, buildings, and transport.

IS 399 is an Irish National Standard for Energy Efficient Design (EED) management[11] developed by the Sustainable Energy Authority of Ireland (SEAI) and the National Standards Authority of Ireland (NSAI). The standard provides a framework for organizations to embed energy considerations into the design of new investment projects, minimizing energy consumption throughout their lifecycle. EED is especially focused upon Green Engineering and provides a tool professionals can use to incorporate energy efficiency into the design and construction of an investment project and for energy auditors to monitor and measure this efficiency. The energy audit is typically the starting point for retrofit projects, scale-ups and improvements in commercial production operations. It is a useful tool for project-level energy management and efficiency certification. According to the standard, the following Venn diagram is used at the early stage of a project and adapted to the study in question.

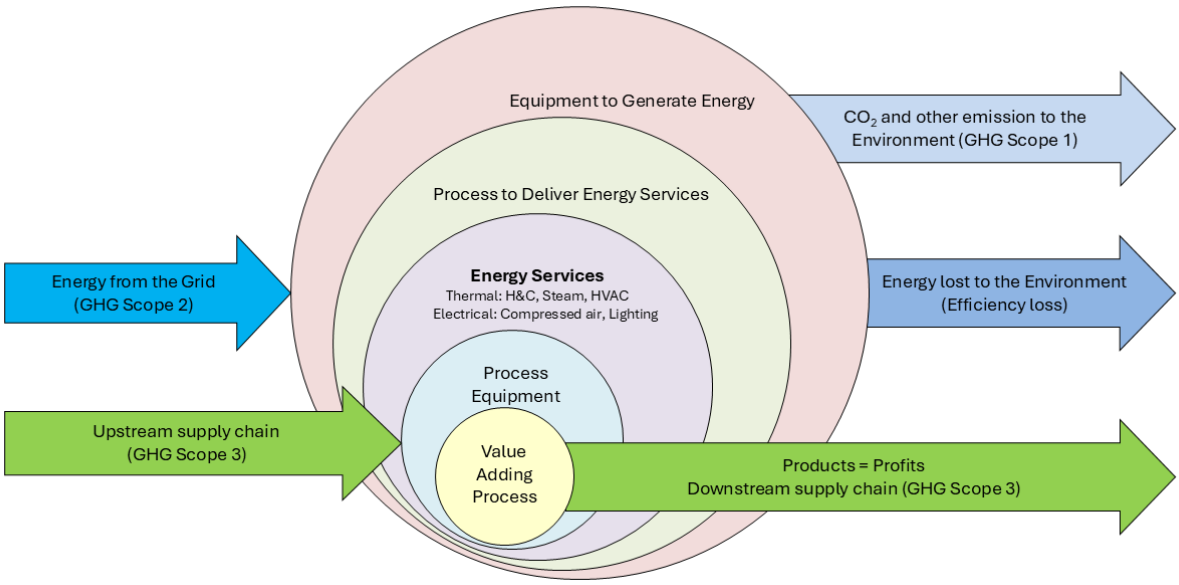

Figure 1: Modified energy Venn diagram adapted from IS 399

Challenge & Analyse Criteria

IS 399 requires a project team to apply C&A thinking to each layer of the Venn diagram in Figure 1, beginning with the innermost layer representing the value-adding process, capturing the thinking in a C&A register. Each Challenge question sets criteria to help identify barriers and weigh the options when aiming to embed energy efficiency at the design stage of systems, products, or processes. Criteria identification and use is described further for the case study below.

Framework for Early-Stage Sustainability Assessment (FESSA)

Selecting the best option amongst alternatives from a sustainability perspective is complicated by the competing issues at play. A guidance framework can help teams to think systematically about the wide range of criteria which go into deciding whether a proposed innovation enhances sustainability or not. Such a framework, which may be readily combined with WSM-MCDA (Weighted Sum Method Multi Criterion Decision Analysis) calculations to generate outcome score, has been presented.[11]

The two-level hierarchical framework for early-stage sustainability assessment (FESSA) provides at the top-level five main criteria covering the requirement for a sustainable manufacturing process. These are technical feasibility, the business model (including techno-economics), supply chain feasibility, environmental impact, and social impact. Technical and supply chain feasibility are included as prerequisites for a sustainable operation characterised by its economic, environmental, and social impacts. The top-level criteria are helpful for decision

analysis, but in practice each is multi-faceted and too broad in coverage to support a sufficiently focused process of consensus scoring by the decision-making team. Each top-level criterion is therefore split into several contributory sub-criteria.

To make scoring manageable and consistent between applications to different projects, a series of sub-criteria for each of the five main criteria is proposed by FESSA. In this way a suitable WSM-MCDA method, such as CURE (Computed Uncertainty Range Evaluation) can be exploited to combine the sub-criteria scores into a composite score for each of the five high-level criteria. Sub-criteria descriptions and selection is described in more detail for the case study below.

2 The Case Study

Angelini Pharma focused on recycling solvent from the part of the process concerned with synthesising the API and recovering it as a salt. The solvent used in this stage is acetone, and total use is in the region of 2k tonnes per year. The specifications for the purified solvent have been set in accordance with the ICH Quality Guidelines,[12] a set of internationally harmonized standards developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The guidelines focus on ensuring quality, safety, and efficacy in pharmaceutical development, manufacturing, and lifecycle management. They enable global harmonization, reducing duplication and facilitate faster, more consistent drug approvals across markets.

The following steps were undertaken: full characterization of the acetonic mother liquor, preliminary *in silico* assessment and simulation of the distillation process for solvent recovery, laboratory trials to verify the accuracy and reliability of the *in silico* model, and pilot-scale trials to confirm that the predefined quality objectives were met, using gas chromatography analysis (GC).

The key performance indicators employed were the increased quantity and quality of recycled solvents in the manufacturing process of the API, with the aim of reducing the overall environmental impact. In the current process, spent acetone that is not recycled is eliminated by incineration, which whilst effective carries a high energy cost. The recovery rate of acetone that passes through the existing distillation column is 80-85%.

The Acetone Recovery Process

In general terms, the recovery of acetone by distillation is a common process in pharmaceutical manufacturing. The spent acetone may contain water, residual active pharmaceutical ingredients (APIs), or other solvents. The distillation process can be represented as a process definition diagram.

A process definition diagram is a dimensionless tool used to describe the experience of materials in the process. Specific tasks are identified within the process with the initial and final states represented from left to right across the task box. The addition and release of materials or energy. The colour convention indicates organic components in red, and vapour phases in green.

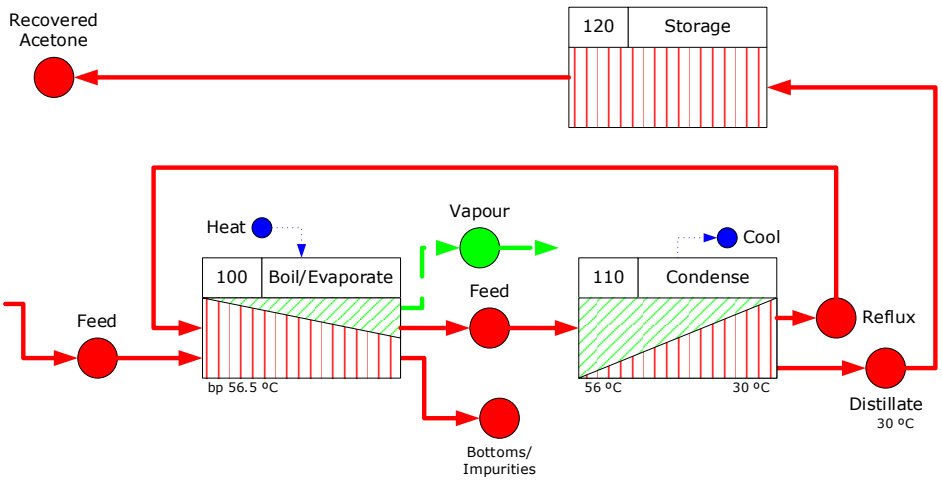

Figure 2: Process definition diagram (PDD) for the acetone distillation process currently in use.

Challenge & Analyse

In the current case study, the existing solvent distillation scenario for acetone recycling served as the baseline. The team explored whether aligning the process with core sustainability principles could enhance energy efficiency (see Table 1). Challenges were assessed with respect to potential energy-efficient approaches, and the most feasible solutions were selected for further development.

Table 1: Sustainability principles for challenging energy usage[11]

Principle / Criterion	EED Challenges & Analyse Question
Elimination	Can this energy service be REMOVED?
Minimisation	Can this equipment be REPLACED with more efficient equipment?
Moderation	Can this energy service be SUBSTITUTED with something with a lower carbon footprint?"
Segregation	Can the energy required to maintain this service be REDUCED ?
Simplification	Can the energy rejected by the process be RECOVERED, and REPLACE a process heating service or STORED and REUSED for heating at another time/place?

Table 2 overleaf shows the outcome of C&A exercise for the criteria against each layer of the current acetone recovery process. An opportunity identified in the value adding layer is the upgrade of the distillation equipment to increase the efficiency of acetone recovery.

An opportunity for minimising the energy consumption by recovering some of the energy from the acetone vapour was seen as an opportunity in terms of the process equipment. To achieve this a partial condenser could be added to pre-heat distillation column feed. This would reduce the GHP Scope 1 emissions, as well as reducing the requirement for cooling service (*i.e.* GHP Scope 2 reduction). Also within the process equipment layer, the challenges to substitute (replace steam with hot water) and moderate (reduce the steam pressure) were not considered to be viable options.

In the energy service layer of the Venn diagram, the energy rejected by the process could be recovered, and replaced by a process heating service in the form of a Mechanical Vapour Recompression heat pump (MVRP) that would recover the latent heat of vaporisation from the condenser and return it to the column reboiler. The benefit of electrification of the process is that GHP Scope 1 emissions would be removed and replaced with GHP Scope 2 emissions equivalent to around 25% of steam energy delivered.[b] This could be Included as an option for later development. It was beyond the scope of this study to challenge and analyse the remaining three layers of the Venn diagram (*viz*. equipment Plantroom, control and operations & maintenance) .

[b] Assuming electricity from the Italian grid. The Scope 2 emission reduces to zero if renewable electricity is sourced.

Table 2: The challenge and analyse criteria for each layer for the case study.

Layer	Baseline Scenario	Challenge	Analyse	Conclusion	Opportunity[3]
Value Add Process	Manufacture of trazadone (step conversion to HCl salt.	Can the acetone be recovered?	Distillation will certainly work, requires input of latent heat of vaporisation. Steam is 'obvious' heat source. Modest temperature. Selective freezing - requires removal of latent heat of fusion and cooling service. Very cold. Handling solids. Membrane filtration - good to remove residual product, starting materials , impurities and co-products. Unlikely to be selective to acetone vs water and IBA.	Use distillation to recover acetone with steam as heat source and cooling water for condensing recovered acetone. This is the baseline.	Implemented
		Can a greater proportion of acetone be recovered?	Redesign/re-use of unused distillation column can do this.	Repurpose existing spare distillation column to give greater recovery capacity (more latent heat = more energy). Large benefit for Scope 3 emissions for small increase in Scope 1.	YES. Distillation upgrade
Process Equipment (Distillation Process)	Conventional distillation column heated with steam using cooling water for condensing recovered acetone	MINIMISE - Can additional energy requirement be reduced?	Recover some of the energy from the acetone vapour?	Add partial condenser to pre-heat distillation column feed. Reduces Scope 1 emissions. Also reduces requirement for cooling service (Scope 2 reduction)	YES. Include in distillation upgrade
		SUBSTITUTION - Can steam be replaced with hot water?	Atmospheric boiling point of acetone is 56°C. Heating with hot water is just about feasible. Reducing pressure in column will reduce boiling point and make boil-up with hot water feasible.	Option doesn't make much difference to energy requirement (latent heat) but reduces required heat grade. Introduced vacuum service requires more electric energy to drive it (increases Scope 2). Only worth considering if a reliable source of hot water at a suitable	NO

[3] To be recorded in Opportunity Register

Layer	Baseline Scenario	Challenge	Analyse	Conclusion	Opportunity[3]
				temperature is already available (eliminates Scope 1 emission). Capital cost may be increased if a large reboiler is necessary.	
		MODERATION - Can the steam pressure be reduced?	Atmospheric boiling point of acetone is 56°C. Heating with lowest pressure steam available will work.	Doesn't change the energy required but does lower the grade. Only worth considering if an adequate source of lower pressure steam from elsewhere on site is available. Note that capital cost may be increased if a large reboiler is necessary.	NO
Energy Service	Steam Data required: flowrate XXX [kg/hr] temperature XXX [°C], pressure XXX [bar]	Can the energy rejected by the process be RECOVERED, and REPLACE a process heating service?	Use mechanical vapour recompression (MVR) heat pump to recover latent heat of vaporisation from condenser and return to column reboiler.	Electrification of process. Removes GHP scope 1 emission replacing with Scope 2 emission equivalent to circa 25% of steam energy delivered.	YES. Include as an option, especially for future new build.
Process for Energy Services	Flue gases from burning natural gas burnt pass through tubes with boiling water on shell side to raise steam.	Can the steam be REPLACED?	See above.		

Application of FESSA-CURE Methodology

The steps to follow when implementing the methodology are

1. List the alternative options/process routes.
2. Agree the list of study criteria.
3. Assign initial weightings for the criteria.
4. Score the criteria for each alternative identified in terms of a minimum, most likely and maximum value.
5. Review the results and evaluate the sensitivity by adjusting the weightings for the criteria.

Step 1: Problem Definition

Angelini recover acetone for re-use from acetone/water mother and wash liquor from their process for isolating the active pharmaceutical ingredient (API) as its HCl salt. Repurposing an existing distillation column can recover more acetone than their existing distillation system. Several design options are possible. Simply stated, Angelini wish to identify which process change alternative gives the best combination of reducing environmental impact of the API production process together with an economic benefit.

Step 2: Defining the Alternatives

The five alternatives are summarised in Table 3. At this stage, any alternatives can be included for consideration, even those that may at first appear counter intuitive.

Table 3: The five alternatives for process modification to increase acetone recovery

Alternative	Description
A_1	Existing semi-continuous distillation operation = base case
A_2	Repurposed column operating semi-continuously
A_3	As A2, but with a partial condenser to preheat feed
A_4	As A3, with mechanical vapour recompression (heat pump) = electrification
A_5	As A3, operating fully continuously

Alternative A_1 is typically used as the reference for “do nothing”/status quo option.

In this example, all the alternatives except A_4, are steam heated. Steam is generated using a combined heat and power (CHP) plant fuelled by natural gas. Hence steam and electricity generation on the site share energy demands and overall efficiency. Apart from the base case, all alternative changes proposed use the same distillation column design. The differences relate to the energy sources employed.

Step 3: Defining the Criteria

The decision is then made as to how much weight to give each criterion within the decision set-up. Weights are expressed as fractions or percentages for each criterion to give a sum of 1.0 (or equivalently 100%). Appropriate weightings are first agreed by the decision-making team for the high-level criteria, see Table 4.

Table 4: Reasons for the weighting given to each of the criteria in this study.

Title	Weights	Reason for weight	Description	Reasoning	Data source(s)
Technical Feasibility	33%	Selected option needs to work and to be implemented from available technologies.	Is the alternative technically viable?	An essential requirement for success.	Team knowledge and experience
Business Model	33%	Reasonable return for the necessary capital investment is a requirement to proceed.	Does it make business sense?	The economic pillar of sustainability	Case Study Heat and Mass Balance.xlsx

Title	Weights	Reason for weight	Description	Reasoning	Data source(s)
Environmental Impact	33%	Reduced environmental impact for the trazodone process is a major justification for the project. This should include reducing the energy footprint.	The environmental pillar of sustainability	Includes efficiency of use of materials and resources.	Case Study Heat and Mass Balance.xlsx
Supply Chain Feasibility	0%	Supply chains for virgin acetone and for disposal of distillation residues are unaffected by any of the alternatives.	Stability and flexibility of supply chain to support the alternative.	Alternative improves or accesses a secure supply chain.	Not applicable
Social Impact	0%	Negligible change in impact between the alternatives. Trazodone availability to society unaltered. No adverse impact on personnel at Angelini.	Does the new product / process have significant positive or negative societal impact?	Third pillar of sustainability	Not applicable

The weights reflecting the relative contributions to each high-level criterion of its sub-criteria then must also be agreed. In the current case study, not all the sub-criteria were found to be relevant or meaningful. Such criteria were removed from the analysis by applying a zero weighting. The remaining sub-criteria under each main criterion were then equally weighted, see Table 5 (a), (b) and (c) below, which show the weightings and rationale for these ratings for the remaining high-level criteria (technical feasibility, business model and environmental impact).

Table 5 (a): Details of the sub-criteria with weights and reasoning in assigning the weights that contribute to the technical feasibility high level criterion. wj refers to the normalised weights.

Technical Feasibility	Type	Weights	Weights, w_j	Reasons for weights applied
Innovation flexibility	Unused	0	0%	Not relevant to this case study. Process is for a single product.
Enabling technology	Unused	0	0%	Process is for a single product. All technologies are bought in rather than innovative.
Will it work?	Qualitative	2	40%	Critical requirement.
Does it scale?	Unused	0	0%	All new options are at same scale. Assumed that new equipment will be available to satisfy required thermal duty, so not considered a differentiator.
Does solution affect product quality?	Unused	0	0%	Does the route affect the recovered acetone purity? Probably not going to be a differentiator
Does solution affect production capacity?	Qualitative	2	40%	Matters because the objective is to increase availability of recovered acetone.
Adequately specified?	Unused	0	0%	The required purity for recovered is known and understood and not a differentiator.
Acceptable / manageable variability?	Qualitative	1	20%	Potential impact if stability / reliability of energy source is a variable.

Table 5 (b): Details of the sub-criteria that contribute to the business model high level criterion.

Business Model	Type	Weights	Weights, w_j	Reasons for weights applied
Improves Net Present Value (NPV)	Qualitative	55	55%	Return on investment is required.
Extends existing market share?	Unused	0	0%	Not relevant - options are not changing product throughput.
Opens access to new markets?	Unused	0	0%	Not relevant - product is fully commercialised.
Improves time to commercialisation	Qualitative	15	15%	There may be significant differences in lead time for implementation.
Resilient to existing and new competition?	Qualitative	15	15%	Reduced operating costs would help maintain market share with this generic product. Angelini patent expiry in 2027.
Product flexibility	Unused	0	0%	Not relevant - single product produced.
Capacity flexibility	Unused	0	0%	Not really a differentiator, all options have turndown capability.
Feedstock flexibility	Unused	0	0%	Ability to move away from natural gas as primary energy source may be advantageous with growing global uncertainty. Disabled - accounted for under Environmental criteria
Resilient to Regulatory changes?	Qualitative	15	15%	Options don't change the product validation, but process/plant changes (e.g. tanks) may require regulatory approvals.

Table 5(c): Details of the sub-criteria that contribute to the environmental high-level criterion

Environmental Impact	Type	Weights	Weights, w_j	Reasons for weights applied
Process safety	Unused	0	0%	Options not really sensitive to this. Problems of electrical installations in flammable atmospheres are well known and understood.
Elimination	Unused	0	0%	Not included as a differentiator to avoid double accounting. Changing from steam to electricity could be included here but is covered as Substitution.
Substitution	Qualitative	1	50%	Potential to move from two energy sources (steam and electricity) towards one (electricity).
Minimisation	Qualitative	1	50%	Reducing usage of virgin acetone (scope 3 like emissions) and reducing energy usage (scope 2 like emissions).

Environmental Impact	Type	Weights	Weights, w_j	Reasons for weights applied
Moderation	Unused	0	0%	Not a differentiator. No scope to adjust the temperature of the distillation process itself.
Segregation	Unused	0	0%	Not a differentiator. Energy source in all options is high grade with respect to utilization.
Simplification	Unused	0	0%	Not included as a differentiator to avoid double accounting. Changing from steam to electricity could be included here but is already covered as Substitution.
Location flexibility	Qualitative	0	0%	Not a differentiator. Installation can only be at existing manufacturing site.
Critical raw materials	Qualitative	0	0%	Not a differentiator. No option technology is based on critical raw materials.

Step 4: Scoring the Alternatives

Each of the alternatives identified were scored for each relevant aspect so that they could be compared using the CURE algorithm. The scores were speculative but may be updated when real data is acquired, such as operation efficiency or yield. Sufficient understanding of the processes and operation parameters allowed for informed consensus estimates of the upper and lower limits of the scores to be made.

The underlying calculations in the CURE algorithm[9] generate a normal probability distribution (Figure 3) as an output for each alternative. This reflects the likelihood of obtaining any given outcome score for each alternative given the uncertainty in the inputs. The output score is a normalized value between zero and one, with higher values being more desirable.

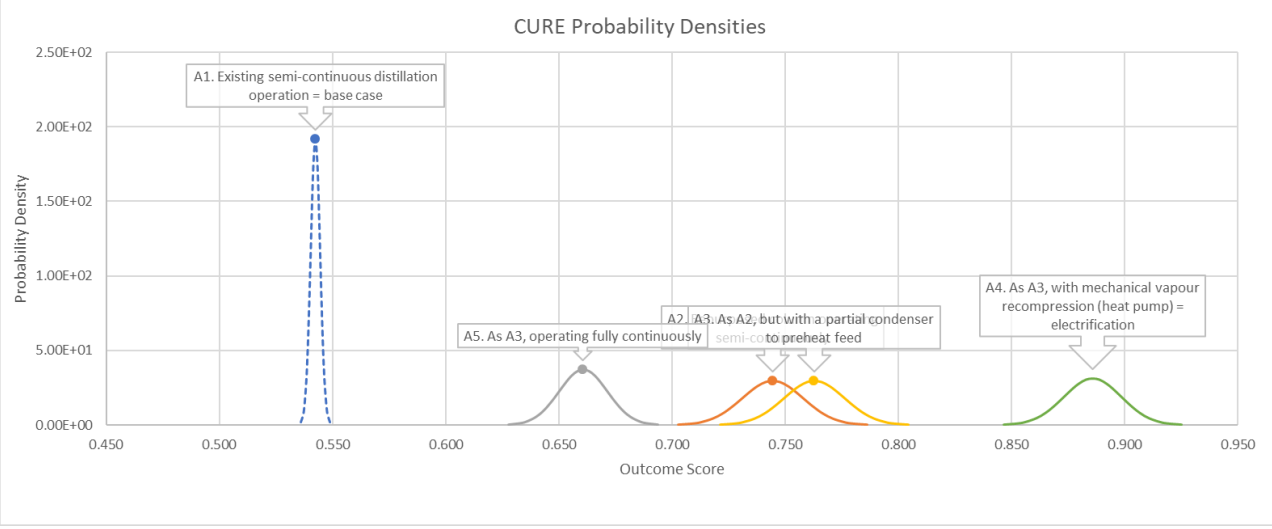

Figure 3: Output from FESSA displayed as probability distributions.

The results indicate that option A_4 is preferred, with A_3 in second place as a modest improvement on A_2. All alternatives score significantly higher than the existing base-line case (do nothing) option. Examining the contribution to the overall scores from each of the main criteria can help us understand the results more thoroughly.

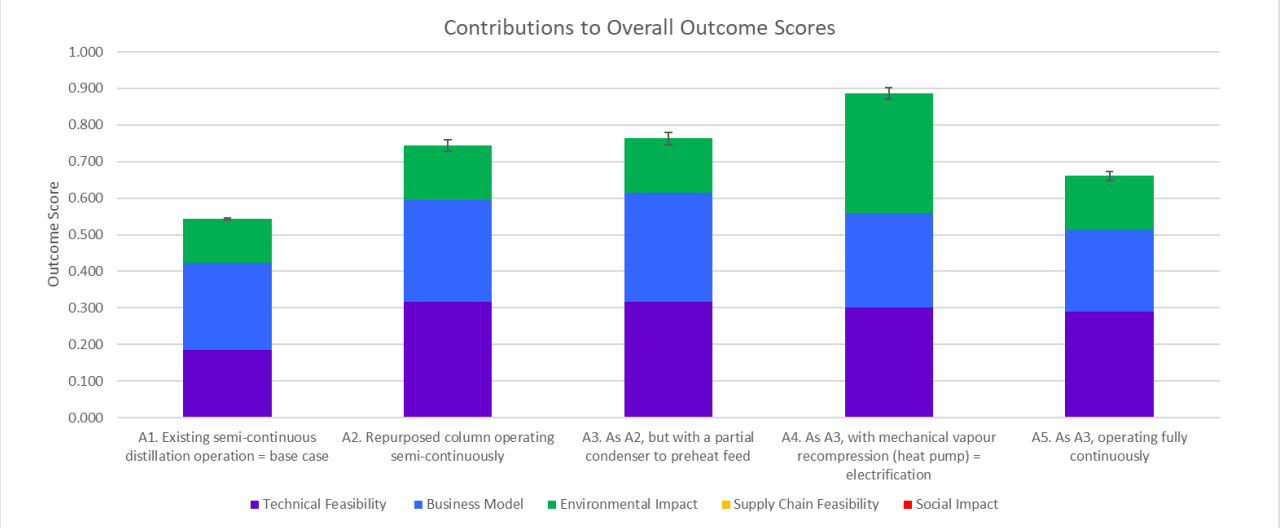

Figure 4: Summary FESSA outcome scores including contributions from first-level criteria

Figure 4 shows there are differences in the main criteria scores across the alternatives. To explore this more completely, the contributions from the sub-criteria should be examined.

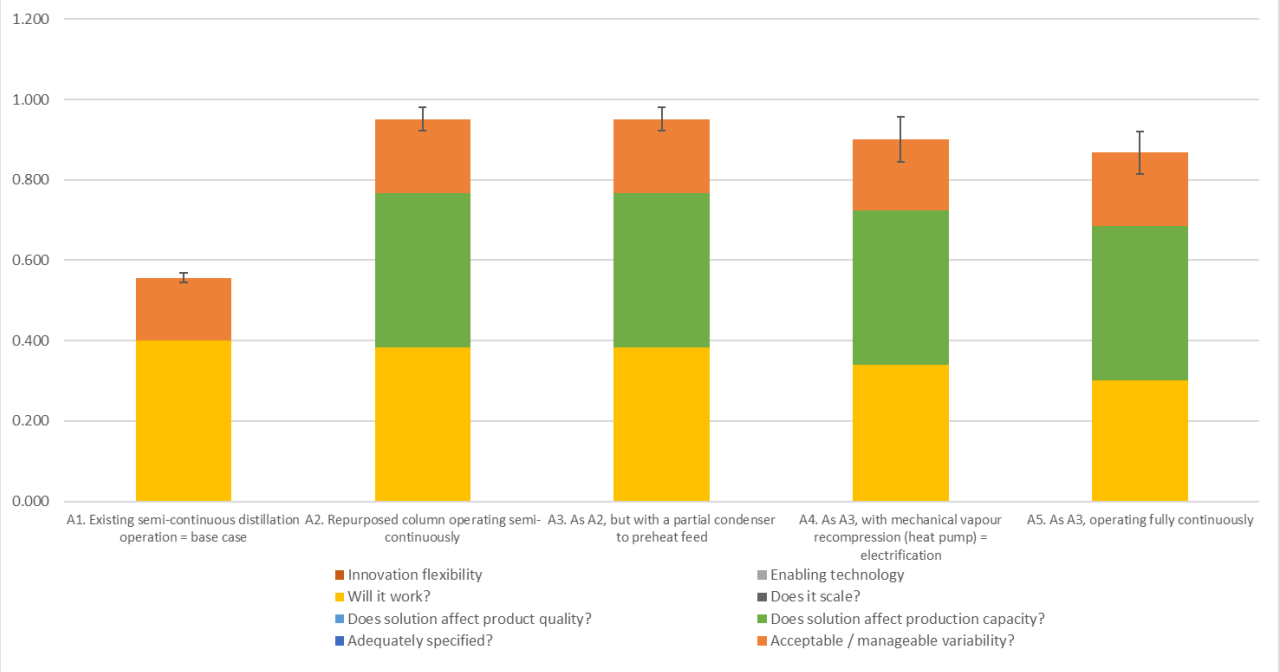

Figure 5: Breakdown by sub-criteria for technical feasibility (33% of total weight)

It is clear from Figure 5 that A_1 (staying with the status quo) should be ruled out because it fails to deliver the additional acetone recovery (production capacity) required. Options A_4 and A_5 score slightly less than A_2 and A_3, on the question, 'Will it work?' because they are more complex to engineer.

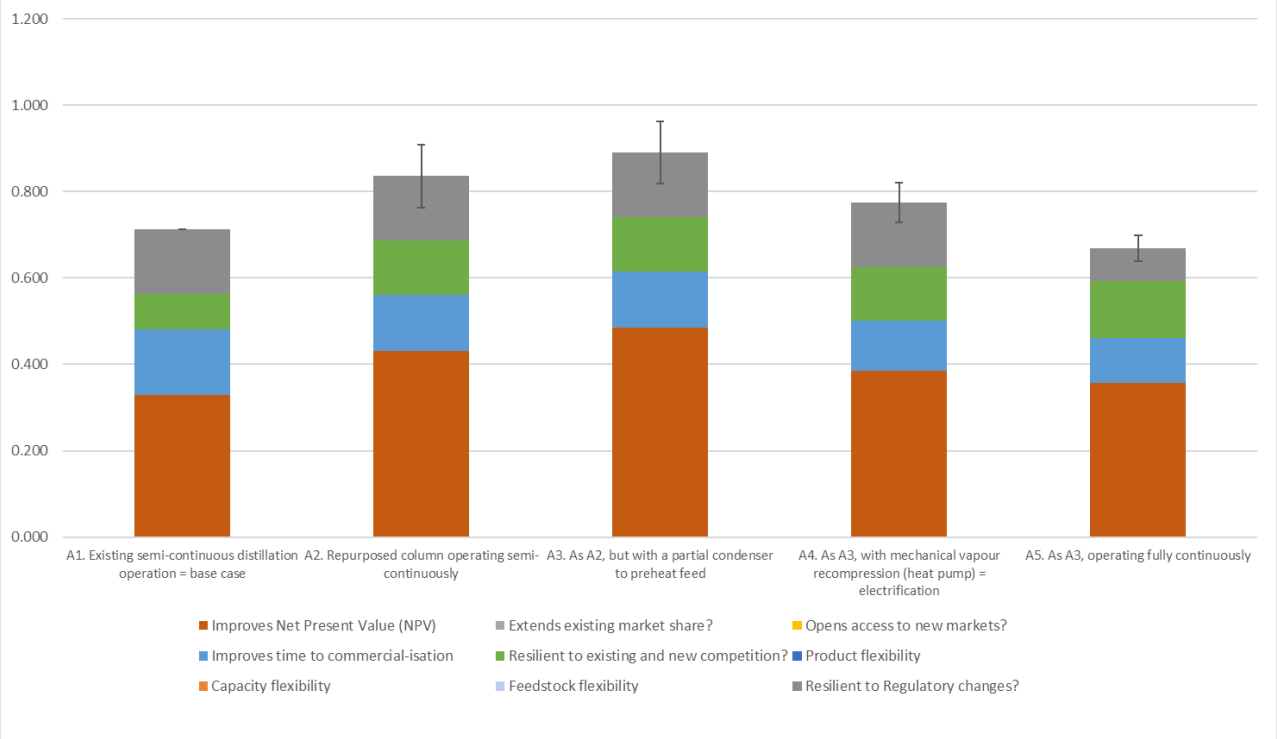

Figure 6: Breakdown by sub-criteria for business model (33% of total weight)

From Figure 6, it is evident that the best economic solution (Net Present Value) is found in alternative A_3. A_4 and A_5 require more capital to implement, which lowers the NPV for these options. A_4 is also adversely affected under regulatory constraints, because of the impact that increasing the inventory of flammable solvent (in larger tanks) will have on the site's licence to operate. While A_5 is technically acceptable in terms or the business model (installing a larger or a greater number of storage tanks to allow for semi-continuous solvent distillation is not economically prohibitive) the regulatory constraints in obtaining for larger storage capacity of solvents makes this a less attractive option. This was scored at 0.5 whereas the other alternatives scored 1 (i.e. they do not entail regulatory changes). This is then a regulatory constraint in terms of safety and environment (loss of containment) rather than a pharmaceutical/medicine regulation constraint. In the context of medicines manufacturing more generally, however, in some instance the EMA and other regulations should be considered.

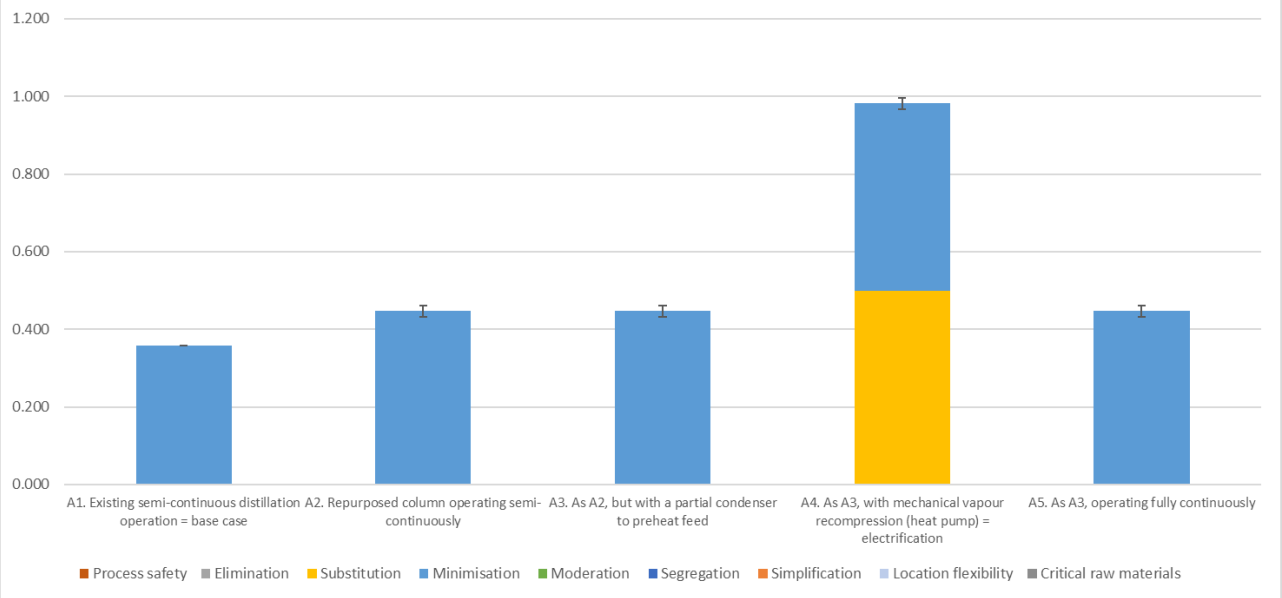

Figure 7: Breakdown by sub-criteria for environmental impact (33% of total weight)

Finally, in Figure 7, it is simply the replacement of natural gas with (renewable) electricity that differentiates A_4 which, given the straightforward even weightings applied at the high-level ultimately leads to it being identified as the overall most preferred option according to the overall output scores. The environmental aspect of A_4 (installation of the MVP) has a clear advantage in terms of environmental impact over the alternative that can be attributed to the environmental benefits of converting the process from a reliance on steam generation through gas to and electrification of the energy supply.

Techno-Economic and Environmental Impact Analysis

As a further step in the assessment, calculations have been performed to estimate the economic and environmental impacts of the different alternatives. In Table 6 the impacts are expressed economically as cost savings compared to the base case, A_1, and the environmental impacts as CO_2 equivalent greenhouse gas emissions reduction.

Table 6: Results of Techno-Economic and Environmental Impact Analysis (based on ten year project lifecycle, with A1 as base case)

Alternative	A_1	A_3	A_4	Units	Comments
Overall energy cost saving	0	57,077	239,912	Euro	Operating cost benefits from installation of MVR heat pump
GHG Scope 2 emissions reduction	0	143	1,007	te CO_2 eq.	GHG Scope 2 emissions reduction from installation of MVR heat pump
Overall acetone cost saving	0	31,899,000	31,899,00	Euro	Cost benefit from reduced purchases of fresh acetone
GHG Scope 3 emissions reduction	0	69,972	69,972	te CO_2 eq.	GHG Scope 3 emissions reduction from greater internal re-use of acetone

3 Conclusions

The Challenge and Analysis technique borrowed from IS 399 has been helpful in identifying potential energy saving alternatives for this Case Study. FESSA has been successfully used to compare the alternatives. The leading alternative was electrification of the distillation to recover acetone using a mechanical vapour recompression heat pump. The second highest scoring alternative was a re-engineered distillation column, with some energy saving achieved using a partial condenser to use latent heat from the distilled acetone to preheat the distillation column feed. Both alternatives recover significantly more acetone than the existing system used as a base case in the analysis. A relatively simple techno-economic analysis was then used to compare the two options with the base case.

Over ten years operation, both the alternatives would show the same economic benefit in terms of savings on avoided purchase of acetone (€M 31.9) because a greater proportion of the acetone used in the manufacture of trazodone can now be supplied through on-site recovery. This in turn leads to a GHG Scope 3 reduction to 69,972 te CO_2 eq. The difference between the alternatives lies in the savings in primary energy usage. In A_3 a conventionally steam heated column depends on combustion of natural gas to raise the steam. Recovering more acetone requires more energy compared to the baseline but this is offset by using a partial condenser on the distillate to preheat the feed. This leads to modest saving in both energy cost and associated GHG Scope 2 emissions. Using a form of heat pump in the other alternative gives a substantial reduction in the energy cost, despite electricity having a higher cost per kWh than natural gas and, assuming the electricity is sourced renewably, a substantially higher reduction in GHG Scope 2 emissions. These differences on the energy side are more than an order of magnitude less significant than the benefits associated with the additional acetone recovery which are the same for either alternative. It seems clear from Table 6, that the energy cost and scope 2 emissions savings obtained with alternative A_4 would not justify the additional capital cost for the heat pump given that all the capital cost of alternative A_3 is required *in addition* to the cost of the heat pump.

The overall conclusion from this test of the assessment methodology is that the decision made by Angelini to adopt alternative A_3 in Case Study 2 has been validated. FESSA-CURE approach with a focus of EED has proved to be an efficient and easily comprehensible methodology to compare proposed alternatives in manufacturing process changes. While this example application focused on the re-use of a solvent in the manufacture of a pharmaceutical, the principles can be applied to virtually any industrial manufacturing process at any scale.

In terms of future development, Angelini might consider green sources of electricity (e.g. solar power generation). Design efficiency suggests that steam should be generated as close as possible to the process that needs it, and only the relevant sections of the process should be reviewed in terms of EED. LCA should be looking at the whole process, but acetone saving (CO_2 emissions reduction: 2.5 kg CO_2/kg acetone made) justifies the approach before conducting a full LCA. This study has demonstrated that even with limited preliminary data, it is possible to arrive at an indication of the most feasible course of action: even if the exact numbers change in the light of further evaluation, the conclusion should stay the same. This approach will potentially have an impact on Environmental Product Declarations (EPDs) that are based on LCAs. A review of the changes to EU regulations for medicines requiring an LCA for new and existing products has been published[13] by other authors from the ETERNAL project.

The experience of this case study has been used as the basis of a draft CEN Workshop Agreement (CWA) Methodology for Early-Stage Sustainability Assessment and Efficient Energy by Design which is available for comment by registered Workshop participants throughout the latter part of 2025 and early 2026. The launch announcements of the CEN Workshop chaired by Britest containing further details can be viewed on the CEN website.[14]

Acknowledgements

The ETERNAL project has received funding from the European Union's Horizon Europe Framework Programme (HORIZON) under grant agreement No 101057668. The work of UK-based Associated Partners has been funded by UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee.

References

[1] The European Green Deal: Striving to be the first climate-neutral continent, European Commission, 2019. https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/european-green-deal_en (Accessed 08/09/2025)

[2] ETERNAL: Establishing safe and sustainable pharmaceutical lifecycles by design. ETERNAL RIA, 2023. https://www.eternalproject.eu/ (Accessed 08/09/2025)

[3] Update of benchmark values for the years 2021 – 2025 of phase 4 of the EU ETS, European Commission, 2021. https://climate.ec.europa.eu/system/files/2021-10/policy_ets_allowances_bm_curve_factsheets_en.pdf (Accessed 08/09/2025)

[4] Acetone Market Summary, Grand View Research, 2024. https://www.grandviewresearch.com/industry-analysis/acetone-market (Accessed 08/09/2025)

[5] Acetone Market Analysis 2015 – 2035, ChemAnalyst, 2025. https://www.chemanalyst.com/industry-report/acetone-market-272 (Accessed 08/09/2025)

[6] Safe and sustainable by design, European Commission, 2022. https://research-and-innovation.ec.europa.eu/research-area/industrial-research-and-innovation/chemicals-and-advanced-materials/safe-and-sustainable-design_en#documents (Accessed 08/09/2025)

[7] EEA Glossary, Life Cycle Assessment, European Environment Agency, undated. https://www.eea.europa.eu/help/glossary/eea-glossary/life-cycle-assessment (Accessed 08/09/2025)

[8] Satta, M., Passarini, F., Cespi, D. *et al.*(2024) Advantages and drawbacks of life cycle assessment application to the pharmaceuticals: a short critical literature review. *Environ Sci Pollut Res*. https://doi.org/10.1007/s11356-024-33964-w (Accessed 08/09/2025)

[9] Henderson J, Peeling R (2024) A framework for early-stage sustainability assessment of innovation projects enabled by weighted sum multi-criteria decision analysis in the presence of uncertainty. Open Res Eur 4:162. https://doi.org/10.12688/openreseurope.18195.1 (Accessed 08/09/2025)

[10] Directive (EU) 2023/1791 of the European Parliament and of the Council of 13 September 2023 on energy efficiency and amending Regulation (EU) 2023/955 (recast), European Commission, 2023. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ%3AJOL_2023_231_R_0001&qid=1695186598766 (Accessed 08/09/2025)

[11] I.S 399 Energy Efficient Design Management, Formal Launch, Sustainable Energy Authority of Ireland, 2014. https://www.seai.ie/sites/default/files/publications/IS399-Energy-Efficient-Design-Management-overview-.pdf (Accessed: 08.09.2025)

[12] Quality Guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, undated. https://www.ich.org/page/quality-guidelines (Accessed 08/09/2025)

[13] Harrison, S., Barnett, C., Short, S. *et al.* Continuous improvement towards environmental protection for pharmaceuticals: advancing a strategy for Europe. *Environ Sci Eur* **37**, 128 (2025). https://doi.org/10.1186/s12302-025-01180-z (Accessed 08/09/2025)

[14] Launch of the CEN Workshop 'Methodology for Early-Stage Sustainability Assessment for Chemical and Biochemical Manufacturing Processes', European Committee for Standardization (CEN), 2025. https://www.cencenelec.eu/news-and-events/news/2025/workshop/2025-05-06-lca/ (Accessed 08/09/2025)