Implementation of a Knowledge-based Assessment Tool to Classify Pharmaceutical Processes

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Abstract

This work presents a newly developed knowledge-based assessment tool intended to evaluate and classify pharmaceutical processes, this way guiding drug development in providing reliable and efficient processes at a rapid pace. This tool incorporates commonly known green chemistry metrics, including atom economy, E-factor, volume-time-output, and the semi-quantitative EcoScale tool. By gathering all these inputs and assembling them in a structured framework, chemical processes can be evaluated in terms of synthesis strategy, waste generation, productivity, quality, process conditions, raw materials classification, and health, safety and environmental considerations, achieving a final classification based on every single one of these key aspects to truly determine process efficiency. The developed assessment tool was successfully implemented on various drug development projects at Hovione FarmaCiência S.A., providing cross-project comparison and the creation of a centralized database for the company's process knowledge. Additionally, a critical aspects analysis allowed for a rapid detection of what criteria should be improved on a given process, and a case study evaluation of a project with multiple process revisions over time allowed for its improvement-evolution assessment.

Keywords: Industry 4.0, Process efficiency classification, Drug development, Green metric calculator, Lifecycle assessment

1. Introduction

The pharmaceutical industry faces many challenges nowadays, with increasing "time to market" pressures, tighter regulatory demands for product quality, and growing product competition – which ultimately leads to an overall decrease in research productivity in an already risky business to begin with. [1] Besides this, the manufacturing process of active pharmaceutical ingredients (API) can be quite complex, with multistep production and various intricate unit operations, such as the chemical reaction stage, workup stages (extraction and/or distillation), isolation stages (crystallization, filtration, and/or drying), and sometimes the necessity for more uncommon purification operations (e.g., chromatography and charcoal filters). Designing an efficient process in such a short timeline can be quite challenging, adding to the fact that this requires several scale-ups and optimal condition's studies. [2, 3]

The concept of green chemistry [4] proposed to change the way chemistry and chemical engineering was done, by enabling a "greener" and sustainable process, which involved waste prevention, lower energy consumption, synthetic efficiency, and reduced hazardous components (used and generated). In order to dismantle the subjectivity inherent in this type of evaluation, scientists have developed several quantification metrics over the years, which would allow for a clear and fast way to obtain information on the greenness of any type of chemical process, resorting to simple mass and energy calculations, health, safety and environmental (HSE) considerations, and lifecycle impact approaches. These metrics would also enable to predict how a certain modification, such as replacement of a solvent or elimination of a unit operation, would influence the environmental impact and efficiency of a process. [5]

However, these metrics often represented individual approaches of evaluating one single aspect of the API process, this way not providing enough information to fully evaluate its efficiency, for it depends on numerous factors. Process greenness does not exclusively relate itself with environmental impact prevention, and the ultimate goal to achieve this is working towards a truly efficient process in every aspect of it, i.e., productivity, HSE considerations, product quality, cost, and schedule timelines. This is why only a holistic approach of assembling several relevant green metrics can provide an adequate assessment

of chemical processes. Researchers have already suggested some unified methodologies for this evaluation, namely the "eight criteria defining a good chemical manufacturing process" [6], Green Motion^{TM} [7], Life Cycle Assessment [8], and Green Aspiration Level^{TM} [9].

It is crucial for the industry to evolve towards Industry 4.0, in order to enhance its efficiency, and allow for swift process optimization and agility to innovate, while maintaining high purity and low cost for its products. A key element for this transformation is believed to be the recognition and assessment of each company's knowledge on performance, risks and solutions, across the lifecycle of a pharmaceutical product starting in the early development. [10, 11]

By combining a holistic lifecycle classification tool that can evaluate process's efficiency, with an organized framework that can harvest the historical company's knowledge on products and processes, the pharmaceutical industry can gain with an accelerated and more comprehensive drug development.

2. Knowledge-based Assessment Tool

This work presents a data- and knowledge-based assessment tool, developed with green chemistry metrics that, when fully integrated, will allow for the quantitative evaluation of diverse chemical processes along their lifecycle, and the harness of historical knowledge in appropriate databases – therefore contributing to a more efficient API process development in the pharmaceutical industry. This assessment tool developed by Hovione FarmaCiência, S.A., a contract development and manufacturing organization (CDMO), is an adapted version of Boehringer Ingelheim's methodology [6].

2.1. The Evaluation Method

Various green chemistry metrics were incorporated into the knowledge-based assessment tool, in order to evaluate all key aspects of the API process, summarized in Table 1.

Atom economy (AE) [12] was chosen to evaluate the theoretical efficiency of the synthetic strategy of the process, without the need for any laboratory experiments, as it quantifies how many atoms from the reactants remain in the final product. Therefore, reactants do not include solvents, catalysts or reagents that do not integrate the target molecule in any way, but they do include components that are incorporated in a reaction intermediate, even if not present in the final product itself (e.g., addition and removal of a protecting group). Additionally, because AE does not account for reaction yield and stoichiometric conditions, reaction mass efficiency (RME) [13] was introduced as well, translating into the actual mass efficiency of the synthetic design. Both AE and RME were calculated for individual steps and overall API process.

Table 1: Quantitative green chemistry metrics incorporated into the knowledge-based assessment tool. MW stands for Molecular Weight.

Green metric	**Formula**
AE (%)	$\frac{MW_{product}}{\sum MW_{reactants}}$
RME (%)	$\frac{mass_{product}}{\sum mass_{reactants}}$
SE	$\frac{number\ of\ isolated\ steps}{number\ of\ chemical\ steps}$
E-factor (kg/kg)	$\frac{\sum mass_{input\ materials} - mass_{product}}{mass_{product}}$
VTO (m^3h/kg)	$\frac{nominal\ volume_{all\ reactors} \times cycle\ time}{mass_{product}}$
PEIMY (%)	$\frac{average_{yield}}{(median_{yield} + highest_{yield})/2}$
PEICT (%)	$\frac{(median_{cycle\ time} + lowest_{cycle\ time})/2}{average_{cycle\ time}}$
QSL (%)	$\frac{\sum quality\ level\ points}{total\ number\ of\ batches}$

The environmental factor, commonly known as E-factor [14, 15], was the mass utilization metric chosen to evaluate waste production and environmental impact of chemical processes, calculated for individual steps and overall API process, and for each manufacturing batch. In the developed assessment tool, E-factor calculations were performed considering all water, solvent and reagent inputs (defining waste as everything but the desired product), and excluding recycling, for unavailability of reliable data. Although it should consider commodity type materials as the starting point for the evaluation, here it only the internal processes were accounted for, excluding waste generation from other chemical industries who produced non-commodity raw materials used in Hovione's processes, since the access to reliable data of this nature would prove arduous. Some metrics were designed to consider the waste's nature (i.e., concrete environmental impact) [16, 17], but they were not incorporated due to insufficient information and consensus on how to quantify ecotoxicity of materials, this way supporting a simple and quicker evaluation on environmental efficiency of worst-case scenarios.

To quantify the process strategy's complexity

in terms of number of isolated steps per chemical steps, thus reflecting a certain degree of telescoped synthesis, the metric step economy (SE) [18] was incorporated into the assessment tool, and calculated for the overall API process. This concept can influence waste minimization, efficiency, cost, execution time, and equipment usage.

In terms of manufacturing efficiency, volume-time-output (VTO) [6] was chosen to translate the reactor capacity and time schedule allocated per kilogram of product output, which can be very useful to project capacity demand in pilot and/or manufacturing scale. VTO was calculated for each process step's batch, by selecting nominal volumes of all reactors involved (excluding transfer tanks and containers), and a cycle time referring to the amount of time the reactors in question were allocated to the process.

Process excellence indexes for molar yield (PEIMY) and cycle time (PEICT) [6], and quality service level (QSL) [6] were chosen to evaluate the manufacturing production's reproducibility in terms of yield, cycle time, and product quality, respectively. In this assessment tool, QSL was derived from three quality level points attributed per batch: 1 point for quality assurance accepted batches; 0.5 points for accepted batches that were reprocessed/reworked; 0 points for discarded batches. These three metrics were calculated for each individual step.

Additionally, the semi-quantitative EcoScale tool [19] was added, integrating 24 questions (with categorical and numerical answers) directed towards yield, quality, equipment, process, raw materials, and HSE concerns (see Figure 1). Each question/answer pair had an assigned score range, where the first row of answers provided the maximum score for those questions, and summing them up resulted in the final EcoScale score for each laboratory process step. An average value of all steps was given for the overall API process calculation. Additionally, all volume-type answers were given in L/kg of starting raw material (SRM) units (simply designated L/kg), in order to normalize the volume values, regardless of the experiment's scale. SRM designates the limiting reactant of the chemical synthesis.

Two separate classification categories were introduced, laboratory and manufacturing, and each metric was assigned to a category, accordingly. AE, RME, SE, E-factor, and the EcoScale analysis were incorporated in the laboratory classification, where as VTO, PEIMY, PEICT, QSL, and E-factor were incorporated in the manufacturing classification. Each metric had target values allocated to them, according to the company's reality and area of focus, and

Category		Question	Criterion
Yield	1	Molar yield	95% ≤ Molar yield < 100% 80% ≤ Molar yield < 95% 60% ≤ Molar yield < 80% 0% < Molar yield < 60%
Quality	2	Purity	98% ≤ Purity < 100% 95% ≤ Purity < 98% 0% < Purity < 95%
	3	Specification accomplishment	All items are well inside There is some risk, mitigation measures included (reprocess/rework) There is risk with no mitigation measures in place
Equipment	4	Reaction temperature and pressure	Room temperature and atmospheric pressure -5≤T≤100ºC 3<P<9 bar 100<T<130 or -15<T<-5ºC -80≤T< -15ºC T≥130ºC or P≥9 bar
	5	Maximum occupied volume in the main reactor (L/kg)	0 < vol < 7 7 ≤ vol < 15 15 ≤ vol < 30 30 ≤ vol < 100
	6	Maximum to minimum volume ratio	1 ≤ volume ratio < 3 3 ≤ volume ratio < 10 10 ≤ volume ratio < 20
Process	7	Distillation volume (L/kg)	No distillation <10 10 ≤ vol < 30 >30
	8	Distillation pressure conditions	Atmospheric pressure Vacuum
	9	Reaction time (h)	0 h < time < 5 h 5 h ≤ time < 10 h 10 h ≤ time < 20 h 20 h ≤ time < 48 h 48 h ≤ time < 100 h
	10	Number of in-process controls	0 < IPC < 2 2 ≤ IPC < 4 IPC = 4 IPC > 4
	11	Maximum number of samples per in-process control	samples = 1 2 ≤ samples ≤ 3 samples > 3
	12	Number of phase separations and pH adjustments	No separations or pH adjustment ≤ 3 separations and pH adjustments (less than 4h each) > 3 separations and pH adjustments (less than 4h each) Single separation time more than 4h or total sep. time more than 24h
	13	Columns needed?	No columns Only charcoal Chromatography
	14	Existing holding points?	Exist and are known Not known Process known to be non-stop
	15	Filtration needed?	No Yes
	16	Polish filtration possible?	Yes, at room temperature Yes, but requiring high temperature Not possible to perform a required polish filtration
	17	Filtration of solid waste needed?	No < 0.01kg waste/kg product < 0.1kg waste/kg product ≥ 0.1kg waste/kg product
	18	Drying conditions	No drying necessary Easy dry (≤ 48h) Long dry (> 48h) Long dry (> 48h) + special requirements Possible degradation with impact on quality
Raw materials	19	Solvents ICH classification	All solvents at class 3 At least one solvent with class 2 At least one solvent with class 1
	20	Substances of very high concern (as per REACH) used?	No Yes, in candidate list Yes, in authorisation list
	21	All components are commodities?	Yes No, with ≥2 suppliers No, with 1 supplier
Health, Safety, Environment	22	Reaction highly exothermic?	No Yes, but manageable with addition control Yes, but manageable with engineering solution Yes, but manageable with potential risk of runaway
	23	Highly corrosive, toxic or hazardous for the environment material needed?	No special controls required and normal IPEs Special charging devices and/or waste treatment devices Redundant systems required (Special IPEs and advanced controls)
	24	Highly flammable or explosive material needed?	No special controls required and normal IPEs Special charging devices and/or waste treatment devices Redundant systems required (Special IPEs and advanced controls)

Figure 1: EcoScale analysis tool incorporated into the knowledge-based assessment tool, with each question and possible answer. IPC designates In-Process Control, ICH stands for International Council for Harmonisation, REACH stands for Registration, Evaluation, Authorisation and Restriction of Chemicals, and IPE designates Individual Protection Equipment.

weighting scores that contributed to each category's final classification – however, these targets/scores were still arbitrarily given, to some extent, for the assessment tool's first trial, until data was gathered and assessed. Also RME and E-factor did not yet contribute for the final laboratory and manufacturing classification, respectively, and were merely observable quantifications.

2.2. Template Preparation

After the conceptualization of all criteria to be evaluated on the knowledge-based assessment tool,

a software was developed by a specialized team within the company, and a user-friendly template was prepared and organized to gather all inputs needed for the software to automatically calculate the green metrics applied, and to attribute the point system to each criterion. The software's outputs are provided both in organized tables, and through a user interface for visual representation of all evaluating criteria. Databases were introduced, to allow some automatic calculations by the software. Thus, the functional requirements of this system are simple answers to the EcoScale criteria (given by each project's assigned chemist, and according to the manufacturing technique), a list of components used in the process (indicated in the manufacturing technique), and the necessary mass and time inputs registered, during the process, in record sheets from both laboratory and production areas.

The software is prepared to group all the information given as input and efficiently evaluate it in terms of project name, lifecycle phase, process revision, process step name, and type of chemical reaction. At laboratory level, the lifecycle phase can be either Assessment, which is the data gathered from the client's technique, or Demo Run, which is the last kilo lab scale experiment performed by the company before transferring the process to pilot scale, and after all process conditions have been studied and selected. At manufacturing level, the lifecycle phase accounted for is simply Manufacturing. The process revision relates to other optimization studies that might have occurred during the process development which resulted in significant changes when compared with the prior revision. Also, there is a field to capture information on what types of chemical reactions the process steps may have, to broaden the knowledge gained from the evaluation.

2.3. Proposed Goals and Targets

The user interface made available by the developed software offers not only the quantified results from each evaluating criterion, associated with graphics and data tables, but also a dynamic interface that enables a straightforward analysis of every criteria gathered from every project evaluated in this platform – therefore, providing an overview of the company's reality, and cross-project comparison.

By categorizing the project's data in terms of lifecycle phase, a global evaluation of a project will provide an analysis since its arrival (usually between preclinical and phase I clinical trials), passing through the last optimization studies carried out, and finally until its production in manufacturing scale. With the added functionality of associating data to each process revision, this assessment can capture the successive improvements made over the years, and continuously evaluate a project's performance until it is well under commercialization. This way, a project analysis can be made over its current process, or by analysing the whole history of knowledge gained since its conception.

Figure 2: Chart visualization of the green metric values and final laboratory classification, provided by the knowledge-based assessment tool. This visualization is available for one project at a time, to support a direct focus on individual project assessment.

Additionally, through the EcoScale evaluation, the user interface also featured a list of critical aspects of every project's process step, which are considered the criteria with the five lowest scores, to facilitate the project's team assessment of what could be changed in the process in order to improve it.

These functionalities were demonstrated in two types of thorough analysis: on one hand, a global evaluation of each criterion that enabled project comparison; and on the other hand, a case study evaluation of a ten-year developing project, with Assessment phase data and multiple process revisions over the years, that could enable a validation study of both the project's improvements and the assessment tool's framework.

3. Results

3.1. Overall Project Evaluation

In this section, several drug development projects were evaluated and compared. These projects had an average of four process steps each, and the evaluation was based on their most recent process revision, including their Demo Run and Manufacturing lifecycle phases. Figure 2 exemplifies the type of pie charts provided by the user interface of the assessment tool, available as a first visualization of the calculated metrics and their relative "goodness" in terms of efficiency. The colour codes are provided according to the target ranges implemented to the framework.

Additionally, a critical aspects analysis was conducted, which encompasses the five lowest scored criteria in the EcoScale evaluation (see Figure 3). In general, this analysis provided very useful information on what process criteria should be addressed, and what aspects can be improved, while some processes exhibited critical aspects intrinsic to the chemistry or API molecule, where

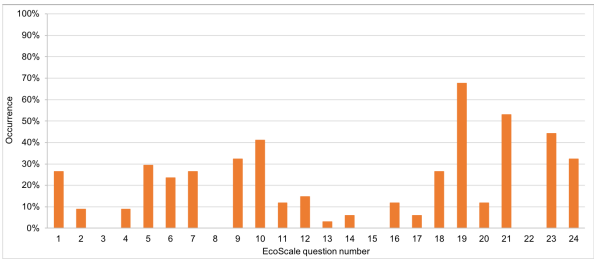

Figure 3: Representation of the percentage of processes that have each EcoScale criterion (in the horizontal axis) as a critical aspect, through the five lowest score analysis. The plot's scale has a 10% resolution, starting from 0 until 100%.

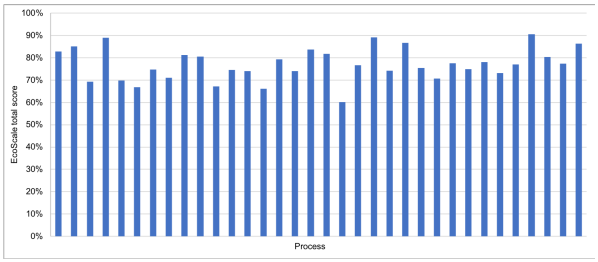

Figure 4: Final score results, in percentage, from the EcoScale analysis for each process evaluated with the knowledge-based assessment tool. The average value was 77±0.07%. The plot's scale has a 10% resolution, starting from 0 until 100%.

modifying them could prove almost impossible without changing the whole process strategy – in these cases, one could conclude that the process is in its most improved form, regarding this analysis. Some of the critical aspects with the highest percentage of occurrence in these processes, such as criteria #19, #21, #23, and #24, were related with raw materials and HSE considerations. Unfortunately, these criteria can be difficult to improve, whether for lack of studies on replacement solvents and reactants [20], or due to the CDMO's context of developing its client's product, therefore having an SRM usually provided exclusively by said client.

As for the cross-project comparison, the results of all evaluating criteria are summarized in Tables 2 and 3, in the form of percentages of processes that obtained maximum and minimum score ranges, and the average and standard deviation value for the numerical criteria.

The EcoScale results were satisfactory, revealing good scores overall (see Table 2 and Figure 4), including high molar yields (53% of processes had yields between 80–95%) and quality standards, which are parameters of the utmost importance in pharmaceutical processes. Some of the lower scores obtained (in Figure 3) were mainly due to complicated telescoped synthesis, unoptimized processes that are still under development, and inherent process conditions for complex chemical processes.

In terms of green chemistry metrics, the results were not so good, generally speaking (see Table 3). AE obtained good scores (44% of processes evaluated through this platform had an AE value between 70–90%), although it also revealed efficiency issues in telescoped synthesis, as this type of synthesis requires more reactants per mole of product, mostly high-molecular weight protective groups and other reaction auxiliaries that do not incorporate the final product. In fact, AE and SE values proved to be correlated. SE values also quantified the occurrence of both various telescoped synthesis and isolated steps without chemical reactions, namely recrystallizations with the only purpose of enhancing the API's purification.

RME exhibited lower results and bigger data dispersion, which made its assessment difficult. As previously said, RME accounts for AE, reaction yield, and molar excess of reactants, being the only metric to evaluate this last parameter. Although stoichiometric conditions provide relevant information on the reaction synthesis, RME did not seem to be easily interpreted, therefore, may not facilitate a future improvement strategy in drug development. Instead, perhaps the use of a green metric called stoichiometric factor [21] itself may prove more insightful than RME, on account of being more intuitive.

The E-factor average and standard deviation values, for both laboratory and manufacturing classifications, did not have any physical meaning, since their deviation greatly surpasses the average values. This evaluation did help the quantification of process's waste generation, however, a comparison analysis between significantly different processes did not prove to be adequate. Nonetheless, the E-factor analysis showed promising values for the laboratory category, but some processes were still largely inefficient in terms of waste reduction, which was better observed through the manufacturing E-factor. It was observed a correlation between the laboratory E-factor values, the maximum occupied volumes in the main reactor (question #5), distillation volumes (question #7), and number of extractions (question #12), in other words, all unit operations that display solvent and reagent inputs. The correlation was not perfect, due to the lack of proper filtration operation's data that also influence greatly a process's waste generation. Additionally, since E-factor depends

Table 2: Percentage of processes that obtained maximum and minimum score ranges in each EcoScale criterion evaluated for individual steps, including the average value and standard deviation for the numerical answers.

EcoScale category	**Question**	**Processes with maximum score range**	**Processes with minimum score range**	**Average**	**Standard deviation**
Yield	1 Molar yield	3%	12%	79%	14%
Quality	2 Purity	68%	9%	98%	3% [1]
	3 Specification accomplishment	85%	0	-	-
Equipment	4 Reaction temperature and pressure	21%	0	-	-
	5 Maximum occupied volume in the main reactor	6%	18%	100[2]	45[2]
	6 Maximum to minimum volume ratio	38%	18%	5.9	4.4
Process	7 Distillation volume	50%	12%	86 [2]	55 [2]
	8 Distillation pressure conditions	9%[3]	91%[3]	-	-
	9 Reaction time	53%	3%	9.3h	14h [4]
	10 Number of IPC's	3%	38%	4	2
	11 Maximum number of samples per IPC	26%	12%	3	3
	12 Number of phase separations and pH adjustments	44%	3%	-	-
	13 Columns needed?	97%	3%	-	-
	14 Existing holding points?	94%	0	-	-
	15 Filtration needed?	6%	94%	-	-
	16 Polish filtration possible?	64%[3]	0	-	-
	17 Filtration of solid waste needed?	94%	6%	0.06[2]	0.02[2]
	18 Drying conditions	6%	6%	-	-
Raw materials	19 Solvents ICH classification	21%	0	-	-
	20 Substances of very high concern (as per REACH) used?	85%	3%	-	-
	21 All components are commodities?	44%	24%	-	-
Health, Safety, Environment	22 Reaction highly exothermic?	35%	0	-	-
	23 Highly corrosive, toxic or hazardous for the environment material needed?	50%	24%	-	-
	24 Highly flammable or explosive material needed?	68%	12%	-	-

[1] Here, the upper confidence limit exceeds 100%, therefore the limit considered is 100%.
[2] This value was normalized at Hovione's request, in arbitrary units.
[3] Only considering processes with this operation.
[4] Here, the lower confidence limit drops below 0, therefore the limit considered is 0.

on the amount of product obtained in each step, molar yield also influenced its value.

VTO provided overall low scores and great dispersion of values as well. It depends on nominal volume of reactors, which can exhibit equipment constraints of CDMO's for not providing reactors with adequate nominal volume for the intended batch size; cycle time, which is a parameter extremely prone to small variations, including the added variations of having an unoptimized process that may require an extra unit operation not incorporated in the preceding batch; and product output, which is influenced by the reaction yield. Therefore, the inefficient values obtained were mostly due to the VTO's inherent variability in processes still under development, and they helped retain some of the common issues that may arise during a production batch.

The reproducibility factors PEIMY, PEICT and QSL exhibited high scores, with PEICT having lower values due to the variability in cycle time. Except for QSL, which evaluates a more regular but extraordinarily important aspect of the manufacturing production, PEIMY and PEICT's low values can still be expected in processes under development, specially in manufacturing scale, which requires a lot of optimization studies for scale-up.

To conclude, the final laboratory classification (see Figure 5) revealed reasonably low values, mainly due to the elevated weighting contributed by the EcoScale. Although its high total score, an additional EcoScale score sum was added, only considering the criteria with the lowest scores – this way helping indicate various issues regarding aspects which were not exactly evaluated through the green chemistry metrics, such as equipment, process, raw materials, and

Table 3: Percentage of processes that obtained maximum and minimum score ranges in each green metric evaluated for individual steps, including their average value and standard deviation.

Green chemistry metric	**Classification categories**	**Processes with maximum score range**	**Processes with minimum score range**	**Average**	**Standard deviation**
Atom Economy (AE)	Laboratory	35%	21%	86%	16% [1]
Reaction Mass Efficiency (RME)	Laboratory	18%	41%	59%	23%
Step Economy (SE)	Laboratory	22%[2]	11%[2]	0.82	0.44
E-factor	Laboratory	59%	18%	18 [3]	20 [3]
	Manufacturing	42% [4]	28% [4]	39[3]	100 [3]
Volume-Time-Output (VTO)	Manufacturing	48% [4]	12% [4]	24 m^3h/kg	37 m^3h/kg [5]
Process Excellence Index Molar Yield (PEIMY)	Manufacturing	53%	18%	97%	3%
Process Excellence Index Cycle Time (PEICT)	Manufacturing	38%	21%	85%	12%
Quality Service Level (QSL)	Manufacturing	76%	1%	97%	7% [1]
Laboratory classification		0	53%	43%	8%
Manufacturing classification[6]		-	-	87%	6%

[1] Here, the upper confidence limit exceeds 100%, therefore the limit considered is 100%.
[2] Percentage of projects conducted within the company.
[3] This value was normalized at Hovione's request, in arbitrary units.
[4] Percentage of batches conducted within the company, considering all processes evaluated.
[5] Here, the lower confidence limit drops below 0, therefore the limit considered is 0.
[6] Target ranges were not attributed to this classification.

HSE concerns. The manufacturing classification obtained good scores, however, its weighting contributions were arbitrarily given in this first trial, and did not reflect realistic priorities in terms of green metrics.

3.2. Case Study Evaluation

In this section, a case study was performed for project *D*, which was under development for ten years, and included three different process revisions for each step (with no change in their type of chemistry), two laboratory lifecycle phases, and data gathered since initial pilot plant batches until final validation campaign – this way, allowing for an in-depth lifecycle assessment of the API in question. Additionally, each step's process had their own revisions, regardless of the other step's process version, therefore the revision numbers were not consistent throughout. Combining the corresponding process revisions of each step amounted to five different project versions that were conducted over this API's development.

With the EcoScale analysis tool, a progression of decisions regarding the process was clearly visible. As for the molar yield and quality parameters, both exhibited improvements over time, however, the other criteria presented different patterns, whether remaining constant or actually introducing downfalls to the process. Even so, it is important to note that some of these modifications might have helped improve other important factors, such as an increase in the number of workup/isolation operations, or an addition of a more efficient (but toxic) extraction solvent, can improve reaction yield and purity. Therefore, a thorough analysis on the process alterations' implications must take place to evaluate their benefits/drawbacks.

In terms of green metrics evaluated, some were not expected to suffer any modifications after the chemical development studies, mainly AE and SE. However, AE exhibited a change in one of the process steps, where an experiment of changing the SRM and another reactant for other higher-molecular weight components reflected in a downfall of AE values over time, being appropriately reseted in its final process revision.

Regarding the laboratory E-factor, all steps, except one, managed to reduce their Assessment phase's E-factor, on account of an optimization both in number and amount of solvents/solutions used. Furthermore, the overall E-factor for the API process decreased alongside the various project versions, evidencing a definitely more efficient process than the one proposed by the client. In an internal analysis of these values, only the final step exhibited higher E-factor values in its final revision than in the previous one, while improving its molar yield – a higher volume of solvents was added during its purification stage, which perhaps allowed for a better recovery of its API, at the expense of this process's greenness. The manufacturing E-factor revealed overall improvements alongside each process revision, reaching constant and low values for its step's validation batches, which is quite good in order to demonstrate consistency between

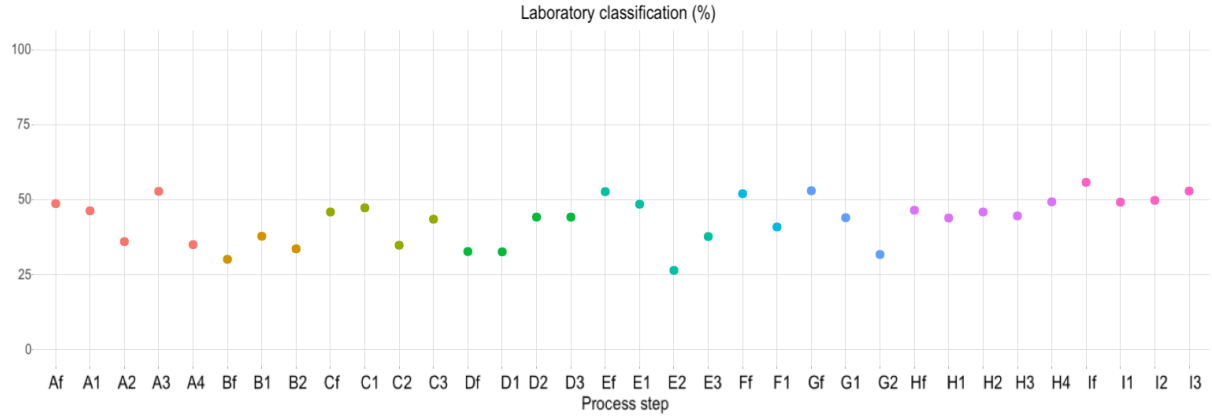

Figure 5: Data plot with laboratory classification values for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project, and f character designates the final step of said project.

batches for API commercial approval.

VTO values also revealed improvements alongside this drug development, specially when comparing the first revision with the final validation one. In fact, the first batch of all steps showed higher VTO values than the rest, possibly confirming constraints with the first scale-ups from kilo lab to pilot plant. As E-factor, the validation batches presented constant and low VTO values, in general.

To conclude, the final classification results for both categories by themselves did not demonstrate any relevant improvements over process revisions, providing final values slightly different from their initial process revisions – however, each criteria evaluated individually revealed these process modifications, and allowed for an adequate and useful evaluation.

4. Conclusions

Two main objectives were proposed for this present work: the development of a data-driven tool that would allow the quantification of chemical processes' efficiency, by embracing productivity, quality, greenness, and robustness, with the additional feature of establishing easily accessible databases with comprehensive knowledge gathered by this company over time; and to demonstrate the assessment tool's implementation in classifying chemical processes, with consequent cross-project comparison. Both objectives were successfully achieved – the calculation of each metric brought additional value into understanding these chemical processes, specially the EcoScale analysis that enabled the quantification of otherwise subjective parameters, and a global overview of the company on how it proceeds in drug development processes was provided.

Additionally, other types of evaluations were possible with this tool, such as a critical aspects analysis, which provided useful information through hard data on what process parameters should be addressed for improvement, and an improvement-evolution assessment over the drug development of a case study project from this company, which allowed for an evaluation of what process modifications occurred over time, and what benefit/drawbacks they implicated.

The knowledge-based assessment tool incorporated many features that allowed for a truly thorough evaluation of pharmaceutical processes in every sense of the word "efficient", and a world of possibilities can be imagined. For now, some objectives were already possible, although this initial trial revealed many aspects that still need to be refined, and other goals lie ahead.

Upon analysing the inconclusive results for the categories' final classifications, specially for manufacturing, an optimization of the underlying model (i.e., what criteria contributes to each final classification, and their corresponding weightings) was still necessary to truly classify pharmaceutical processes using this assessment tool. In the case study evaluation, these final classifications also appeared to not be sensitive enough to detect the performed process alterations, therefore, not allowing a validation of this framework. Also, a better understanding of what target values are to be aspired by each metric, given the purpose of evaluating drug development processes in a CDMO context, would be achieved with more data gathering, this way driving the platform to attain more of the company's knowledge on its processes, and consequently its realistic goals.

One of the useful evaluations to be provided by the assessment tool was an analysis of all criteria per type of chemistry, instead of per process step

or project, the reason why that information was supplied through the organized template. As some of the criteria presented in this work, e.g., molar yield, AE, RME, reaction temperature, reaction time, etc., depend more on type of reactions occurring rather than the type of process, this analysis would assess possible clusters of data, thus a target value that the company could aspire to accomplish, within its context and area of focus. It could also permit the behavior analysis of other criteria, as to understand its influence according to type of chemistry, this way guiding the drug development while resorting to historical knowledge with precise data. However, this type of analysis was not yet possible in this first trial, due to a lack of recognized databases for types of chemistry.

To improve the assessment tool's evaluating skills, and enable the capture of as much process knowledge as possible, some upgrades can be performed:

- Dynamically assigning target ranges, depending on what type of process/chemistry to be evaluated, therefore granting more realistic goals;
- Having chemical steps evaluated separately rather than just the isolated ones, this way better evaluating more chemistry focused criteria;
- Enabling the manufacturing phase integration in the EcoScale analysis, and its green metric's calculation on the overall process level, the same way as laboratory phase;
- Having more consideration over the drying step's criticality, by calculating a volume-time-output specific for this stage, to cover more process bottleneck analysis;
- Properly assessing the filtration stage's efficiency, by integrating a filtration flux in its EcoScale criterion and determining an optimal target;
- Implementing more connections with other databases to simplify the template's data entry;
- Having the responsible for each area answer the organized template according to their expertise (specially for the EcoScale's safety and raw materials categories);
- Having new company clients input their Assessment phase's data, to prevent insufficient offer of hard data from their laboratory experiments, often only with typical process values available, which made this evaluation exercise not fully accurate.

Whilst the development and implementation of the assessment tool presented in this work, researchers at F. Hoffmann-La Roche Ltd. developed a very similar analysis tool for evaluating chemical syntheses called ChemPager [22], integrating commonly calculated metrics as process mass intensity (a similar metric to E-factor) and VTO, production costs, and simple answers in terms of process parameters and raw materials classification. Their platform is able to efficiently evaluate projects in terms of robustness, economy, safety, greenness, and project difficulty, providing a set of scores/weightings for each parameter/category. Since ChemPager also provides adequate visualization of the evaluated data, and equally offers the possibility of cross-project comparison and data aggregation, it is safe to say that this tool exhibits what the knowledge-based assessment tool should aspire to become, with a more complete and interchangeable layout that allows for a more thorough evaluation.

Although the present platform was only implemented in a trial basis, with much work to be done even so, the knowledge-based assessment tool proved its tremendous potential of enhancing the analysis of a pharmaceutical project's performance, which in the future will improve the company's decision-making process based on data instead of biased perception, thus providing structured guidance for drug development and process optimization.

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