TÉCNICO LISBOA

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

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Thesis to obtain the Master of Science Degree in

Biological Engineering

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November 2018

Abstract

The pharmaceutical industry faces many challenges nowadays, with increasing ”time to market” pressures, and growing product competition, therefore, it is of the utmost importance that drug development provides reliable and efficient processes at a rapid pace. This is possible through a progression towards Industry 4.0, based on hard data and gathered knowledge over the lifecycle of a pharmaceutical product.

This work presents a newly developed knowledge-based assessment tool intended to evaluate and classify pharmaceutical processes, within the context of a contract development and manufacturing organization. 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 which uses a set of scores and final weightings, 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 classification, Drug development, Green metric calculator, Lifecycle assessment, Process efficiency

Resumo

Actualmente, a indústria farmacêutica enfrenta inúmeros desafios, passando por um aumento da pressão para comercialização rápida de medicamentos, e uma crescente competição empresarial – portanto é imperativo que o desenvolvimento farmacêutico forneça processos fiáveis e eficientes atempadamente. Para tal, é necessária uma progressão na direcção da Indústria 4.0, fundamentada em dados concretos e conhecimento adquirido ao longo do ciclo de vida de um produto farmacêutico.

Este trabalho apresenta uma ferramenta de análise baseada em conhecimento, recentemente desenvolvida com o intuito de avaliar e classificar processos farmacêuticos, num contexto de uma *contract development and manufacturing organization*. Esta plataforma incorpora métricas conhecidas de "química verde", incluindo o *atom economy*, *E-factor*, *volume-time-output*, e a ferramenta semi-quantitativa *EcoScale*. Ao agrupar todas estas contribuições de maneira estruturada, permitindo o cálculo das suas respectivas pontuações, é possível avaliar processos químicos em termos de estratégia de síntese, geração de resíduos, produtividade, qualidade, condições do processo, classificação de matéria-prima, e aspectos relacionados com saúde, segurança e impacto ambiental, o que permite obter uma classificação final baseada em todos estes parâmetros relevantes na determinação da eficiência de processos.

A ferramenta de análise foi implementada eficazmente em projectos em desenvolvimento farmacêutico na Hovione FarmaCiência S.A., permitindo a comparação entre projectos diferentes e a criação de uma base de dados com este conhecimento adquirido. Adicionalmente, uma análise dos aspectos críticos de processos possibilitou a detecção rápida de elementos a melhorar, e uma avaliação a um projecto da empresa com múltiplas revisões de processo proporcionou uma análise de melhoria contínua ao longo do seu desenvolvimento.

Palavras-chave: Indústria 4.0, Classificação de processos, Desenvolvimento farmacêutico, Cálculo de métricas verdes, Avaliação do ciclo de vida, Eficiência de processos

Contents

List of Tables

List of Figures

Nomenclature

AE	Atom Economy
API	Active Pharmaceutical Ingredient
CDMO	Contract Development and Manufacturing Organization
FDA	Food and Drug Administration
HSE	Health, Safety and Environment
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPC	In-Process Control
IPE	Individual Protection Equipment
MW	Molecular Weight
MY	Molar Yield
OOS	Out Of Specification
PEICT	Process Excellence Index Cycle Time
PEIMY	Process Excellence Index Molar Yield
Q&A	Question and Answer
QSL	Quality Service Level
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RME	Reaction Mass Efficiency
SE	Step Economy
SF	Stoichiometric Factor
SRM	Starting Raw Material
VTO	Volume-Time-Output

Chapter 1

Introduction

The pharmaceutical industry faces many challenges nowadays, with increasing ”time to market” pressures, tighter regulatory demands, and growing product competition – which ultimately leads to an overall decrease in research productivity. It is crucial for the industry to transform from its traditional ”blockbuster era” thinking, 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. [1, 2]

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. If this precious knowledge on products and processes can be properly harvested in an organized framework, the pharmaceutical company can gain with an accelerated and more comprehensive development, and a decrease in repeated deviations and search time for existing data – therefore enabling shorter ”time to market”. [1, 2]

This work presents a data- and knowledge-based assessment tool that has been developed and implemented on pharmaceutical drug substance processes from Hovione FarmaCiência, S.A., that will allow for a better understanding of the project's performance, and thus helping future ones. This chapter outlines a small introduction to the context of this industry to fully comprehend its challenges.

1.1 The Pharmaceutical Industry

The main objective of pharmaceutical companies is to deliver drug products necessary to the public, to help improve the quality of life. But before the pharmaceutical industry as we know it existed, human beings were already using drugs to treat diseases for more than 3000 years. These drugs were of plant and animal origin and, until the 18th century, this type of medicine had been entirely based on empiricism and passed through generations without any scientific base related to it. However, in the late 18th century began to emerge the study of potential therapeutic effects of such herbs, which is known today as pharmacology. [3]

The modern pharmaceutical industry can trace its origin to two main sources: companies such as Merck, Eli Lilly and Roche, who started as apothecaries that supplied natural products such as morphine

and quinine, moved into wholesale production of drugs in the middle of the 19th century, whilst newly established dye and chemical companies, such as Bayer, Imperial Chemical Industries, Pfizer and Sandoz, discovered medical applications for their products. Nevertheless, growth was relatively slow, and at the start of the 1930s most medicines were still sold without a prescription. [3, 4]

In the early part of the 20th century, a number of major advances were made. For example, in 1897 the chemically modified version of salicylic acid was developed with improved efficacy and the product, aspirin, was manufactured, along with both penicillin and insulin (between 1920s and 1930s), although at a modest scale. The Second World War also stimulated the growth of this developing industry, with requirements for the large scale manufacture of analgesics and antibiotics, and increasing demands from governments to undertake research to identify treatments for a wide range of conditions. All of this helped motivate further commercial investment in research, development and manufacture of pharmaceutical drugs, combined with increased government regulation. [3]

Although the United States of America already had consumer protection laws during the late 19th century, it was with the creation of the Food and Drug Administration (FDA) in the 1930s that pharmaceutical companies started to follow well-established paths to ensure the safety and efficiency of medicines. [5] Even though the FDA regulates drug commercialization in the United States, many drug regulatory agencies from other countries (such as the European Medicines Agency or the Federal Drug Control Service of Russia) consider their guidelines and methodologies as well, due to their strict compliance reputation. Additionally, all the regulatory agencies demand that the manufacturing of drugs to be consumed by humans should comply with current Good Manufacturing Practices. [6]

1.1.1 The Drug Development Process

The development of a new pharmaceutical drug undergoes five basic stages: discovery/concept, preclinical research, clinical trials, FDA review, and FDA post-market safety monitoring (Figure 1.1). Nowadays, this process can take 12 to 15 years and cost millions of euros – as of 2014, the cost of taking a new drug from concept to commercialization was above US$ 1.3 billion. Besides this, an analysis made by the Centre for Medicine Research in the United Kingdom found that, between 2008 and 2011, only 18% of drugs made it out of phase II clinical trials for phase III testings; and in the United States, another study showed that approximately 1 in 1000 potential drugs have approval for human clinical trials and still only 1 out of 10 pass this phase. Therefore, apart from being time-consuming and extremely costly, the usual low chance of a successful outcome makes this a very high risk industry. [7]

In the first step of this development, researchers typically discover new drugs through new insights into a specific disease, or high-throughput screening techniques can be used to identify possible substances that might be suitable candidate drugs. At this stage of the process, it is not uncommon to have thousands of potential leads that need further testing in order to be refined to three or four candidates for further investigation. These potential leads may exhibit the relevant biological activity but they may also be accompanied by other undesirable toxicological properties which will be studied during this refining period. [7, 8]

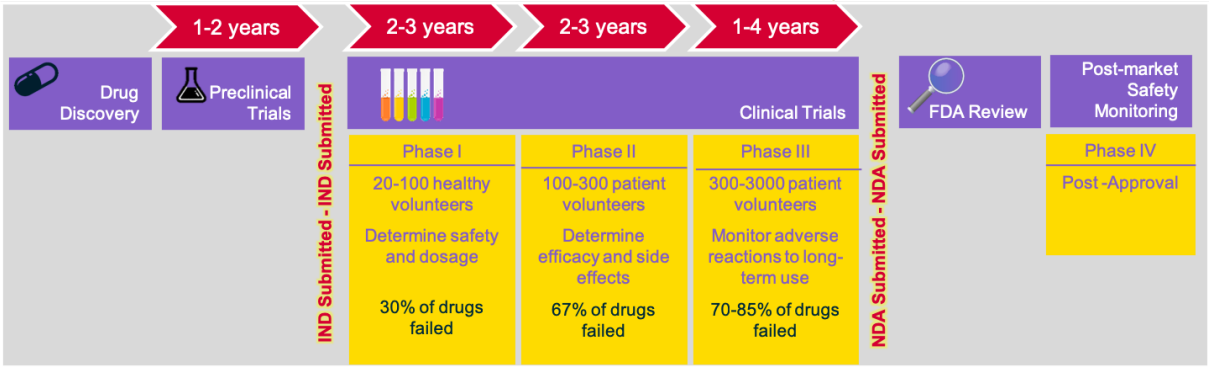


Figure 1.1: Overview of the drug development process. IND designates investigational new drug application and NDA stands for new drug application. [7, 8]

The first step of clinical trials is actually a preclinical research trial where the lead candidate drugs are generally tested in animals (they can also be done *in vitro* through tissue engineering), to find out their toxicity and potential to cause serious harm to humans. Although they are not long, these trials are very important to provide detailed information on dosing and toxicity levels in order to begin the first human tests. After the preclinical trials, the pharmaceutical company must submit an investigational new drug application to the FDA before beginning the clinical research. [8]

The third step of the drug development process consists on three clinical trial phases, with tests done on healthy humans (phase I) and then on humans with the targeted condition (phase II and III). Phase I studies, although conducted mainly on healthy volunteers, can have some exceptions with trials for drugs that target cancers, where the treatment is likely to make healthy individuals sick, so in these cases volunteer patients participate in the trials. The main focus of this phase is to determine the drug dosage range that the body can tolerate and how intense its side effects can be. Some early information about effectiveness can be obtained, that could help the design of the phase II studies.[7, 8]

In phase II trials, the researchers begin to evaluate the therapeutic effect of the drug and continue with dosage and safety studies, now with a larger number of test subjects. It is usually in this phase that some candidate drugs are discovered to have no influence on the targeted disease. [8]

The purpose of phase III is to confirm the drug's effectiveness on a specific disease and to provide most of the safety data, due to the larger timelines and targeted population (thus some less common side effects can be detected). [8]

After the clinical trials, all of its data is compiled in a new drug application given to the FDA to demonstrate that the drug in question is safe and effective for its intended use in the population studied. After the FDA's approval, the pharmaceutical company quickly begins to market the drug in order to get as much return profit as it can get with the remaining years of patent life (5–10 years after its filing, usually in the beginning of the preclinical trials). [3, 8]

In truth, there is a phase IV clinical trial done to patients after the FDA review. These tests relate to the FDA's post-market safety monitoring and they help detect any rare or long-term adverse effect within a longer time period than phases I to III. [3]

1.1.2 The Manufacturing Process

As long as a pharmaceutical drug is undergoing all the development stages discussed earlier, there has to be chemical synthesis and manufacturing of said drug, in order to provide product for each clinical trial. Besides understanding the efficacy and safety of the drug during these stages, the respective active pharmaceutical ingredient (API) synthesis process also needs to be understood, developed and optimized to eventually be transferred to manufacturing. As we go along the timeline of drug development, different amounts of product will be needed, so the manufacturing process will require scale-up from simple laboratory reactors (producing 10mg–10g), passing through kilo labs (100g–10kg produced) and pilot plants (with 10–100kg of product), until finally the use of manufacturing plants (producing more than 100kg). [9]

The drug discovery stage, where the researchers determine the initial chemical synthesis route and purification steps, is typically developed in laboratory scale. Here, the synthesis is designed to quickly produce a few grams of API needed to support exploratory tests and biological activity assessments, therefore this initial route is usually not well-designed for further scale-up to kilogram scale. [9]

In early development stage, during preclinical and phase I trials, the API needs begin to increase and the synthesis has to adapt to the so-called kilo labs, which are typically the first scale-up to produce the necessary quantities of product for these tests. The objective is the selection of an appropriate and practical chemical route for initial scale-up, and the chemists/engineers begin to focus on understanding some process parameters, such as process safety, number of chemical/isolated steps, availability of reagents, raw materials and intermediates, and ability of the synthesis to address API quality. In terms of process safety, in this stage is very important to assess and identify possible hazardous reactions and compounds, and evaluate safe operating limits. [9, 10]

So far, these first steps are mainly focused on chemical development – however, throughout phase II trials, the researchers start to focus more on process development. Now, the chemical synthesis and sequence of unit operations must become finalized and efficiently scaled-up to pilot plant scale, in order to provide kilograms of API product to the clinical trials. In contrast to kilo labs, pilot plants are much larger, with designs that more closely resemble the commercial manufacturing plant. In addition, some business risk analysis at this stage will help develop a robust, efficient and economical future manufacturing process, in regards to yield, cycle time, equipment usage, waste output, and need for analytical technology. [9, 10]

Finally, during phase III of clinical trials, the API process will be transferred to chemical production and evaluated in the manufacturing plant, with focus on the final optimization of process parameter ranges and full understanding of unit operations, including possible mitigation measurements. [9]

Near the finalization of this stage, just before the new drug application submission, the drug manufacturing process will require validation for its commercial distribution. Besides demonstrating a safe and quality-driven process, it is essential to prove consistency between batches throughout the drug's lifecycle. It is common policy in the pharmaceutical industry to prove process validity with three successfully manufactured batches (also called "validation batches"), although the FDA does not explicitly demand any minimum number of batches. To sum up, according to the FDA Guidance for Industry

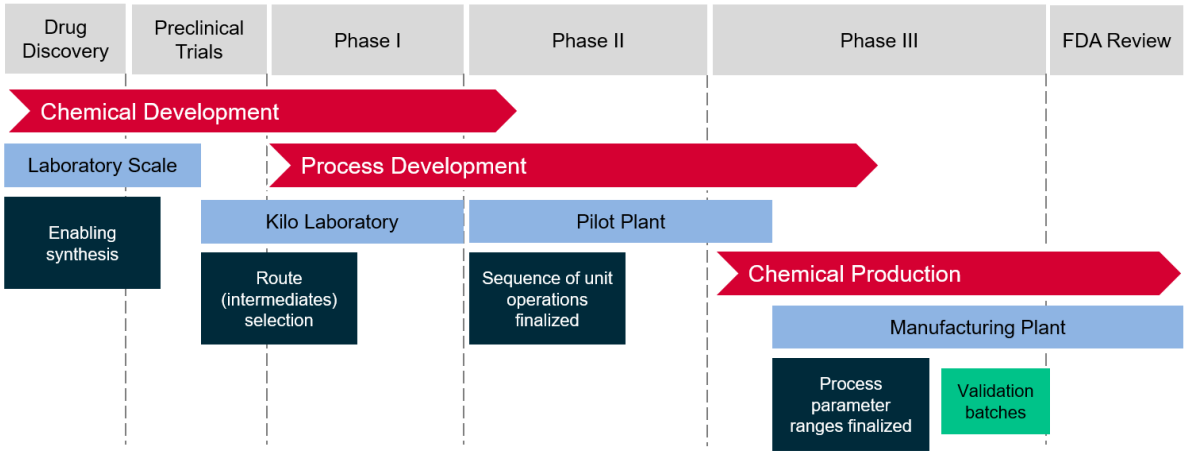


Figure 1.2: Timeline for the manufacturing process scale-up across the different drug development phases. [9, 11]

on Process Validation [12], the number of batches should be determined on the basis of knowledge in order to be able to show the efficient transfer of the process design and the development studies to commercial scale. [12, 13] This may cause confusion within the manufacturing industry, and although some researchers have tried to develop a method to determine the number of validation batches needed [14], the FDA generally accepts the 3-batch consistency.

Figure 1.2 summarizes all the drug development stages concurrently with manufacturing development.

1.1.2.1 The Fine Chemical Process

The industrial production of APIs and drug products is typically set in batch-operated multipurpose manufacturing plants, in order to have a flexible design that will allow different products to be run in separate equipment trains, depending on the demand. This is achieved by building facilities and installing equipment that can be swiftly modified for new manufacturing processes. [15]

This flexibility is not always easy to achieve, for that reason some pharmaceutical companies outsource their manufacturing (and sometimes development) needs to other companies, who will produce the API and/or drug product for them. These are called contract development and manufacturing organizations (CDMO), and they have the advantage of being better prepared to undertake flexible process designs without having the responsibility of drug discovery and drug marketing (further explained in subsection 1.1.3). [16]

Starting from the synthesis of an API until the formulation of a drug product, the chemical process can be broken down into a sequence of various standard unit operations. A typical process would have a unit operation sequence as shown in Figure 1.3.

First of all, the reaction unit operation is where the synthesis of the API occurs, after charging all the reaction components such as raw materials, reaction solvent, and possibly catalysts or reaction aids. This step can be very complex, where reagent and solvent selection, stoichiometry, sequence of charging components, and temperature can affect dramatically the yield and degree of by-product

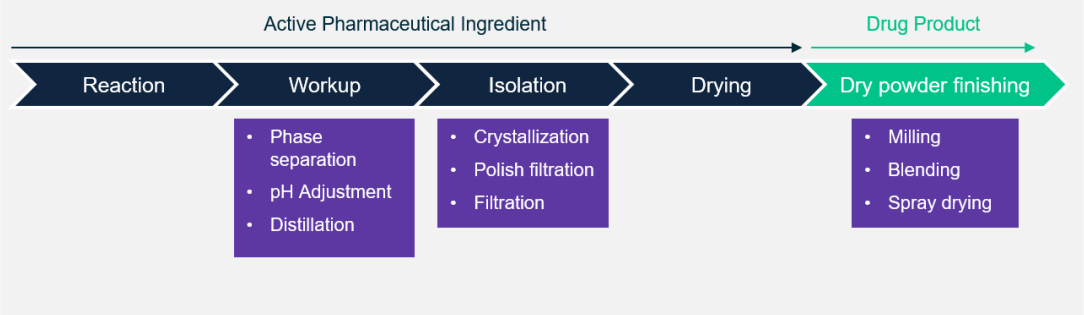


Figure 1.3: Typical sequence of unit operations for a single-step drug process. [10]

(impurity) formation, which are two of the most important process characteristics. [9]

During the workup stage, various unit operations can be conducted, depending on the type of product and components involved, such as extractions and distillations. There can be one or more phase separations, where the objective is to remove undesired components (organic impurities or inorganic salts) from the product solution, by adding an immiscible liquid and removing the undesired phase. An auxiliary operation that can be performed before the liquid-liquid separation is a pH adjustment, since this parameter is critical in this unit operation. With a pH adjustment, the API can be converted into a free acid, free base or salt to enable a preferential distribution into the desired liquid phase for further processing. [9, 17]

Another very important unit operation in chemical processes is distillations, generally used with the objective of changing the solvent composition of the solution to facilitate the downstream processing. It can be performed with different designs, such as continually adding a new replacement solvent at a constant volume, or sequentially, and sometimes repeatedly, adding the new solvent and then distilling down to a specified volume (put/take method). [9]

In the beginning of downstream processing, there will always be an isolation stage. Here, the most complex unit operation is a crystallization, which creates solid API particles with the correct form and desired physical properties (size distribution, density, and surface area). Additionally, the product becomes purified from soluble impurities that stay in the liquid phase. [9, 18] One aspect that can aid this operation is employing a polish filtration, in which an API solution is filtered through a small-pore cartridge filter to remove any small particulates or undissolved contaminants that may interfere with the following crystallization step. Usually, this type of filtration is only done to the final product, which has the most critical quality specifications. [19]

The last stage before drying is typically a filtration operation, with the objective of recovering the crystals previously formed in high purity from the supernatant (mother liquors), and efficiently wash impurities and other contaminants. [9]

Although not so common in chemical pharmaceuticals, other isolation operations using charcoal filters or chromatographic columns may prove useful in particular situations, where a higher purification efficiency is needed. Charcoal filters use an activated carbon bed, which is highly porous, to very efficiently adsorb particles, namely carbon-based impurities in liquids. After the operation, the carbon filter needs reactivation to promote the release of the contaminants, which can be through a regeneration

process or by simply replacing it for a new one. [20] Chromatography techniques use a differential migration process to selectively isolate target molecules with very high purity, by having them adhere to a specific stationary phase within the column and conducting an elution stage, where a specific solution is used to gradually remove the adherent particles from the column. Therefore, various components from a mobile phase will elute at different rates according to their adherence to the stationary phase. [19, 21]

Finally, in the drying step the remaining solvent will be removed from the wet API in order for it to meet the final product specifications, while maintaining a consistent and stable powder. Although being an isolation step itself, it was given more relevance to this particular operation for its criticality in the process, whether in terms of final quality or cycle time. [9]

APIs can be very large and/or complex molecules, and producing them often requires multistep processing, where the product of one step becomes the starting raw material (SRM) for the next step, until the final API is synthesized. Overall, each process step used to synthesize and purify an intermediate, and eventually the final API, will undergo most of the unit operations sequence described in Figure 1.3, making the entire API production process very intricate. [15]

Only after the final step of API manufacture that the product goes through the dry powder finishing stage, where the addition of excipients and formulation of the drug product occurs through unit operations such as blending, milling, or spray drying. [10] This last stage will not be addressed in the present work.

1.1.3 Difficulties and Constraints

With everything already discussed in this section, one can conclude that, besides the benefits that medicinal drugs bring to society's quality of life, a lot of issues can arise in this industry. These issues can cause, not only millions of euros lost, but also the failure of a lot of development projects for potentially life-saving drugs.

In terms of drug development, Figure 1.1 indicates how low is the success rate of a drug being selected from the beginning of the discovery phase, passing all the clinical trials and subsequent FDA approval, keeping in mind the 12–15 years it takes to complete the drug development and the billions of dollars it costs [22]. Plenty of factors can contribute to the failure of a program, such as the drug not having the therapeutic influence intended, or having unacceptable safety risks and toxicological effects. Those factors can depend on the chemical itself, interaction with other drugs, or the possible drug dosing regimen (e.g. decisions regarding formulation, route of administration, drug dose, dosing interval and treatment duration). [22, 23]

The manufacturing of drugs also comes with some constraints, besides the responsibility of producing a product with maximum quality and safety. Due to the small time-window to profit between the FDA's approval to market and the patent's expiration, there is significant pressure to deliver a safe, environment-friendly, and economic process in time for the new drug application submission. 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 in a very complex manufacturing process. [24]

This is why about two-thirds of pharmaceutical companies outsource most of their manufacturing work,

and some development work, to CDMO's. As mentioned in subsection 1.1.2, with this service the client can cut costs on upfront investment, improve equipment usage constraints, and better manage changes in product demand, which ultimately allows for a speedy "time to market" for new products. Additionally, in speciality areas such as formulation and particle engineering, it can be highly advantageous to hire a qualified CDMO that provides more knowledge and experience on these matters. However, some disadvantages have raised concerns, for instance uneasiness about the quality and safety of some of the materials sourced from markets in India or China, or possible data security and intellectual property issues that can create a scenario where the CDMO can eventually develop their own similar product and compete with its former customer. [16, 25]

Nonetheless, there are still a lot of complications in manufacture that those organizations can encounter, the most relevant being the process's scale-up. There are many scale-up factors in a chemical process that should be taken into account, such as stability of the reaction mixture with respect to undesired side reactions, heat transfer of most unit operations, and proper mixing of the solution. Attention should also be paid to processing times (which normally do not increase proportionately) and possible safety concerns (that become far riskier and dangerous with the production scale-up). [9, 19]

Some process aspects can be optimized to allow a more flexible scale-up and ease into commercial manufacture, like minimizing the number of extra unit operations that in early development might have been added to ensure the necessary quality (mostly phase separations and filtration washes), or the full understanding of the reaction taking place and its condition's proven acceptable ranges. With a comprehensive optimization and subsequent improvement of critical process parameters, one can reduce the number and impact of side reactions, and with less impurities forming, the need for those extra operations will be lower. [9]

A more timely process understanding and optimization can provide fewer scale-ups at kilo and pilot plant scales, less analytical load, fewer waste production, and a process designed to perform as expected (and right the first time) in manufacturing scale. [24] Having a robust program of drug development and drug manufacturing is therefore essential to alleviate the risks associated with this industry.

1.2 Green Chemistry

Green chemistry has been around since the late 1990s, with the publication of the book *Green Chemistry: Theory and Practice* by Paul Anastas and John Warner. [26] This movement expressed the need to change the way chemistry and chemical engineering was done, and over the years different considerations and process designs have been thought of. The book introduced the twelve principles of green chemistry that would allow for a "greener" and sustainable process, which involved waste prevention, lower energy consumption, synthetic efficiency, and reduced hazardous components (used and generated). [26]

Nonetheless, various definitions of what green chemistry is has brought some confusion to the scientific community, which often does not help the progress and acceptance of this matter. Some think that it implies the use of new and modern technologies like ionic liquids, or supercritical fluids; others may think it is simply having a "good process chemistry" with high yields and cost-effectiveness; and some

even feel that it is just environmental criticism towards the chemical industry, and that the objective of this movement is to prevail reduction of environmental impact over having an efficient and quality-driven process. [27]

Green chemistry is much more than that, and at the same time much simpler. This concept just intends to alert the scientific community to possible unnecessary environmental burdens in unoptimized unit operations that should raise concern, while regarding the same synthesis and high quality objectives. Just the act of questioning whether a toxic reagent can be replaced for a benign one, or at least its quantity reduced, in a given process already allows for more discussion and awareness on the subject. [27]

However, it is still important to point out the corporate advantages of a sustainable process design, to encourage companies to implement the principles of green chemistry. First of all, it boosts the reduction of some environmental and safety risks, such as greenhouse gas emissions, pollutants and toxic releases, and minimization of hazardous materials (reagents, raw materials, solvents) transportation – with the increasingly restrictive regulations and waste management costs, this change would already make a difference in the company's expenses. Second, having a more efficient process in terms of mass and energy usage would itself make the company more profitable, attached to the extra competitive advantage of it. Having this environmental priority enables higher synthetic and operational efficiency, with reduced process time and cost. Finally, the well-being of the surrounding community in which the company operates should always be a concern. [28]

1.2.1 Pharmaceutical Perspective

One must not forget that the pharmaceutical industry has inherently more responsibilities than an average fine chemical industry, having to deliver life-saving medicines to the population. Thus, when designing a sustainable pharmaceutical chemistry process, attention must be paid to which green chemistry principles may apply to this industry. [26]

For instance, designing for degradation, which translates to "chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment", can be unsuitable for a product such as an API, which the desired biological activity depends on its specific molecular structure and must display appropriate stability and shelf life. The use of renewable feedstocks, another green chemistry principle, may also be difficult to encounter for so many different products with possibly limited manufacturing schedules. [27]

Certainly other principles would technically be achievable in this industry, but should be carefully studied beforehand, on account of the sensitive specifications the product holds. For example, designing safer and less hazardous chemical reactions, reducing protection/deprotection steps, and using safer solvents would be ideal, however, if by replacing a toxic solvent with a benign one decreases throughput that measure should not be taken. [27]

In fact, due to the short and costly development programs, regulation's requirements on quality and safety of pharmaceuticals, and high project attrition, it takes significant effort to introduce process changes

late in the product timeline. Therefore, using established methodologies that minimize timelines and regulatory issues becomes very appealing – interestingly enough, this uneasiness might be one of the biggest inhibitors of green chemistry in the pharmaceutical industry. Nevertheless, chemists must be willing to challenge themselves and search for new techniques that might offer greater process efficiency. Striving for the correct choice of raw material, ideal synthetic strategy, adequate use of solvents/reagents, and efficient design of downstream operations is key for the success of this endeavour. [27, 29]

1.2.2 Green Metrics

The twelve principles of green chemistry are specially helpful in causing awareness in the scientific community and providing well-defined solutions to promote sustainable development, although the evaluation of these principles may lead to subjectivity. Applying green chemistry may not be so easy if the industry does not know how to evaluate the greenness of a chemical process. Since the acknowledgment of this concept, scientists have developed several metrics that would quantify greener processes and products, although a unified set of metrics has yet to be established by the community. [30]

These metrics include simple mass and energy calculations, health, safety and environmental (HSE) considerations, and lifecycle impact approaches, which can be used to evaluate a whole chemical process or its individual steps. These metrics must allow for a clear, simple and fast way to obtain information on the greenness of any type of chemical process, and 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. [30]

In the next sections, some of the most well-known green chemistry metrics and evaluation methods will be further explained.

1.2.2.1 Atom Economy

When developing chemical processes, chemist's key focus is on maximizing reaction yield (Equation 1.1, where starting raw material (SRM) is defined as being the limiting reagent), and selectivity. Although the chemical yield retains extreme importance in an efficiency-driven evaluation, reflecting the actual productivity of the chemical steps, it does not take into account an important aspect, the synthesis strategy. This is where the atom economy (AE), first introduced in 1991 by Trost [31], can be useful. It represents the ratio of the molecular weight (MW) of the target molecule to the total sum of the molecular weights of all substances incorporated in the final product/intermediates – these substances are called reactants, which include the SRM (Equation 1.2). In simple terms, this metric 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). [32]

$$Molar\ Yield = \frac{mass_{product} \times MW_{SRM}}{mass_{SRM} \times MW_{product}} \times 100\ (\%) \tag{1.1}$$

$$Atom\ Economy = \frac{MW_{product}}{\sum MW_{reactants}} \times 100\ (\%) \tag{1.2}$$

Although this parameter does not consider the actual reaction yield and molar excess of reactants, it allows for a quick evaluation of the theoretical efficiency of the chemical synthesis, even before any laboratory experiments are performed. The higher the percent AE value, the more efficient the synthetic strategy is designed to be. Additionally, AE can be calculated for each individual step or the entire API process, by simply readjusting the considered "product" (in the initial steps, the product is in fact a process intermediate) and accounting for all reactants added. [33]

1.2.2.2 Environmental Factor

The environmental factor, commonly known as E-factor, was published by Sheldon in 1992 [34] and is one of the most popular green chemistry metrics. It represents the amount of waste produced per kilogram of final product (Equation 1.3), and can be calculated for each individual step or the entire multistep process. This allows for a strong visual demonstration of the waste generation in the manufacturing industry.

In fact, the author used this parameter to show the scientific community how an oil refining industry can manufacture a product with such a negative connotation, but have minimal waste generation compared to the pharmaceutical industry (Table 1.1). This is mostly because the oil industry deals with relatively simple chemical processes which were continuously optimized over the years, unlike the pharmaceutical manufacture and all its development constraints (as discussed in subsection 1.1.3). [27]

Table 1.1: E-factor values for different types of chemical manufacturing industry, with the respective product output. Ideally, the E-factor value is zero. [34]

Industry segment	**Product annual tonnage**	**E-factor (kg waste/ kg product)**
Oil refining	$10^6 - 10^8$	< 0.1
Bulk chemicals	$10^4 - 10^6$	< 1.5
Fine chemicals	$10^2 - 10^4$	$5 - 50$
Pharmaceuticals	$10 - 10^3$	$25 - 100$

One of the first challenges this metric brought was the definition of what classifies as waste. In the original publication, waste was defined as everything but the target product, thus it included solvent losses, and incompletely consumed reactants and reagents, only excluding the water input from the calculation – its inclusion would most likely lead to extremely high E-factor values that could complicate comparison between processes. Another aspect that can be taken into account is the recycling of solvents, a normal practice in the fine chemical industry, although, if the precise details of solvent losses were not known, the authors suggested a 10% loss assumption. [35] Nowadays, the current rationale is to include water mass in the calculation (even if considered benign, the industrial wastewater treatment is still quite expensive), and total inclusion of solvent input (unless reliable recycling data is available), in order to obtain a more realistic assessment. [36]

$$E\text{-}factor = \frac{mass_{waste}}{mass_{product}} = \frac{\sum mass_{input\ materials} - mass_{product}}{mass_{product}}\ (kg/kg) \tag{1.3}$$

In spite of this, there are still some inconsistencies regarding this parameter. One of them is the starting point of the calculation, whether it should take into account the E-factor of the raw material manufacturing company and outsourced intermediates, which would complicate an otherwise effortless evaluation. Recently, the original E-factor authors advised that those amounts of waste should be considered, to account for possibly less regulated outsourcing markets, thus defining the starting point as commodity-type materials. [36]

Another constraint is the fact that the E-factor does not consider the nature of the waste produced, which is significant for a true environmental impact assessment. The original authors later tried to suggest an alternative metric, called the environmental quotient [37], obtained by multiplying the E-factor with an "unfriendliness quotient" – this value, arbitrarily assigned to each component, would increase proportionally to the environmental impact brought by it. This was obviously very ambiguous and there was never any consensus over the quantification of these quotients, specially because the environmental impact of a compound does not depend only on its chemical and physical properties, but also on the processed volume, ease of recycling, and even the manufacturing facility's location. [35]

With the lack of ecotoxicity considerations on the E-factor calculation, Hudlickly et al. [38] proposed, in 1999, another environmentally focused metric designated effective mass yield, which was the ratio of the mass of desired product to the mass of all non-benign materials used in the process. Although the authors defined the term benign (i.e., materials that "have no known environmental risk associated with them for example, water, low-concentration saline, dilute ethanol, autoclaved cell mass, etc."), it still renders subjectivity and absence of definitional clarity. Until there is sufficient ecotoxicity information available, these sorts of green metrics will not become accepted and routinely implemented in chemical processes. [32]

1.2.2.3 (Process) Mass Intensity

A very similar metric to the E-factor was also developed by researchers at GlaxoSmithKline in 2001 [28] called mass intensity, which is very simply the ratio of the total mass of input materials (excluding water) to the mass of the desired product, with an ideal value of 1. More recently, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable developed a simple calculation tool for the process mass intensity, identical to mass intensity but already including process water (Equation 1.4). [39]

$$Process\ Mass\ Intensity = \frac{\sum mass_{input\ materials}}{mass_{product}}\ (kg/kg) \tag{1.4}$$

Process mass intensity and E-factor both account for reaction yield, stoichiometry, and solvent and reagent inputs, which are by far the largest contributing fractions to these parameters, so these types of metrics are very important for green chemistry assessments. [36]

1.2.2.4 Reaction Mass Efficiency

In studies performed by a GlaxoSmithKline research team [28, 32], the authors observed, for dozens of chemical reactions, a lack of correlation between AE data and mass intensity values, and that most reactions run in nonstoichiometric conditions, which AE does not consider – meaning that, although AE reflects the synthetic strategy efficiency, it does not relate to the efficiency in reactant mass utilization. This begins to suggest that, when considering the greenness of processes, one should not depend on one green metric only. To try to prevent this dilemma, the researchers developed a metric called reaction mass efficiency (RME) which is a sort of refinement of AE, applying actual quantities of components (Equation 1.5) instead of a theoretical value. This way, it accounts for reaction yield, excess molar quantities of reactants, and the concept of atom efficiency. [28]

$$Reaction\ Mass\ Efficiency = \frac{mass_{product}}{\sum mass_{reactants}} \times 100\ (\%) \tag{1.5}$$

1.2.2.5 Carbon Efficiency

The same GlaxoSmithKline researchers [28] also developed a similar metric to RME, called carbon efficiency, which is the mass of carbon in the final product divided by the mass of carbon in all reactants (Equation 1.6), therefore demonstrating the percentage of carbon that remains in the final product. This metric also accounts for reaction yield and stoichiometry.

$$Carbon\ Efficiency = \frac{carbon\ mass_{product}}{\sum carbon\ mass_{reactants}} \times 100\ (\%) \tag{1.6}$$

1.2.2.6 Stoichiometric Factor

In 2005, Andraos explored the concept of RME and defined a new auxiliary metric called stoichiometric factor (SF) [40], used to account for reactions run under nonstoichiometric conditions, namely with addition of molar excess reactants. If one or more reactants are introduced in excess, SF will be higher than 1 (Equation 1.7).

$$Stoichiometric\ Factor = 1 + \frac{\sum mass_{excess\ reactants}}{\sum mass_{stoichiometric\ reactants}} \tag{1.7}$$

The authors used this parameter to establish an RME general algorithm, complex but functional for different types of processes with distinct scenarios of reaction linearity, recycling, and stoichiometry. [40]

1.2.2.7 Step Economy

The pharmaceutical industry always deals with high complexity molecules and, consequently, high number of process steps to achieve the final API, and this will inherently bring inflated E-factor values. In 2006, Wender et al. [41] demonstrated the importance of the concept of step economy in minimizing waste generation. Not only that, but it also influences efficiency, cost, execution time, and equipment usage.

However, to achieve more step economy, reaction selection and meaningful exploration of new organic reactions is essential. [36]

In 2007, Clarke et al. [42] had an interesting idea of combining pot, atom and step economy to analyse efficiency of different syntheses, calling it PASE. The pot economy concept addresses the problem of excessive mass intensities due to increasing isolation and purification procedures, with subsequent high volume of solvents. Therefore, it drives the execution of telescoped synthesis, which relates to as many sequential synthetic reactions occurring in the same vessel without the need for product isolation between reactions. [42]

Equation 1.8 shows a simple way of quantifying the step economy concept, setting the goal to have a minimal SE value. This favors a process with more chemical reactions than isolated steps (i.e., telescoped synthesis).

$$Step\ Economy = \frac{number\ of\ isolated\ steps}{number\ of\ chemical\ steps} \tag{1.8}$$

1.2.2.8 Volume-Time-Output

In 2012, a publication from Boehringer Ingelheim's chemical and process development department [11] introduced a new metric called volume-time-output (VTO), which translates the amount of volume and time schedule allocated per kilogram of product output (Equation 1.9). It is important to note that the volume used for the calculation is the nominal volume of all reactors allocated to that process, not just the occupied volume in the reactor – therefore, if the company has to use a high-volume reactor for a small production batch size it will manifest in this metric. Also, cycle time may refer to time between the first and last logbook reactor entry, or VTO can even be analysed specifically for drying or other rate-limiting operations. [11]

$$Volume\text{-}time\text{-}output = \frac{nominal\ volume_{all\ reactors} \times cycle\ time}{mass_{product}}\ (m^3h/kg) \tag{1.9}$$

Not being much of an environmental efficiency metric, VTO can be very useful to project capacity demand in pilot plant or manufacturing scale, by quantifying equipment usage and project time management, in order to implement more efficient strategies of equipment allocation, and demonstrate time constraints in having an extra isolation unit operation, for example. This parameter also relates to the concept of pot economy, where having more telescoped reactions in the same vessel can minimize the nominal volume needed for the same output, when considering the whole API process.

1.2.2.9 Process Excellence Index

In the same article previously mentioned [11], the authors also included this reproducibility related metric, process excellence index (PEI), useful for monitoring performance of commercially manufactured API. They suggested a performance evaluation in terms of yield (Equation 1.10) and cycle time of issue-relevant unit operations (Equation 1.11). The aspiration level calculation (Equation 1.12) attempts to minimize the dependence of PEI values on the best value ever achieved, where in some cases it could

have been achieved ten years ago and it would not make sense in the present company's reality. Note that the best value for yield is the highest ever observed, and for cycle time the lowest, precisely why the PEI cycle time (PEICT) is the inverted formula of PEI molar yield (PEIMY). Additionally, PEICT can be easily calculated for the entire process by multiplying each individual step calculation; as for PEIMY, an overall process value can also be obtained when adapted to the overall molar yield instead of the individual steps yield.

$$Process\ Excellence\ Index\ Molar\ Yield = \frac{average_{yield}}{aspiration\ level_{yield}} \times 100\ (\%) \tag{1.10}$$

$$Process\ Excellence\ Index\ Cycle\ Time = \frac{aspiration\ level_{cycle\ time}}{average_{cycle\ time}} \times 100\ (\%) \tag{1.11}$$

$$Aspiration\ level\ value = \frac{median_{value} + best_{value}}{2} \tag{1.12}$$

1.2.2.10 Quality Service Level

Finally, in the same article previously mentioned [11], it was also suggested another simple parameter to assess the reproducibility regarding product quality, termed quality service level (QSL). The article defines three quality level-failure points: 0 points for quality assurance accepted batches, even if minor deviations occurred; 0.5 points for rejected batches that can still be reprocessed/reworked; 1 point for discarded batches or if only further used for technical purposes. The QSL value is derived from Equation 1.13. Just as with PEICT, a QSL value for the overall process can be obtained by multiplying each individual QSL.

$$Quality\ Service\ Level = \frac{total\ number\ of\ batches - total\ failure\ points}{total\ number\ of\ batches} \times 100\ (\%) \tag{1.13}$$

1.2.2.11 EcoScale

Another interesting method of evaluating process efficiency has been developed in 2006 by Van Aken et al. [43], named the EcoScale. It is a semi-quantitative analysis tool in the format of Q&A, focusing important aspects such as yield, cost, HSE considerations, conditions and ease of workup/purification, therefore guaranteeing a true overall process assessment. Besides starting the analysis with 100 points, a range of penalty points are given to each question/answer pair, giving the most penalty points to answers that impose the most undesirable conditions, and subtracting them from the ceiling points. The authors illustrated a proposed EcoScale layout. [43]

Any chemist can easily modify the EcoScale structure and assign different weighting contributions, according to its process needs and core business directions. This analysis tool is proven to be of very simple use, straightforward, transparent, and very handy to track down areas for improvement and advantages/disadvantages of specific methodologies. [43]

1.2.3 A Holistic Approach

After this thorough consultation of various green chemistry evaluations, one can agree that having only one parameter (for instance, the conventional reaction yield) does not allow a fully adequate process analysis. The need for consistency in this topic is of the utmost importance to achieve a true lifecycle efficiency assessment. Process greenness does not exclusively relate itself with environmental impact prevention. 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.

One proposal to achieve this goal was given by the researchers at Boehringer Ingelheim. [11] They outlined a multicriteria evaluation method to define a ”good manufacturing process”, with different weighting contributions for each green metric discussed in the article, including a modified version of the EcoScale submitted by Van Aken et al. [43], specific to the company’s cornerstones. Thus, each project would be given a final quantitative classification on how efficient it is.

Other methodologies for integrated analysis of chemical processes have been explored, namely the Green Motion^{TM} [44], a semi-quantitative assessment tool that was introduced by Mane SA in 2012 to evaluate HSE impacts of their manufacturing processes, creating seven fundamental categories (based on the twelve principles of green chemistry), and attributing penalty points to each criteria, in a similar way as the EcoScale, but adding an E-factor contribution; the Life Cycle Assessment [45], a qualitative research tool used to understand and characterize the environmental impact at all stages within a product or process, starting from as early as material acquisition until finally the end of product’s shelf life; and the unified Green Aspiration Level^{TM} [46] method of quantifying co-produced process waste across the industry, using modified E-factor calculations.

1.3 Thesis Outline

A lot of changes are happening in the pharmaceutical industry, thus creating challenges that the industry did not account for. The growing concern over the way global corporations impact human lives and the environment enhanced the need for sustainable development. Since pharmaceutical companies are both one of the most waste producing chemical industries, and one of the most regulated and responsibility bearing companies these days, there has to be more consciousness over the industry’s actions. The concept of green chemistry does not only provide ways of efficiently ”looking” into chemical processes and improving them, but also limits environmental risks and reduces the company’s overall costs. [27]

Furthermore, this industry has become more and more competitive, with rapidly changing requirements in product demand and increasing ”time to market” pressures, that ultimately leads to a decline in productivity. In order to overcome these challenges, the industry has to evolve into a data-driven Industry 4.0, and successfully access and manage the industry’s knowledge across the lifecycle of a pharmaceutical product. Through a knowledge management framework, companies can achieve this operational excellence and better its decision-making capabilities, while avoiding the wastes associated with knowledge search and knowledge recreation. [1]

Besides assembling green metrics into a holistic lifecycle classification tool that can guide process optimization, the industry should collect its historical knowledge on performance, known robustness issues and respective solutions, and employ it to that tool, therefore taking full advantage of all useful data ever generated.

The next chapters will present a data- and knowledge-based assessment tool, integrated with green chemistry concepts that can contribute to a more efficient API process development in a pharmaceutical industry, having been given more emphasis to a contract manufacturing type of organization.

The assessment tool will be shown as an organized template suitable to any type of chemical process, which can capture important data from processes (in terms of type of synthesis, process conditions, safety and environmental concerns) as well as data gathered across the different stages of development (e.g. yield, cycle time, and waste production). This platform will also enable a rapid access and analysis of the company's knowledge database on API projects, therefore ensuring free flow and reuse of said knowledge.

Chapter 2

Knowledge-based Assessment Tool

This chapter presents a data- and knowledge-based assessment tool, developed with green chemistry concepts that, when fully integrated, will allow for the quantitative evaluation of diverse chemical processes along their lifecycle, therefore contributing to a more efficient API process development in the pharmaceutical industry. This tool was developed in Hovione FarmaCiência, S.A., a contract development and manufacturing organization (CDMO) working in the fine chemical industry for API production, and here it is thoroughly explained, both its rational and implementation method.

2.1 The Evaluation Method

"To evaluate a chemical process, one must take a holistic approach as no single parameter is sufficient to describe the quality of a process." Dach et al. [11]

As discussed in subsection 1.2.2, one or two green metric calculations cannot possibly give a full comprehension of the overall efficiency of a chemical process, since it involves too many variables. Traditionally, chemists focus on achieving high molar yields above all else, however, one must not forget that a very good yield may not translate into an efficient process if that same process has, for example, enormous amounts of waste produced, or alarming safety hazards. In the paper by Constable et al. [32], a study of various green metric calculations was performed on 28 different chemistries, concluding that yield, atom economy (AE, subsection 1.2.2.1), stoichiometry and mass intensity (subsection 1.2.2.3) do not correlate with each other in any meaningful way, supporting the idea that following one metric individually may not drive a true process greenness assessment.

This is why only a holistic approach can provide an adequate assessment of chemical processes. As mentioned previously, researchers have already suggested some unified methodologies for this evaluation, namely the eight criteria defining a good chemical manufacturing process by Dach et al. [11].

An adapted version of Boehringer Ingelheim's methodology [11], developed by a multidisciplinary team, is introduced in this work. This assessment tool integrates various green metric calculations previously discussed (Table 2.1) and a detailed EcoScale (Appendix A). This allows for an evaluation on

a quantitative and qualitative level, with a weighting contribution associated with each criterion that results in a final overall quantitative classification of the process (whether for the individual steps or the whole API process). Also, this assessment can be easily conducted throughout the process lifecycle, right in the beginning of chemical development and advancing alongside chemical production in commercial scale, this way having a profound knowledge of its efficiency progress.

2.1.1 Green Metrics Applied

One of the main arguments for having a unified set of green metrics to properly evaluate chemical processes is that there are many metrics very similar to each other, resulting in the same type of quantification but complicating the comparison between processes from different companies or backgrounds. For that matter, not all green metrics were chosen to incorporate this assessment tool (Table 2.1).

As explained in subsection 1.2.2.1, the molar yield (MY) is a very important calculation to determine the efficiency of a process, but it lacks relevant details about the reaction such as its synthetic design and stoichiometry. Therefore, atom economy (AE, Equation 1.2) was chosen to evaluate the theoretical efficiency of the synthetic design, by which one can assess the use of high-molecular weight protective groups or selectivity auxiliaries that end up not integrating the final product and burdening the chemical process resources, with consequent higher waste production.

As described in subsection 1.2.2.4, AE and MY do not consider nonstoichiometric proportions of reactants. For that reason, another metric chosen for this holistic evaluation was the reaction mass efficiency (RME, Equation 1.5), that reflects the actual mass productivity of the synthetic design, integrating AE with chemical yield and stoichiometric excesses of reactants. Note that, even though it inherently accounts for atom economy, both metrics were chosen to incorporate the evaluation tool, enhancing it with theoretical and actual synthetic efficiency values. MY was also accounted for separately, as part of the EcoScale evaluation (further explained in subsection 2.1.2).

Additionally, it was decided not to regard the carbon efficiency calculation, for it exhibits the same trends as RME but without offering any additional insight [32], as well as not being so broadening. Also,

Table 2.1: Quantitative green chemistry metrics incorporated into the knowledge-based assessment tool developed and presented in this work, with respective optimum value.

Green chemistry metric	**Description**	**Optimum value**	**Formula**
Atom Economy (AE)	Efficiency of synthesis in terms of raw material strategy	100%	Equation 1.2
Reaction Mass Efficiency (RME)	Efficiency of synthesis in terms of productivity	100%	Equation 1.5
Step Economy (SE)	Efficiency in terms of production strategy	0	Equation 1.8
E-factor	Efficiency in terms of process waste	0	Equation 1.3
Volume-Time-Output (VTO)	Efficiency in terms of reactor capacity and cycle time	0	Equation 1.9
Process Excellence Index Molar Yield (PEIMY)	Reproducibility in terms of yield	100%	Equation 1.10
Process Excellence Index Cycle Time (PEICT)	Reproducibility in terms of cycle time	100%	Equation 1.11
Quality Service Level (QSL)	Reproducibility in terms of product quality	100%	Equation 2.1

the stoichiometric factor (SF) will not be evaluated in this tool, for the stoichiometric excesses are already included in the RME calculation.

Since the majority of the mass input in a given process is due to solvents charge, RME cannot adequately measure sustainability of chemical processes by its own, specially in industrial manufacture where the contribution of workup chemicals and solvent washes are much larger. To that end, E-factor (Equation 1.3) was the mass utilization metric chosen to evaluate waste production and environmental impact of chemical processes. In the developed assessment tool, E-factor calculations were performed considering all water and solvent input (defining waste as everything but the desired product), and excluding recycling, for unavailability of reliable data.

As discussed earlier (see subsection 1.2.2.2), a proper E-factor analysis would include all process steps, from commodity materials to the final API. However, in this tool, the evaluation was only performed internally, 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. Although Roschangar et al. [29] suggests an interesting way to overcome this external E-factor data unavailability, the assessment tool presented here is a simplified version only to evaluate and compare different company projects.

Environmental quotient and effective mass yield were not incorporated into this tool, for insufficient information and consensus on how to quantify ecotoxicity of materials, as explained in subsection 1.2.2.2, this way supporting a simple and quicker evaluation on environmental efficiency of worst-case scenarios. Although almost identical, E-factor was chosen over process mass intensity (in subsection 1.2.2.3), due to the fact that the ultimate zero waste target was a more intuitive goal, and because this metric has the advantage of discounting each step's product mass, thus enabling the simple addition of E-factors of individual steps to obtain the multistep process value, something which cannot be directly achieved with process mass intensity [36].

Step economy (SE, Equation 1.8) was chosen to incorporate the process's degree of telescoped synthesis into the evaluation tool, thus, in a way, assigning a value for the complexity of the manufacturing process strategy, as explained in subsection 1.2.2.7.

Giving more focus to manufacturing concerns, volume-time-output (VTO, Equation 1.9), process excellence index for molar yield and cycle time (PEIMY, Equation 1.10, and PEICT, Equation 1.11), and quality service level (QSL) were all chosen to contribute to the evaluation tool. VTO was calculated for the global process step instead of a single unit operation, therefore selecting volumes of all reactors involved (not including transfer tanks and containers), and a cycle time referring to the interval between the first and last logbook reactor entry, i.e., the amount of time the reactors in question were allocated to the process.

For this assessment tool, an adapted version of the QSL calculation proposed by its authors (Equation 1.13) was introduced. The three quality level points attributed were modified to: 1 point for quality assurance accepted batches; 0.5 points for accepted batches that were reprocessed/reworked; 0 points for discarded batches. This way, the QSL value is derived from Equation 2.1.

$$Quality\ Service\ Level = \frac{\sum quality\ level\ points}{total\ number\ of\ batches} \times 100\ (\%) \tag{2.1}$$

2.1.2 EcoScale Applied

Besides the quantitative evaluation discussed in the previous section, the knowledge-based assessment tool developed in this work incorporates a modified version of the original EcoScale [43], specific to the company's needs and areas of focus for continuous improvement. The EcoScale applied has 24 questions (with categorical and numerical answers), directed towards yield, quality, equipment, process, raw materials, and health, safety and environmental (HSE) concerns (see Appendix A). Both the numerical answers and score ranges were discussed by a multidisciplinary team, based upon their gathered experience within the company. Additionally, all volume-type answers are given in L/kg of SRM units (simply designated L/kg), in order to normalize the volume values, regardless of the experiment's scale.

Every answer within the same question has a point system associated with it, depending on the nature of it. An answer that demonstrates inefficient process conditions will provide fewer points. Unlike the original EcoScale (as explained in subsection 1.2.2.11), here the evaluation begins with 0 points and an efficiency-driven answer will give out the maximum points per question, summing it all up in the end. The final score is then converted into a percentage and added to the rest of the contributing green metrics.

2.1.2.1 Yield and Quality

Looking over the Q&A selected for the EcoScale (see Appendix A), two of the most important factors to evaluate efficiency and quality would be MY and the purity obtained in each step, represented in questions #1 and #2, respectively. Question #3 "Specification accomplishment" evaluates if the quality specifications required during and in the end of the process are easily met, or if the process exhibits some risk of out of specification (OOS) events, with or without having mitigation measures studied and prepared.

2.1.2.2 Equipment

Regarding the equipment category, in order to simplify the classification, question #4 "Reaction temperature and pressure" only deals with operating temperature intervals instead of exact values, highlighting elevated operating temperatures or cryogenic conditions, as well as the pressure issue only arising with the possibility of hydrogenations or other highly pressurized systems. Extreme temperatures and/or high pressures will require more specialized equipment and raise more safety concerns, thus acquiring less score points.

Questions #5 "Maximum occupied volume in the main reactor" and #6 "Maximum to minimum volume ratio" relate to possible equipment usage constraints, regarding the main reaction vessel. For example, the use of substantial volumes per kilogram of SRM means larger reactors needed, and a higher ratio means using a large reactor that may not have an adequate lower impeller that can properly agitate the

system at such a minimum volume. These criteria are significant when the company in question is a CDMO without dedicated facilities/equipment for certain processes, and when applied towards developing projects that might benefit from optimization studies. Additionally, a higher maximum volume occupied in the main reactor may implicate higher volumes of reaction solvent, workup solvent, or solvent swaps during a distillation operation (which are all operations usually carried out in the same vessel), thus having an impact on the environmental load of the process.

2.1.2.3 Process

In the next category, many criteria were conceived to address all the main process aspects. Questions #7 ”Distillation volume” and #8 ”Distillation pressure conditions” direct focus on distillation operations, most common in chemical processes (as explained in subsection 1.1.2.1). This operation is usually performed under vacuum to enable a more speedy recovery, however, maintaining a lower pressure can cause more damage and wear to the equipment. Accounting for the total volume distilled during each individual step helps evaluate either the waste generation during the operation, and its relative duration and/or number of distillations carried out, with consequent increase in cycle time and process laboriousness.

Question #9 ”Reaction time” evaluates the reaction’s contribution to the overall cycle time of the process, since it is one of the key operations in any chemical process and one of the most controlled. Questions #10 ”Number of in-process controls” and #11 ”Maximum number of samples per in-process control” evaluate a possible increase in analytical load, which greatly burdens the overall progress of manufacture. In-process controls (IPC) are analysis performed during production to monitor and, if appropriate, to adjust the process to ensure that the target molecule (or even specific impurities) conforms to its quality specifications. Until the result of the analysis is examined and a decision has been made, the process cannot proceed to the next step, thus the existence of numerous IPC analysis, or samples per IPC, results in a decrease in productivity and increase in work load.

Regarding other possible workup procedures besides distillation, question #12 ”Number of phase separations and pH adjustments” allows for an assessment of potential process constraints, whether in terms of cycle time, waste management, or process complexity. The criterion evaluates these two unit operations together since their impacts on the process are somewhat similar.

Another criterion to help assess the process’s complexity is question #13 ”Columns needed?”, evaluating the possibility of using additional complex and expensive operations, like using charcoal filters or chromatography columns, as part of the manufacture isolation procedure. Although very efficient, chromatography operations involve large amounts of solvent for the elution stage that can drastically burden the process’s environmental load, as well as the waste produced from regeneration/replacement of activated carbon filters (as explained in subsection 1.1.2.1). It is important to point out that, in this criterion, charcoal filters are considered as columns for being a type of depth filters.

Question #14 ”Existing holding points?” refers to the possibility of placing the process on-hold without compromising the product’s quality and stability. In fact, known process holding points represent a valuable attribute when scaling up to manufacturing production, since it might be necessary to put the process on-hold while waiting for an IPC result, usually critical to the process outcome.

Questions #15 ”Filtration needed?”, #16 ”Polish filtration possible?” and #17 ”Filtration of solid waste needed?” regard multiple filtration modes. The first question just evaluates the presence or not of filtrations in the process, since it can be a relatively rate-limiting operation due to possible membrane clogging. On the other hand, although polish filtrations do benefit the crystallization operation by removing small impurities prior to it (as explained in subsection 1.1.2.1), when performed with high temperatures the operation can present some potentially unsafe situations in scale-up [19], besides increasing process burdensomeness. Additionally, having precipitation of impurities can also constitute a disadvantage, due to the need for solid waste filtration during the process, and consequent expensive waste treatment.

Turning to the final unit operation in a typical API process, question #18 ”Drying conditions” evaluates mostly the easiness of this operation, in terms of duration and the need for special requirements such as nitrogen passage. The possibility of the product suffering degradation upon drying, with impact on quality, is considered in the questionnaire, with the lowest score for this question.

2.1.2.4 Raw Materials

To begin addressing raw material concerns, the question #19 ”Solvents ICH classification” evaluates the use of toxic solvents as per Q3C(R6) ICH guideline *Impurities: Guideline for Residual Solvents* [47]. This guideline recommends maximum levels of residual solvents in drug substances and drug products, on account of safety and toxicological data provided, and classifies solvents in three categories: class 1 solvents are known to cause unacceptable toxicities and their use should be avoided altogether; class 2 solvents are associated to less severe toxicity and their use should be at least limited; class 3 solvents have low toxic potential and can be used without concern, although always safely. By using any class 1 or 2 solvents, purification and quality concerns arise, therefore contributing to a lower final EcoScale score.

Criterion #20 ”Substances of very high concern (as per REACH) used?” targets the use of substances which are classified as being carcinogenic, mutagenic, toxic for reproduction, and/or bioaccumulative. This identification is continuously documented in the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation, handled by the European Chemicals Agency, to incentivize the progressive replacement of these substances by less dangerous ones. Although the regulation does not prohibit the use of these substances, it restricts the amount available on the market, placing responsibility on the industry to provide safety information on the chemical’s use and manage its risks. Therefore, a substance of very high concern can either be on the authorisation list (when evidence shows a need for its restrictive use and companies must apply for authorisation) or still on the candidate list for authorisation. If components used in the process have possible (or already in place) restrictions, the EcoScale score will also be penalized. [48, 49]

Question #21 ”All components are commodities?” considers the use of commodity raw materials as positive, both in terms of economics and market safety. If a crucial raw material used in the process only has one available supplier, then the API manufacture might be at risk if by any chance the supplier’s production is interrupted, therefore, the choice of commodity-type chemicals is valorised in the industry.

2.1.2.5 Health, Safety and Environment

In the category of HSE concerns, question #22 ”Reaction highly exothermic?” will provide successively lower points as the means of managing an existing exothermic reaction become more complicated, such as requiring engineering solutions (e.g., cryogenic conditions), or even suffering potential risk of runaway reactions. Final questions #23 ”Highly corrosive, toxic or hazardous for the environment material needed?” and #24 ”Highly flammable or explosive material needed?” both evaluate the necessity of certain control strategies in case materials with those descriptions are used, for example the need for special charging devices (e.g., gloveboxes) or the use of specialized individual protection equipment (IPE) for the operators.

Finally, it is important to note that no question directly associated with monetary concerns was selected for the EcoScale. Evidently, almost all questions can be indirectly linked to cost variations such as higher cycle time, energy, and mass inputs. Nevertheless, this assessment tool has been developed to guide chemists/engineers, and improve chemical and process development, without direct concerns with money, and minimizing its time-dependence. Additionally, not considering the crystallization unit operation in the EcoScale was due to the fact that this operation, although relevant to the process, did not provide concerning factors towards process's greenness and efficiency.

2.1.3 Classification Categories

Besides having all the green metrics and EcoScale criteria selected, it was necessary to categorize the classification process, which was divided into laboratory classification and manufacturing classification (summarized in Table 2.2).

For the first category, AE, RME, and SE were selected, due to their focus on the chemical/process development, whether in terms of synthesis strategy or process strategy. EcoScale was initially selected for laboratory evaluation for its quick assessment of every pertinent aspect of a chemical process, hence the possibility of guiding the process development and scale-up studies, while the project has yet to be transfered to chemical production. As explained throughout subsection 1.2.2, each laboratory classification criterion can be calculated for individual steps and for the overall API process, including the EcoScale (through an average value of all individual EcoScale score), and with the exception of SE, which is a metric only used to evaluate the entire process.

For the manufacturing classification, VTO, PEIMY, PEICT, and QSL were selected for their focus on issues derived from production, in terms of reproducibility between batches and equipment/time schedule. Although PEIMY, PEICT, and QSL could be easily calculated for the overall process (see subsection 1.2.2), it was decided to have the manufacturing classification only for individual steps in this first framework. Likewise, VTO was calculated for each batch production of an individual step, without having in consideration a global value for every individual step and overall process.

E-factor was selected for both classification categories. Considering the growing environmental concerns over mass utilization and waste generation in the industry, it is a powerful metric to apply to larger scales like pilot or manufacturing scale. However, it can also be useful in laboratory scale to have a

first assessment over the waste generation during process development. Just as with VTO, E-factor for manufacturing classification was calculated per batch per individual step; for laboratory classification, an individual value and overall process E-factor were obtained, as discussed in subsection 2.1.1.

All green metrics were assigned with target values and a point system associated with them, mostly based on suggested values from Boehringer Ingelheim (in Appendix B). [11] However, VTO values proposed by their research were not implemented in this tool – its low target value relates more to a dedicated production plant and did not exactly correspond to the reality of a CDMO-type of facility, with multipurpose production, and smaller API volumes not yet aimed for commercialization. Thus, VTO target values were given arbitrarily on a trial basis, until the data was gathered and assessed. Similarly, target values for PEICT were not given according to Dach et al. [11], due to their specific recommended values for commercial processes, which were not evaluated with this tool.

Also note that values for E-factor exhibited in Table 1.1 were not considered for target values, because those were calculated for entire API process's, assuming recycling of solvents, exclusion of water input, and starting with commodity materials (see subsection 1.2.2.2), a system which was not implemented in this assessment tool. Furthermore, the paper did not include SE and RME calculations, thus SE target values were attributed in order to enhance the use of telescoped synthesis, and RME target values were given just as with VTO.

Besides the multipoint analysis system, a colour code system was given to each target range, to improve the visual illustration of this tool. The weighting associated with each criterion, for both laboratory and manufacturing classifications, was discussed internally within the multidisciplinary team who developed this assessment tool, and it is not further broaden on this work.

Although RME and E-factor are a part of the laboratory and manufacturing classification, respectively, they were not assigned to this weighting system, thus not contributing to the final classification score on

Table 2.2: Summary of evaluating criteria incorporated into the knowledge-based assessment tool developed and presented in this work, exhibiting each classification category and which criteria will be evaluated per overall process, individual step and per batch.

Green chemistry metric	**Classification categories**	**Overall process**	**Individual step**	**Batch**
Atom Economy (AE)	Laboratory	x	x	
Reaction Mass Efficiency (RME)	Laboratory	x	x	
Step Economy (SE)	Laboratory	x		
E-factor	Laboratory	x	x	
	Manufacturing			x
EcoScale	Laboratory	x	x	
Volume-Time-Output (VTO)	Manufacturing			x
Process Excellence Index Molar Yield (PEIMY)	Manufacturing		x	
Process Excellence Index Cycle Time (PEICT)	Manufacturing		x	
Quality Service Level (QSL)	Manufacturing		x	

this first trial. Additionally, the EcoScale points were associated to the final classification score in two ways: through a total sum of the points gathered by the Q&A, and through an additional sum of its five criteria with lowest score, thus enhancing the critical aspects of the EcoScale in the final classification score. Unfortunately, a visual representation of the EcoScale score was still not available for this assessment tool's first trial.

Finally, the laboratory classification was attributed per individual step and per overall process, with target and colour ranges given arbitrarily on a trial basis, until the data was gathered and assessed. The manufacturing classification was attributed per production batch, and, in this first trial, its evaluation did not include a target/colour range. All target values, colour codes, multipoint system, and weighting associated with each metric are summarized in Appendix B.

2.1.4 Template Preparation

After the conceptualization of all the criteria to be evaluated on the knowledge-based assessment tool, a software was developed by a specialized team within the company (this development will not be discussed in the present work). 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. An example of a randomly filled out template is illustrated in Appendix C. The software's outputs are provided both in organized tables, and through a user interface for visual representation of all evaluating criteria.

Moreover, databases were built from online data and added to this software to automatically answer some EcoScale criteria, such as #19 ”Solvents ICH classification” and #20 ”Substances of very high concern (as per REACH) used?”. Question #6 ”Maximum to minimum volume ratio” is also automatically calculated, by having the maximum volume given from question #5 and an additional question #6a ”Minimum volume” introduced to the template. For the VTO calculation, the user just needs to provide the reactor code for the process in question, and the software can access an internal database with the respective nominal volumes.

Thus, the functional requirements of this system are simple answers to the rest of 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.

With respect to the EcoScale, when an individual process step involves telescoped synthesis (i.e., has more than one chemical reaction), some criteria would have multiple answers, namely undergoing different reaction temperatures. To get around this issue, the questionnaire should be answered considering the worst-case scenario, in other words, the answers that provide fewer points for each individual step. Additionally, if a question is considered inadequate for that specific EcoScale evaluation, the system can detect a hyphen symbol as an answer, in order to avoid consideration of that question's score altogether. This may happen, for example: if question #7 "Distillation volume" is answered with zero (meaning no distillation step), then #8 "Distillation pressure conditions" should be answered with a hyphen, this way avoiding duplicate influence of the same parameter; or with question #16 "Polish filtration possible?", which is usually only answered for the final process step (see subsection 1.1.2.1); or in the Assessment phase, some questions may even be unknown or not yet studied, therefore not considered for the evaluation.

2.2 Proposed Goals and Targets

This knowledge-based assessment tool has many features that allows for a truly thorough evaluation of pharmaceutical processes in every sense of the word "efficient", which this present work proposes to show. The developed platform will provide data-driven quantification of efficiency by embracing productivity, quality, safety and environmental considerations, having the objective of changing the way chemists, engineers, project managers, and even investors analyse a developing API project.

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.

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 the comparison between different projects, including by type of chemistry.

Through the EcoScale evaluation, the user interface also features a list of critical aspects of every project's process step, which are considered the criteria with the five lowest scores. This facilitates the project's team assessment of what could be changed in the process in order to improve it, specially since this decision-making process would be based on data instead of perception (which may be biased due to lack of information).

The next chapters will demonstrate many of these outcomes, namely the classification of each project evaluated by this tool, and two other types of thorough analysis: on one hand, a global evaluation of each criterion that will enable 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 will enable a validation study of both the project's improvements and the assessment tool's framework.

Chapter 3

Overall Evaluation of Projects

This chapter demonstrates the use of the knowledge-based assessment tool, developed and presented in this work, with results obtained from a global evaluation of several different drug development projects conducted within the company. These projects have 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. Additionally, a thorough analysis of each criterion was performed for every project, allowing a comparison between different projects, and a verification of possible correlations between metrics.

It is important to note that, in this chapter, the word ”project” designates the overall API process, while individual steps represent one process each. Each project and process step had code names attributed to them, where the first letter refers to the project name, the digit next to it refers to the step order, and the *f* character designates the final step of that project. Unfortunately, in the data plots provided by the user interface the final step of every project appeared as the first process, due to an error in the software's design.

3.1 Project Classification

On a first basis, as the project's data is uploaded to the software platform (via the organized template in Appendix C), the user interface provided the classification obtained for each green metric, and a final lifecycle phase classification attributed to each step and overall API process. Each process step also exhibited their critical aspects evaluated through the EcoScale. This visualization is available for one project at a time, to support a direct focus on individual project assessment. Figures 3.1–3.7 exemplify this visualization for one of the projects conducted by Hovione and analysed with this tool.

This visualization of the calculated metrics, with the colour code system easily indicating whether a certain value is favorable or not, and the process's critical aspects detected by the EcoScale, is a powerful auxiliary in developing an API process. Project team members can use this tool to assess the process's efficiency, and decide on new development directions to take, and possible changes that might improve these criteria, thus improving the process itself.

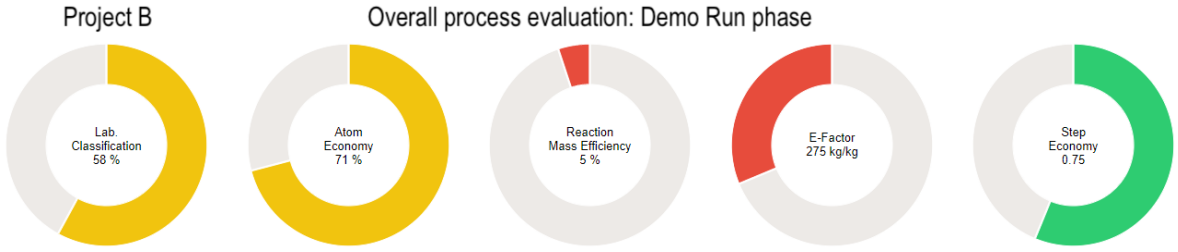


Figure 3.1: Chart visualization of the green metric values and final laboratory classification, provided by the knowledge-based assessment tool, for the overall process evaluation of project *B*, in Demo Run lifecycle phase, and for the current process revision.

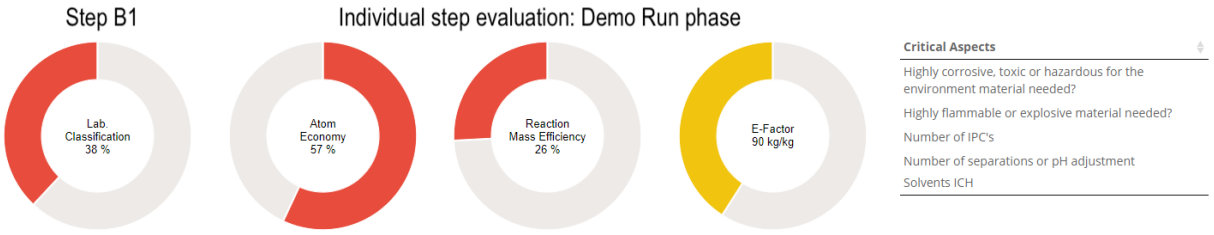


Figure 3.2: Chart visualization of the green metric values and final laboratory classification, including critical aspects list, provided by the knowledge-based assessment tool, for the evaluation of step *B1*, in Demo Run lifecycle phase, and for the current process revision.

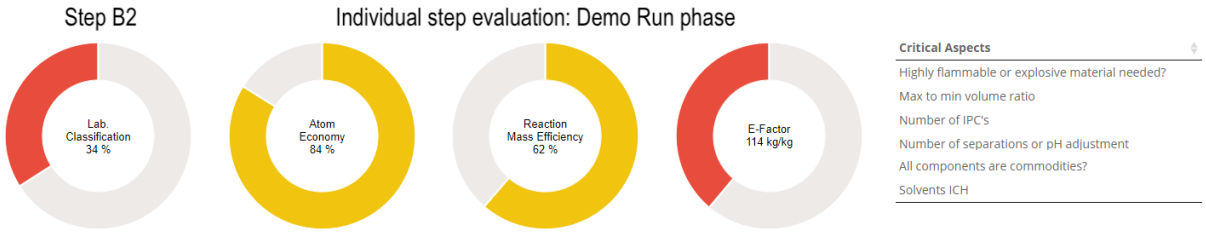


Figure 3.3: Chart visualization of the green metric values and final laboratory classification, including critical aspects list, provided by the knowledge-based assessment tool, for the evaluation of step *B2*, in Demo Run lifecycle phase, and for the current process revision.

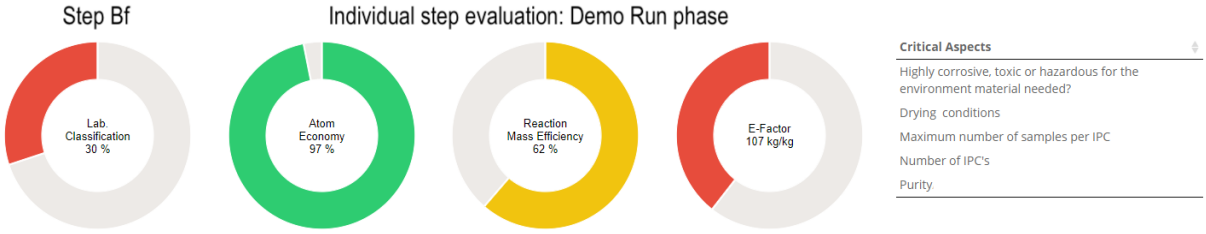


Figure 3.4: Chart visualization of the green metric values and final laboratory classification, including critical aspects list, provided by the knowledge-based assessment tool, for the evaluation of step *Bf*, in Demo Run lifecycle phase, and for the current process revision.

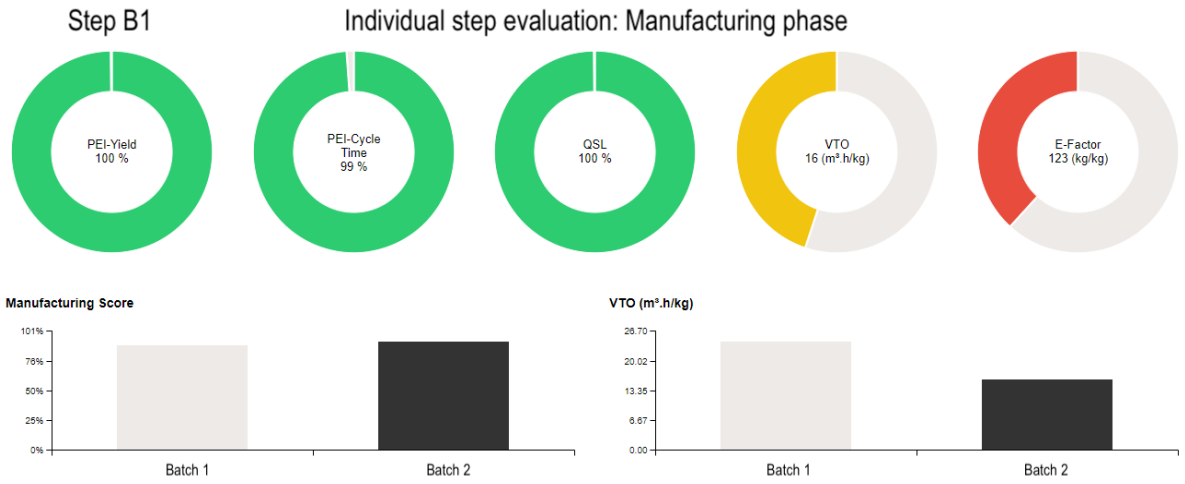


Figure 3.5: Chart visualization of the green metric values and final manufacturing classification, provided by the knowledge-based assessment tool, for the evaluation of step *B1*, in Manufacturing lifecycle phase, and for the current process revision.

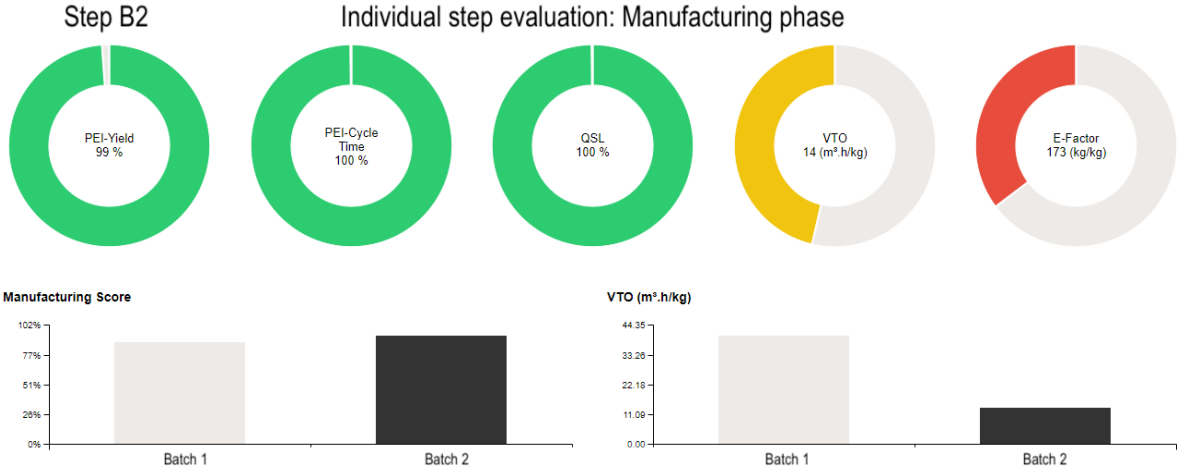


Figure 3.6: Chart visualization of the green metric values and final manufacturing classification, provided by the knowledge-based assessment tool, for the evaluation of step *B2*, in Manufacturing lifecycle phase, and for the current process revision.

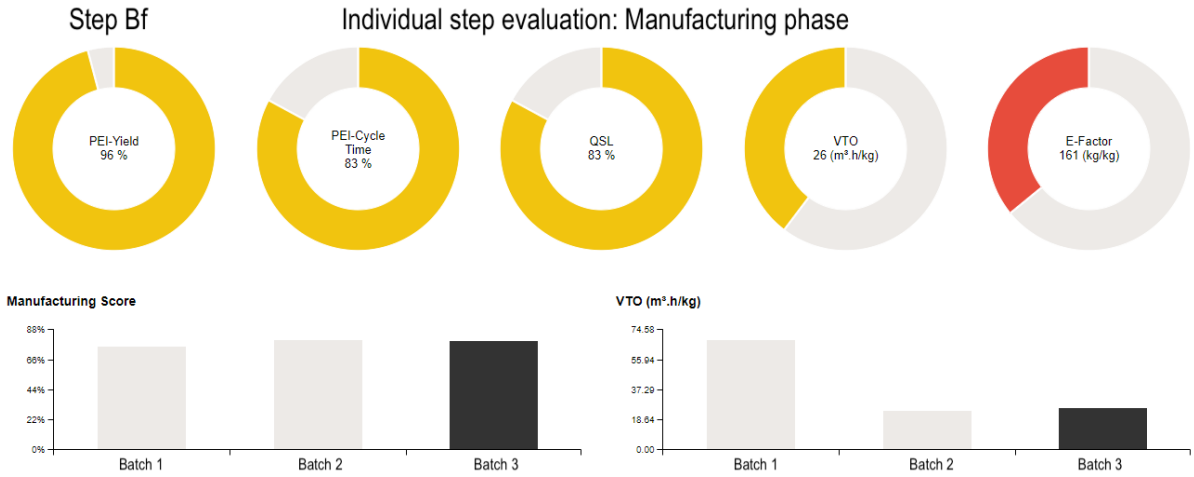


Figure 3.7: Chart visualization of the green metric values and final manufacturing classification, provided by the knowledge-based assessment tool, for the evaluation of step *Bf*, in Manufacturing lifecycle phase, and for the current process revision.

Some metrics are very useful to be analysed and optimized just during the early stages of development, such as step economy (SE), atom economy (AE), and reaction mass efficiency (RME), due to their focus on the chemical synthesis, as explained in subsection 2.1.3. However, a process's greenness depends greatly on its E-factor value, and this evaluation can help assess the need to look through the manufacturing technique, determine which points are causing an elevated E-factor, and analyse possible changes that can minimize this waste production.

3.2 Critical Aspects Analysis

The critical aspects analysis, which encompasses the five lowest scored criteria in the EcoScale evaluation, provides very useful information on what process criteria should be addressed, and what aspects can be improved.

Besides this scenario, one can also have several critical aspects that are simply the lowest scored ones, but not exactly representing low scores themselves (a low score is considered below 2/3 of the maximum score for that criterion), therefore might not even require improvement. This distinction was not yet implemented to the software, nevertheless, with the output data tables provided, an additional analysis was performed, considering the low scored critical aspects of each process evaluated. Figure 3.8 shows the percentage of processes that have each EcoScale criterion as a critical aspects, through both types of analysis (lowest scored criteria and low scored criteria).

Some of the critical aspects with the highest percentage of occurrence, regardless of its score analysis, such as #19 "Solvents ICH classification", #21 "All components are commodities?", #23 "Highly corrosive, toxic or hazardous for the environment material needed?", and #24 "Highly flammable or explosive material needed?", 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 (see subsection 1.2.1), or due to the CDMO's context of developing its client's product, therefore having a starting raw material (SRM) usually provided exclusively by said client.

Interestingly enough, some of the greater discrepancies regarding low score and lowest score analysis, for example #11 "Maximum number of samples per IPC", #15 "Filtration needed?", and #18 "Drying conditions", indicated that the answers given to those criteria were not so critical after all, and that the percentage of projects that might need improvements (when considering the critical aspects analysis) was smaller than the initial software's analysis suggests.

Therefore, it is important to consider, not only the lowest scored EcoScale criteria, but the criteria with scores below 2/3 of its maximum, to truly assess what is unfavorable within each process, and what could be refined. Additionally, if the low scored critical aspects of a certain process are all intrinsic to the chemistry or API molecule, and modifying them proves almost impossible without changing the whole process strategy, then one can even conclude that the process is in its most improved form.

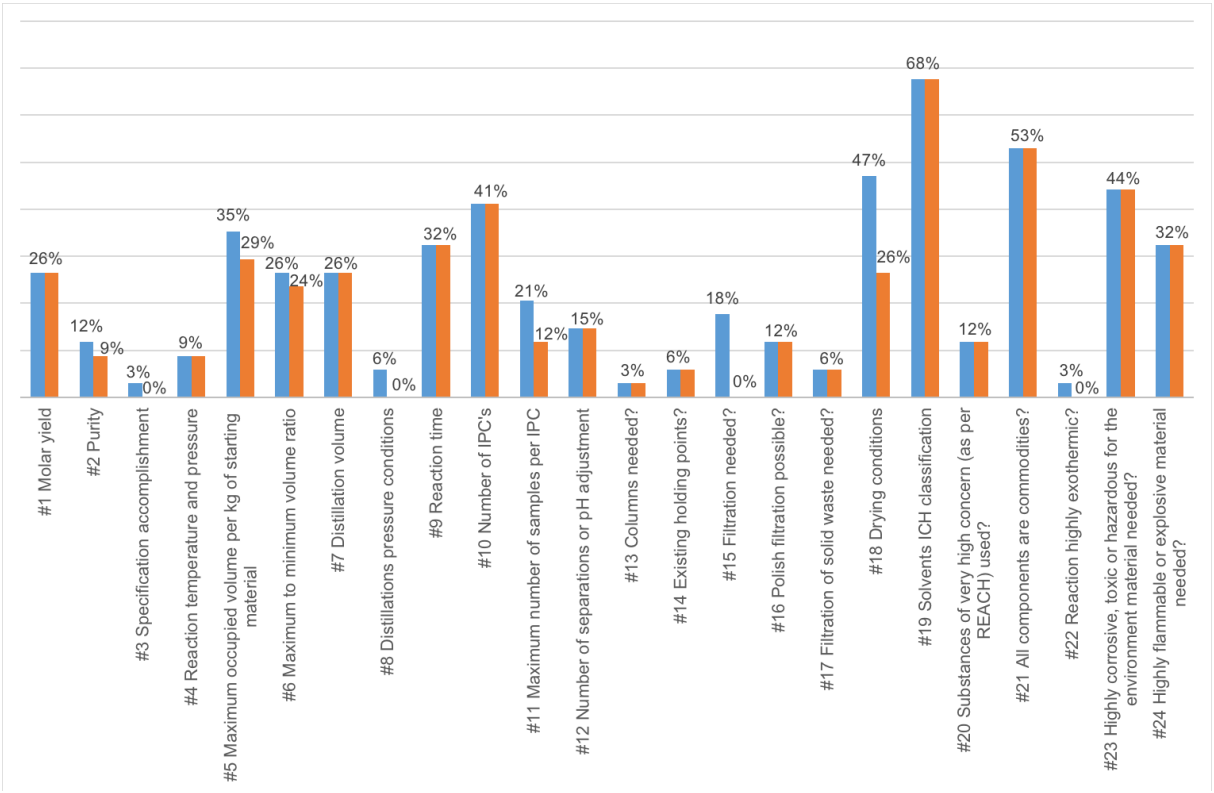


Figure 3.8: Representation of the percentage of processes that have each EcoScale criterion as a critical aspect, through the lowest score analysis (in blue), and just considering criteria with low scores, which are considered below 2/3 of the maximum score for that criterion (in orange).

3.3 Comparison Analysis of Projects

Through the data provided by the assessment tool, a study was performed to evaluate the results obtained for each process, in order to attain a global sense of the company's history of knowledge on chemical and process development. A full comparison of the results between different processes allowed the detection of outliers, and the observation of possible correlations between different criteria.

3.3.1 EcoScale Criteria Analysis

In this section, the chosen and evaluated EcoScale criteria are analysed more closely, with the results summarized in Table 3.1. Besides representing them as a percentage of processes that had score values within both maximum and minimum score ranges (given in Appendix A), average and standard deviation values are also displayed, for the numerical answers.

3.3.1.1 Yield and Quality Results

Figure 3.9 exhibits the expected molar yield (MY) results obtained per process step. As can be seen, only one evaluated process had a molar yield higher than 95%, however, according to Dach et al. [11], yields around 80% are considered very good, and the majority of processes evaluated (53%) had yields between 80–95%, which confirms the productivity of synthesis designed for these projects. Some of the

Table 3.1: 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. These score ranges are featured in Appendix A.

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%[5]	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.
[5] Only considering processes that required polish filtrations.

outliers, about 12% of processes with yields below 60% (see Table 3.1), were due to intrinsic aspects of their own processes. For example, *A3* performs a chiral resolution, which is a chemical step with typically low isolated yields [50], and processes *E2* and *D1* have relatively complicated synthesis with more than two chemical steps, which can take its toll on the production efficiency. Excluding these outliers, the average molar yield was 83%, with a standard deviation of 8%, revealing much less data dispersion.

These expected values were provided by the manufacturing technique, with a certain confidence interval not accounted for in the software. In order to assess the actual productivity obtained in each process's Demo Run test, the laboratory MY was calculated separately, through the assessment tool's database, and compared to each corresponding expected MY and confidence intervals (see Figure 3.10).

Figure 3.9: Data plot with expected molar yield values for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

Although there was some discrepancy between laboratory and expected values, they were mostly within their expected confidence interval, validating the Demo Run experiment. Process *Df* was not included in this analysis due to lack of information on confidence intervals.

In terms of quality, as seen in Table 3.1 and in Figures 3.11 and 3.12, high scores were achieved, having 68% of processes with more than 98% of purity, and 85% of processes without risks for OOS events. The average and deviation values guarantee a low variability in these quality results, which is a parameter of the utmost importance in pharmaceutical processes. Interestingly, process *H4* and *Hf*, the last two steps from project *H*, presented both the maximum purity degree and necessity of mitigation measurements for specification accomplishment, possibly because of the elevated purity the product requires. Additionally, one can observe that process *Bf* had significant low purity associated with its final product, in contrast with the other final step processes. Through this comparison, an outlying behavior may raise flags among chemists in order to ascertain the possible root causes and solutions.

3.3.1.2 Equipment Results

Figure 3.13 illustrates the results regarding the reaction conditions. There was no use of cryogenic or very heated conditions, which would definitely burden the process (see subsection 2.1.2.2), and an equal number of processes using room temperature conditions and temperature ranges from -5–100°C was verified, consistent with common chemical reaction conditions. Process *C2* exhibited high pressures due to a hydrogenation chemical step.

Regarding main reactor volume usage (see Figure 3.14), 53% of processes had maximum volumes between 15 and 30 L/kg, which can be attributed to the fact that the processes evaluated are still under development, therefore could benefit from more optimization studies to minimize the volume required per batch size. Also, some processes may inherently need large volumes per kilogram of SRM in order to

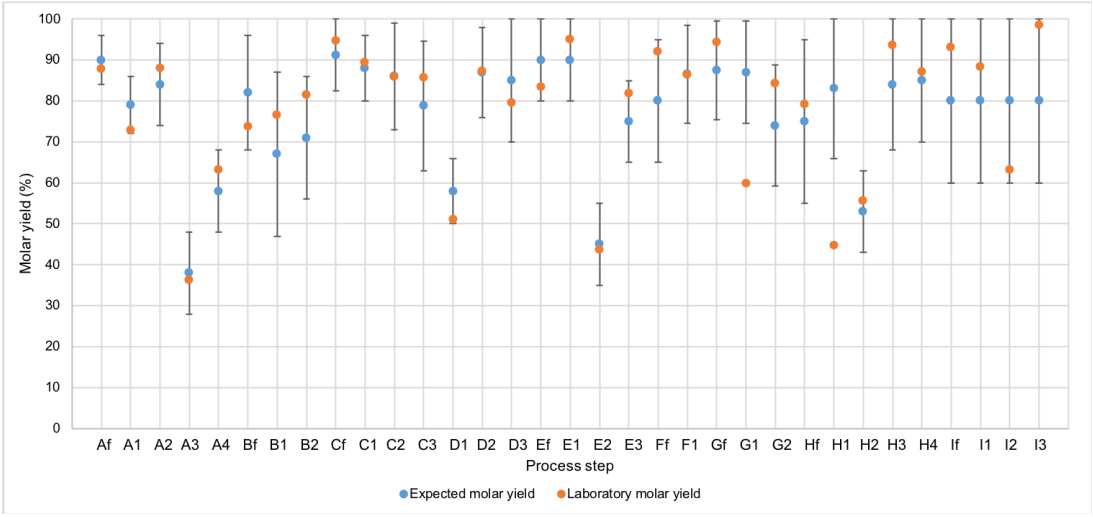


Figure 3.10: Data plot with expected and laboratory molar yields for each process step (in blue and orange, respectively), with confidence intervals for the expected values. Process *Df* was not included in this analysis due to lack of information on confidence intervals.

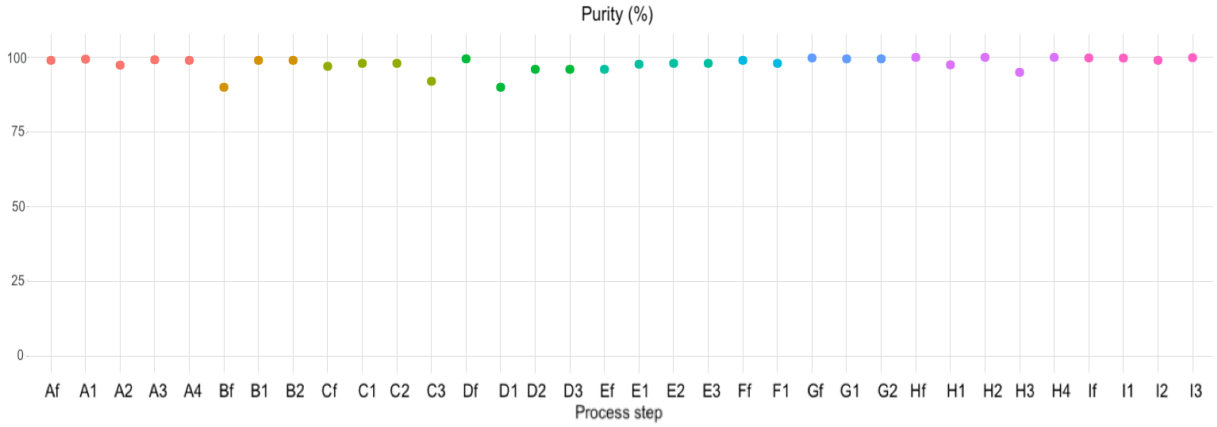


Figure 3.11: Data plot with purity degrees for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

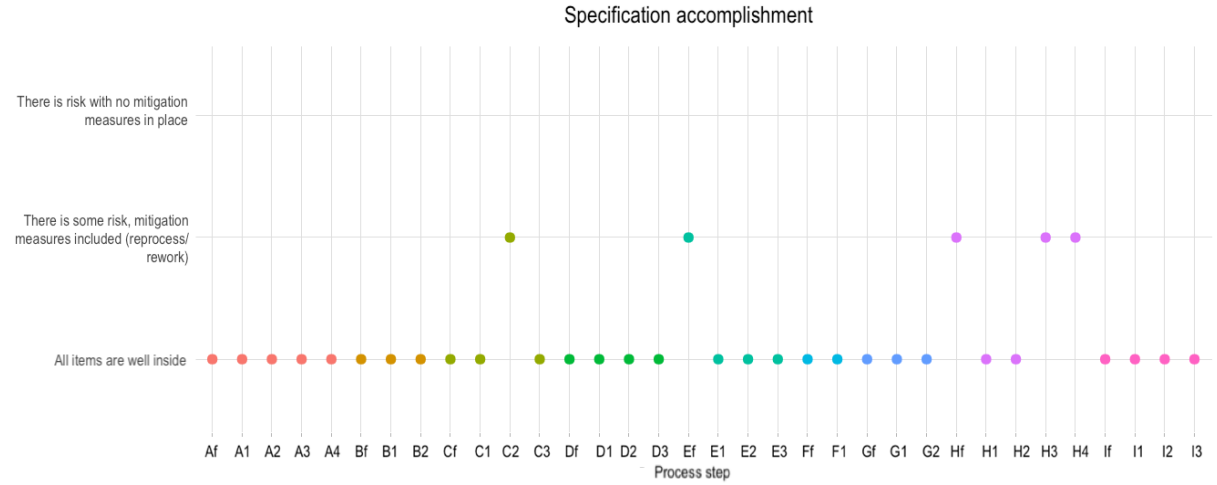


Figure 3.12: Data plot with answers for specification accomplishments of each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

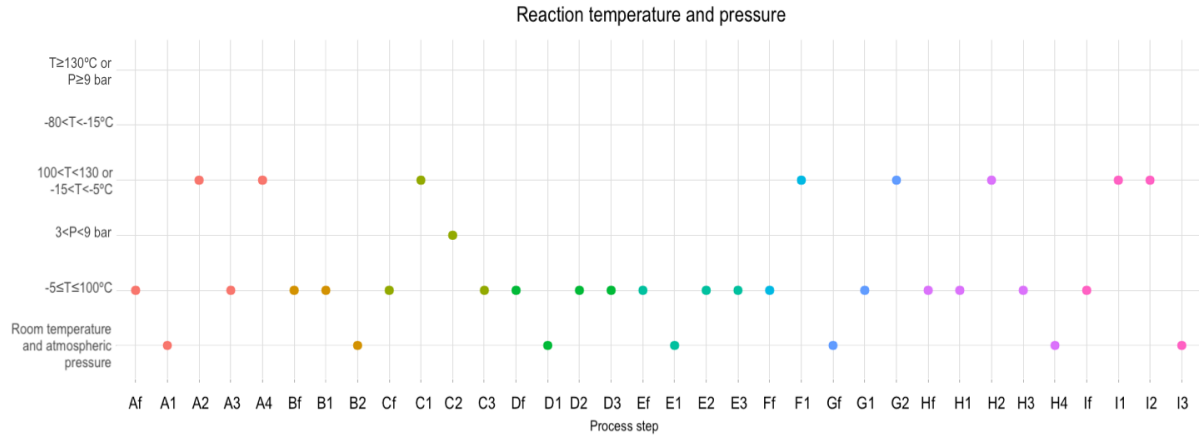


Figure 3.13: Data plot with reaction temperature and pressure answers for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

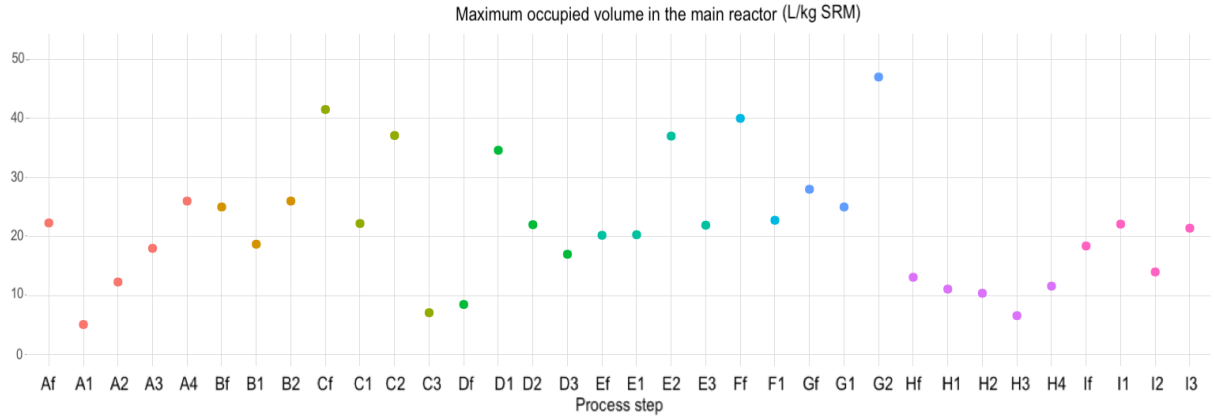


Figure 3.14: Data plot with maximum volumes occupied in the main reactor for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

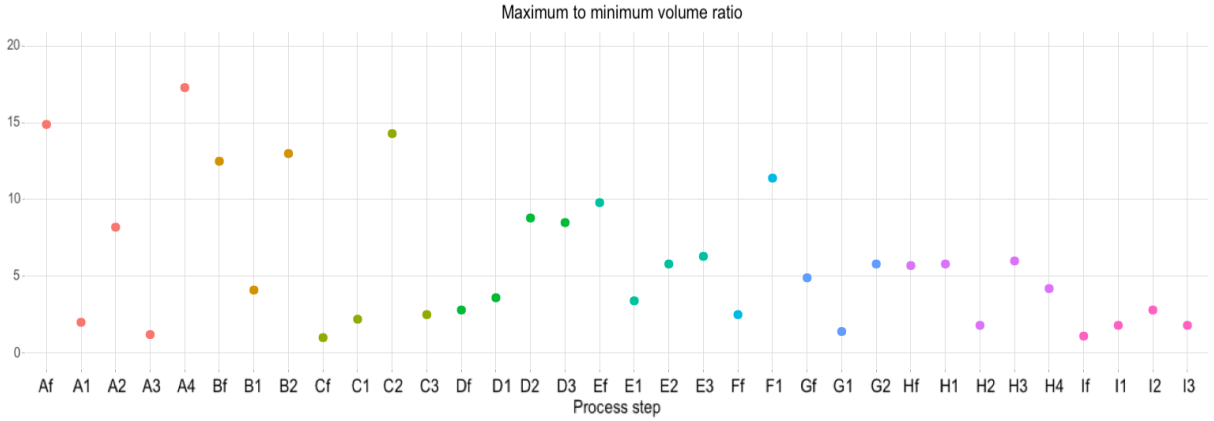


Figure 3.15: Data plot with maximum to minimum volume ratios for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

maintain diluted conditions, since there can be solubility constrains in using concentrated solutions, or fast chemical reactions that may easily form precipitates.

The volume ratio is very important to evaluate in a CDMO (see subsection 2.1.2.2), with 44% of processes having ratios between 3–10, indicating some possible constraints in the choice of reactors that need to be large, but may not be the most suitable for minimum volumes – issues that a dedicated production facility can account for. Because this evaluation was made regardless of type of process strategy, a quite big dispersion of values was observed, even within each project (see Figure 3.15), which was corroborated by their standard deviation (see Table 3.1).

3.3.1.3 Process Results

Concerning distillation operations, from the 50% of processes that had maximum score range in criterion #7 (see Table 3.1), 71% did not have a distillation operation, although every project had at least one, which contributed to a high score output. Considering the 65% of processes that had this operation, the coefficient of variation for the distillation volume was 63%, indicating big data dispersion due to some outliers with very high volumes, such as processes *D1* and *E3* (see Figure 3.16). In terms of distillation pressure, most of the operations were performed under vacuum, as expected, with the exception of processes *Ff* and *Hf*, which were performed under atmospheric pressure.

Regarding the reaction time, *A1* was the only process with a reaction operation that surpasses 24h in laboratory scale, which is not very efficient, considering that 18% of processes had this type of chemical reaction as well. Even excluding this outlier, the dispersion of data was still remarkable, with an average of 7.3$\pm$7.3h (see Figure 3.17). It is also important to note that 9% of processes evaluated did not have a chemical step, namely *Ff*, *I3*, and *If*, since these were only purification steps, carrying out recrystallizations and adequate polymorphic form isolations, which may not need a previous chemical reaction. In these cases, zero hours were considered in the EcoScale questionnaire, however, the parameter #4 ”Reaction temperature and pressure” was still answered according to the isolation conditions. This criterion needs to be properly evaluated per type of reaction, in order to ascertain whether the time spent in this operation is expected, or if process parameters need to be improved, for example by integrating online monitoring, to better determine when the reaction is complete.

In terms of analytical load (in Figures 3.18 and 3.19), 50% of processes had two or three IPC’s, which usually include one analytical control during the reaction operation, and at least one other for the final drying step. Consistently, 80% of processes with telescoped synthesis exhibited more than three IPC’s, to consider more IPC’s per reaction – these answers are not necessarily inefficient for telescoped processes, for they require such controls. This criterion would be best evaluated per chemical step rather then per isolated step.

The majority of processes (62%) had a maximum number of two or three samples per IPC, mainly due to the lengthy drying operation that needs this control to determine when it is complete. Process *Df* was an outlying scenario due to its chromatography operation, which inherently requires a lot of samples for chemical analysis to control the desired product’s elution (see subsection 1.1.2.1).

Regarding the complexity of workup stages, 44% of processes had no need for phase separations or

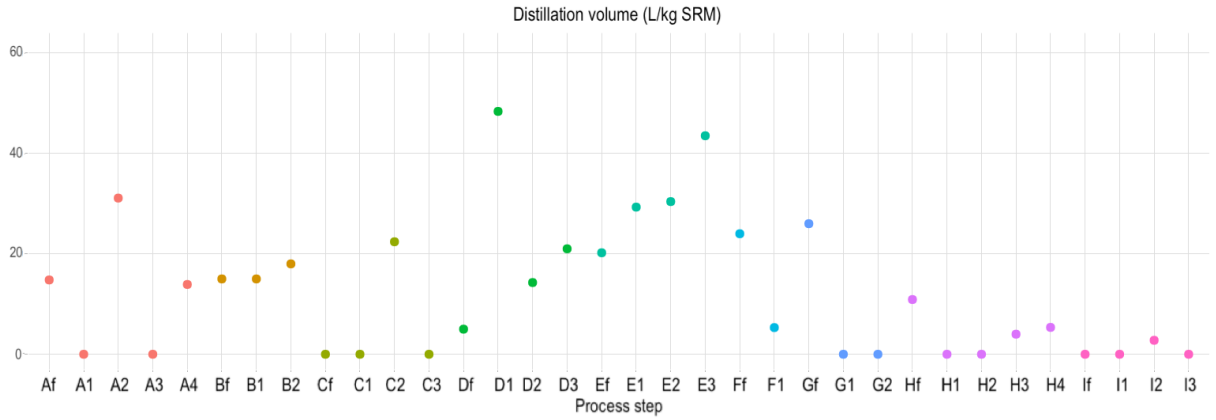


Figure 3.16: Data plot with distillation volumes for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

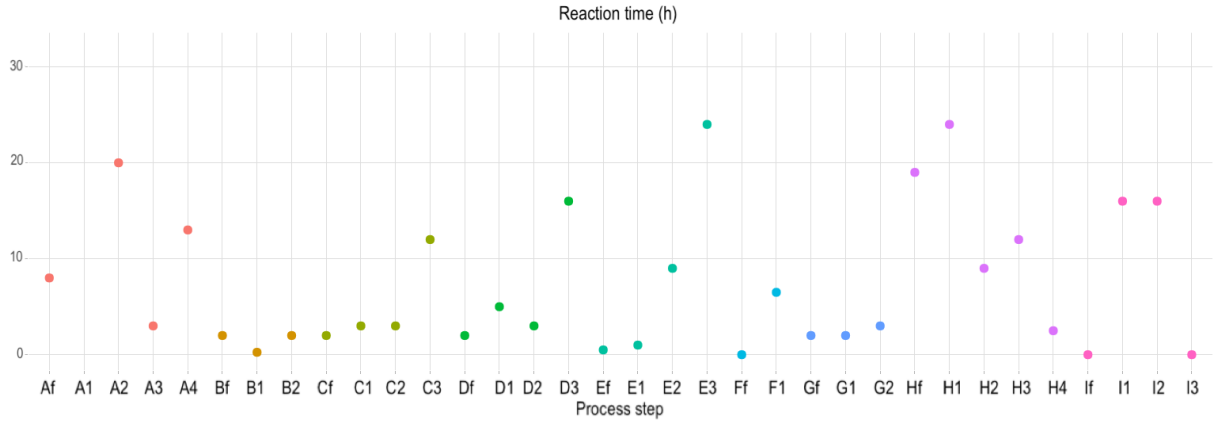


Figure 3.17: Data plot with reaction time values (zoomed in) for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

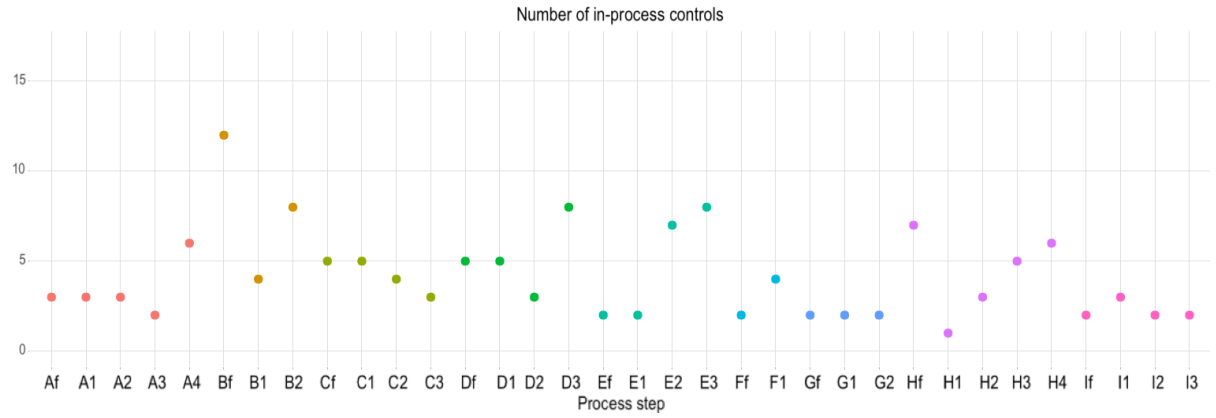


Figure 3.18: Data plot with number of in-process controls for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

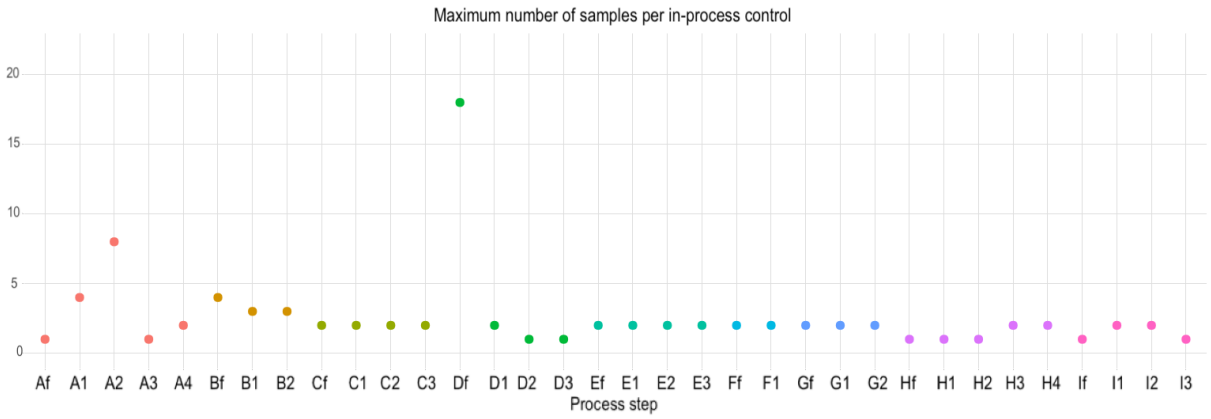


Figure 3.19: Data plot with maximum number of samples per in-process control for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

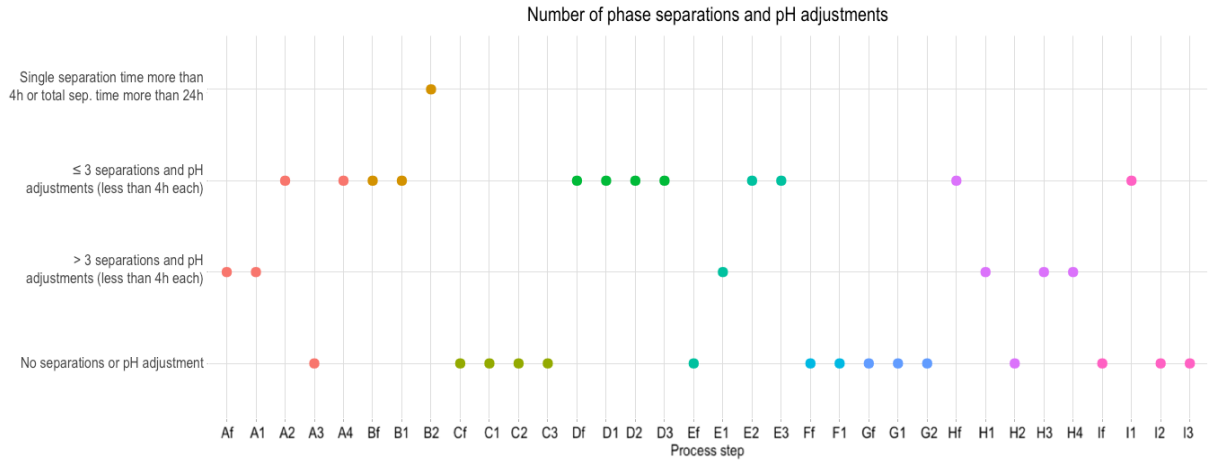


Figure 3.20: Data plot with answers for number of phase separations and pH adjustments for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

pH adjustments (see Figure 3.20), which is quite good considering they can be time-consuming and waste generating. Additionally, 90% of processes with telescoped synthesis had at least one of these operations, which helps correlate the need for workup in one-pot processes. Additionally, evaluated in question #13 ”Columns needed?”, only process *Df* required complex purification procedures, namely through a chromatographic column, evidencing how uncommon these procedures are in big scale chemical manufacturing.

Concerning criterion #14 ”Existing holding points?”, only processes *H1* and *H2* did not have holding points studied and known, due to the fact that these two processes were relatively new within the company, therefore still in early phase of process development.

In terms of filtration procedures, only processes *Df* and *I1* did not have a filtration stage, since the final product of these processes was intended to be a solution, therefore in a non-isolated form – the first one specifically because the purified API solution would later suffer a spray-drying process. Although polish filtrations are more common in final step procedures, some intermediates may require this additional

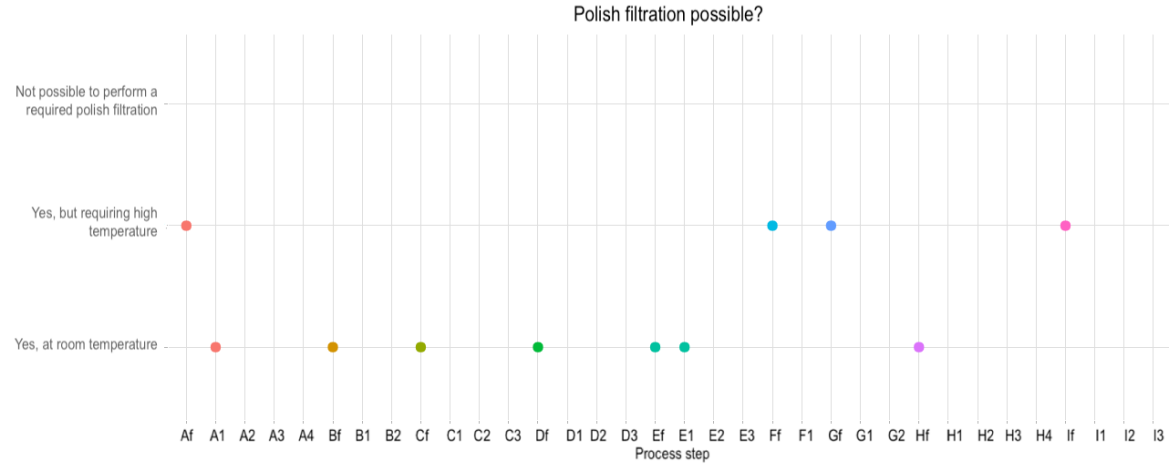


Figure 3.21: Data plot with answers for polish filtration's conditions for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project. Processes without a given answer did not require this operation, therefore not evaluated.

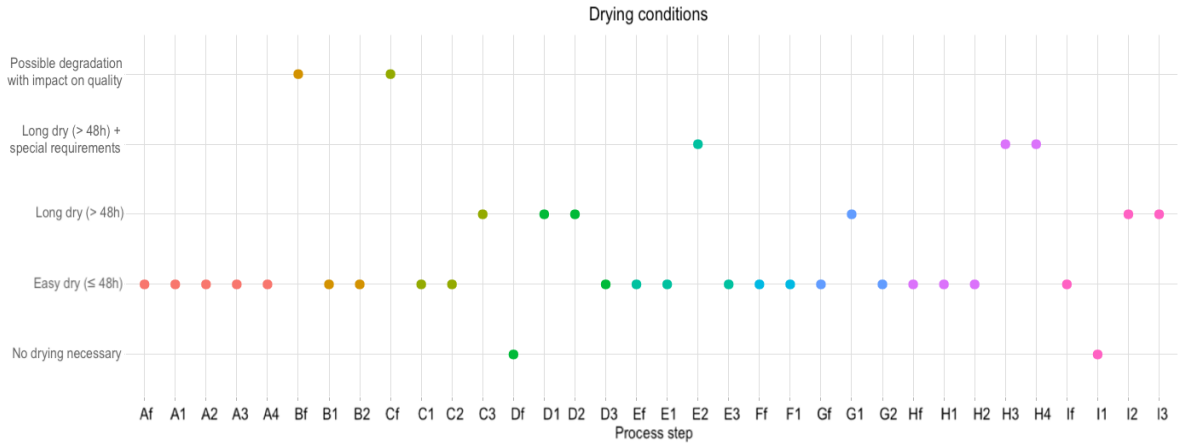


Figure 3.22: Data plot with answers for drying conditions of each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

operation. Therefore, only considering processes that fit in this category, 36% of them performed a heated polish filtration (see Figure 3.21), which is not so efficient in terms of safety (as explained in subsection 1.1.2.1). Additionally, only processes *C2* and *E2* had the need for filtration of solid waste, although already in a considerable quantity, corresponding to the minimum score range (see Table 3.1).

Finally, considering the last API isolation operation (see Figure 3.22), the only two processes that did not need drying were *Df* and *I1*, as discussed previously. Other than that, 62% of processes had an easy, less than 48h dry, which is quite favorable for the process's cycle time, although these answers were mostly based on small scale experience, and a few more issues can arise in manufacturing scale that can hamper the operation.

3.3.1.4 Raw Materials Results

As explained in subsection 2.1.2.4, ICH classification on solvent's toxicity is very important to determine the safety of the process and the final product. In this evaluation (see Figure 3.23), it was verified

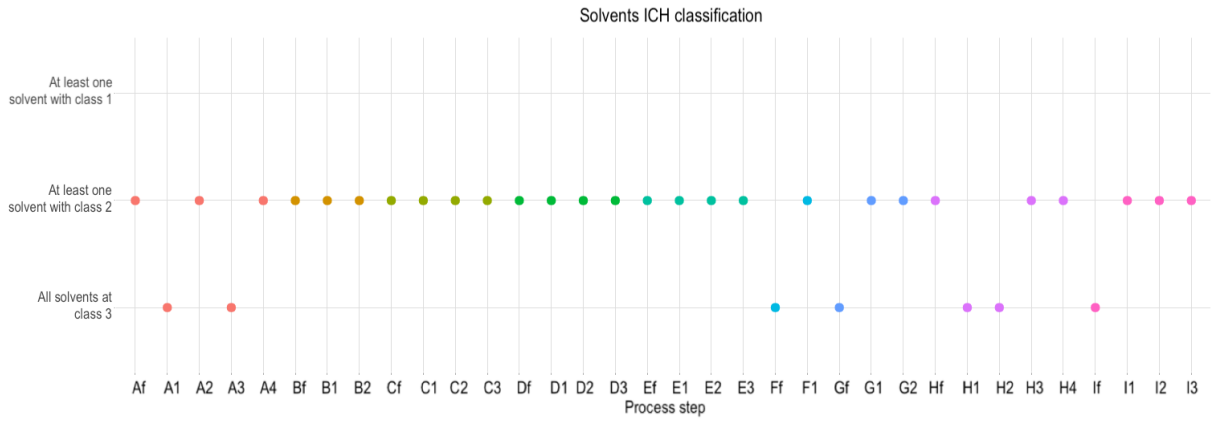


Figure 3.23: Data plot with answers for solvents ICH classification used in each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

that no class 1 solvents were used in company processes, however, 79% of processes used at least one class 2 solvent, which includes final step processes that may raise purification concerns. From these 79%, 41% used dichloromethane, 26% used methanol, and 22% used acetonitrile, which are very common in organic synthesis: dichloromethane, due to its volatility and ability to dissolve a wide range of organic compounds [51]; methanol, due to its complete miscibility with water, and as a reagent for several chemical reactions [52]; and acetonitrile, due to its ability to dissolve a wide range of polar and nonpolar solutes, and as a common two-carbon building block for organic synthesis [53].

Through the principles of green chemistry, the use of these solvents should be minimized (see section 1.2), although thorough studies need to be conducted to find adequate replacements for them, and the fact that these solvents are inexpensive, commodity-type materials, does not help this endeavour.

According to the REACH regulation (see subsection 2.1.2.4), 12% of evaluated processes used at least one substance in the candidate list for restrictive use within the industry, namely dimethylformamide and dimethylacetamide, which are also ICH class 2 solvents. Additionally, a substance in the authorization list for restrictive use was also utilized in process *H2* (see Figure 3.24), therefore the use of these substances definitely takes a toll on process's greenness.

In terms of availability of raw materials (see Figure 3.25) the majority of components are commodities, however, 24% of processes used a component with only one available supplier, which can have its risks (as explained in subsection 2.1.2.4). From the 56% of processes that used at least one non-commodity material, 42% of them were first step processes, which normally account for SRM's provided exclusively by the client.

3.3.1.5 Health, Safety, and Environment Results

Concerning safety risks, one of the most common in the chemical industry are brought by highly exothermic reactions (see Figure 3.26), which 65% of processes exhibited, however, easily manageable with a controlled addition of the substance in question. This still presents itself as a disadvantage, not only for safety concerns, but for the increase in cycle time, which can have at least one extra hour.

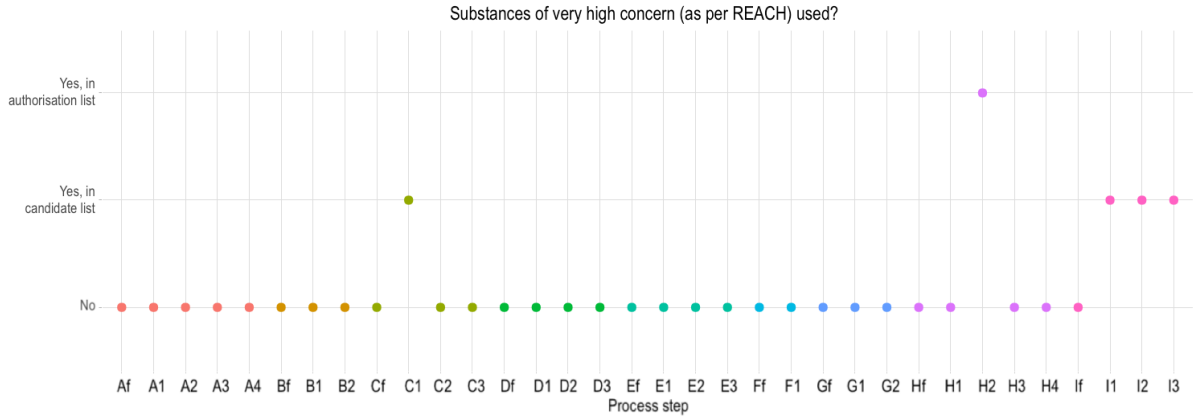


Figure 3.24: Data plot with answers for REACH regulated substances used in each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

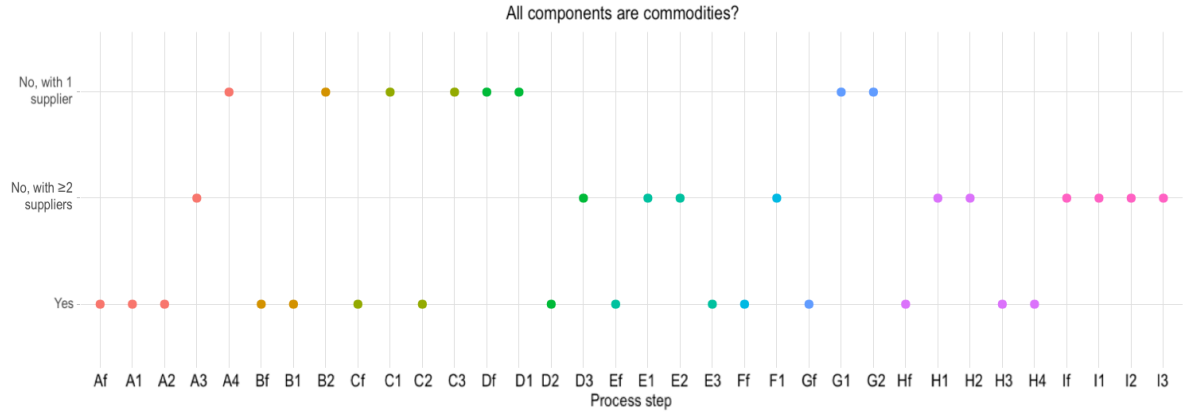


Figure 3.25: Data plot with answers for commodity components used in each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

Finally, in terms of HSE concerns with utilization of highly corrosive, toxic, flammable, or explosive material (see Figures 3.27 and 3.28), most processes did not require special control systems that a chemical industry would not inherently need. Interestingly, in Figure 3.27 it is observed that the three last steps from project *C* required such special EPI's and advanced control systems, which is due to the fact that this product is a highly potent API, and exposure to it can lead to high levels of toxicity. [54]

3.3.2 Green Metrics Analysis

In this section, Table 3.2 and Table 3.3 exhibit the results obtained for each green metric evaluated, as the percentage of processes/projects/batches that had score values within both maximum and minimum score ranges (where the maximum range corresponds to the colour code ”green”, and ”red” to the minimum range, given in Appendix B). Average and standard deviation values are also displayed, calculated considering all processes, regardless of project type.

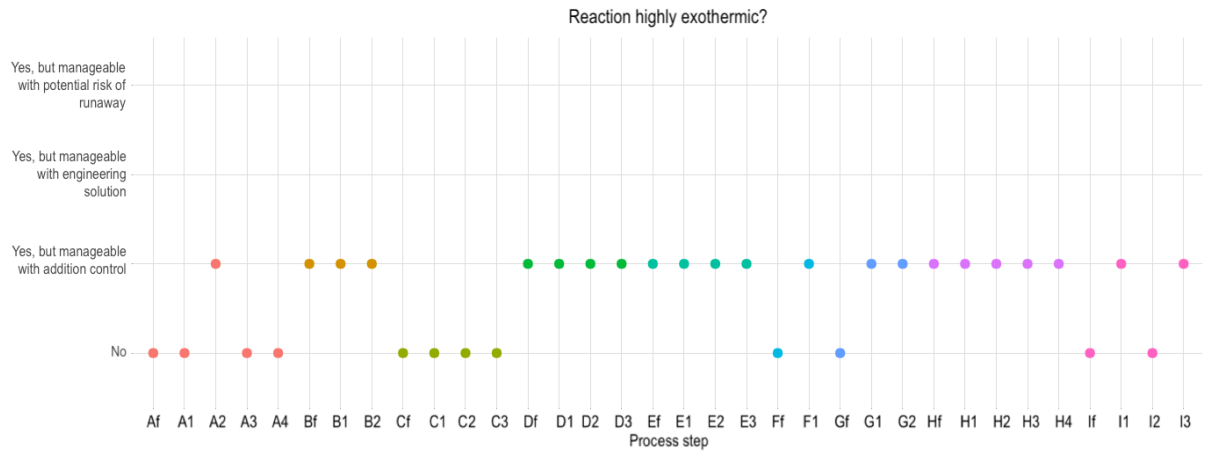


Figure 3.26: Data plot with answers related to highly exothermic reactions for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

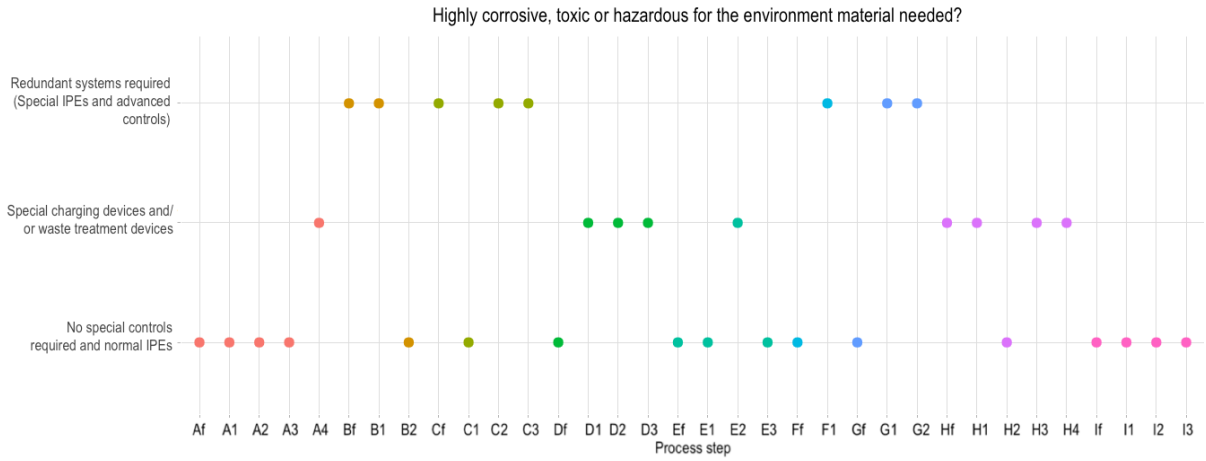


Figure 3.27: Data plot with answers related to safety measures when highly corrosive, toxic, or hazardous for the environment material is needed in each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

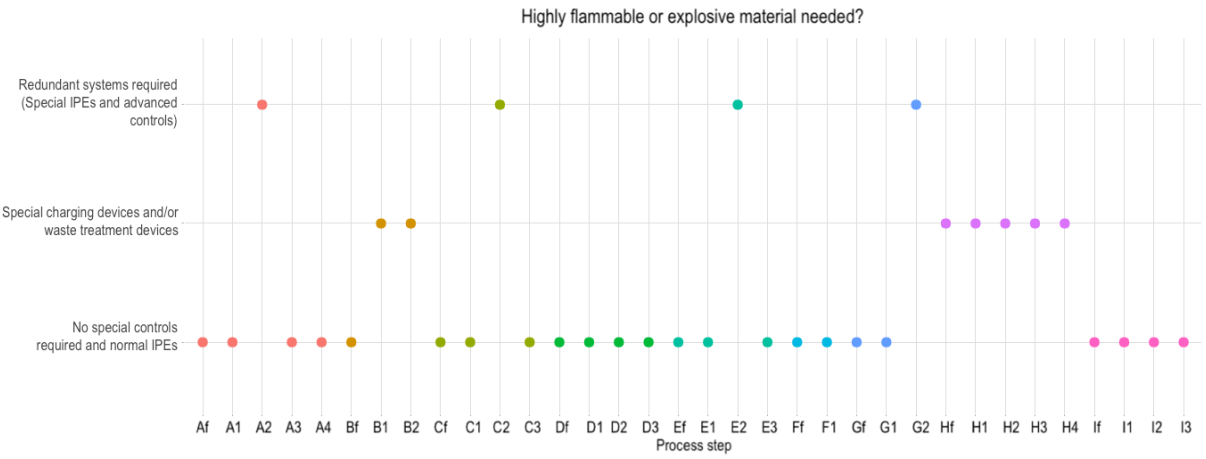


Figure 3.28: Data plot with answers related to safety measures when highly flammable or explosive material is needed in each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

Table 3.2: 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. These score ranges are featured in Appendix B, and qualify themselves as having ”green” and ”red” colour, respectively.

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%
E-factor	Laboratory	59%	18%	18 [2]	20 [2]
	Manufacturing	42% [3]	28% [3]	39[2]	100 [2]
Volume-Time-Output (VTO)	Manufacturing	48% [3]	12% [3]	24 m^3h/kg	37 m^3h/kg [4]
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]

[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] Percentage of batches conducted within the company, considering all processes evaluated.
[4] Here, the lower confidence limit drops below 0, therefore the limit considered is 0.

Table 3.3: Percentage of projects that obtained maximum and minimum score ranges in each green metric evaluated for overall processes, including their average value and standard deviation. These score ranges are featured in Appendix B, and qualify themselves as having ”green” and ”red” colour, respectively.

Green chemistry metric	Classification categories	Projects with maximum score range	Projects with minimum score range	Average	Standard deviation
Atom Economy (AE)	Laboratory	0	56%	64%	15%
Reaction Mass Efficiency (RME)	Laboratory	0	100%	12%	6%
Step Economy (SE)	Laboratory	22%	11%	0.82	0.44
E-factor	Laboratory	0	56%	77 [1]	76 [1]

[1] This value was normalized at Hovione's request, in arbitrary units.

3.3.2.1 Atom Economy Results

As explained in subsection 1.2.2.1, atom economy (AE) is an indispensable metric to evaluate a chemical process, providing a theoretical value for the efficiency of synthesis in terms of raw material strategy. 44% of processes evaluated through this platform had an AE value between 70–90%, which is the aspiration value range for Boehringer Ingelheim [11], and from the 35% of processes that were in the maximum score range, 67% of them had an AE value of 100%, which truly is the ideal goal. While observing Figure 3.29, all processes with 100% of AE, except for *Ef*, *Ff* and *Gf*, were purification steps (recrystallizations, polymorphic form isolations, and chiral resolutions), therefore their product and the step's SRM would be the same molecule. Processes *Ef* and *Gf*, having salt formation reactions, were also expected to have an AE value of 100%. [32]Additionally, process *G1* has a coupling reaction, which many other processes have, but reaching 100% of AE, achieving a remarkable theoretical efficiency of

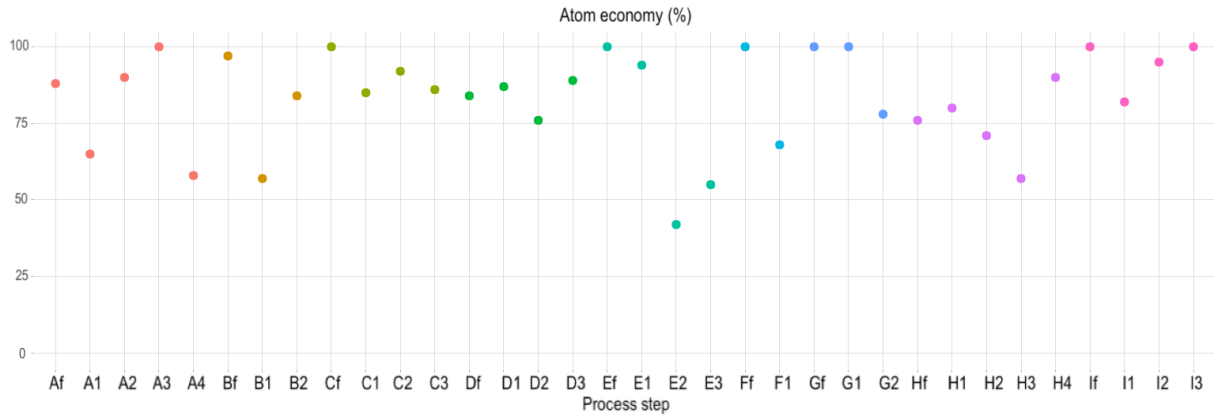


Figure 3.29: Data plot with atom economy values for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

synthesis.

Looking over the 21% of processes with minimum score range, 85% of them have complicated telescoped synthesis, sometimes with more than two reactions per isolated step, this way adding a larger number of reactants, most of them simply auxiliary ones and, as expected, not incorporating the step's final product. This is evidenced particularly in process *A4*, which has two telescoped reactions, and uses a high-molecular weight protective group, resulting in a low AE value as seen in Figure 3.29.

Comparing the AE values of each step with the overall API process (see Figure 3.30), it is obvious that there would be a certain trend in having lower AE values for entire projects, when its calculation considers all reactants in each step and a final API that could not have incorporated all those molecules. Additionally, all 56% of projects that had low AE values (see Table 3.3), have complex telescoped synthesis. Although this type of synthesis strategy has its advantages, such as promoting one-pot processes, and minimizing the need for so many isolation stages (see subsection 1.2.2.7), it has some disadvantages, particularly the tendency to have by-product formation, and the overuse of reagents that were not tactically selected to serve multiple roles throughout the process. [55]

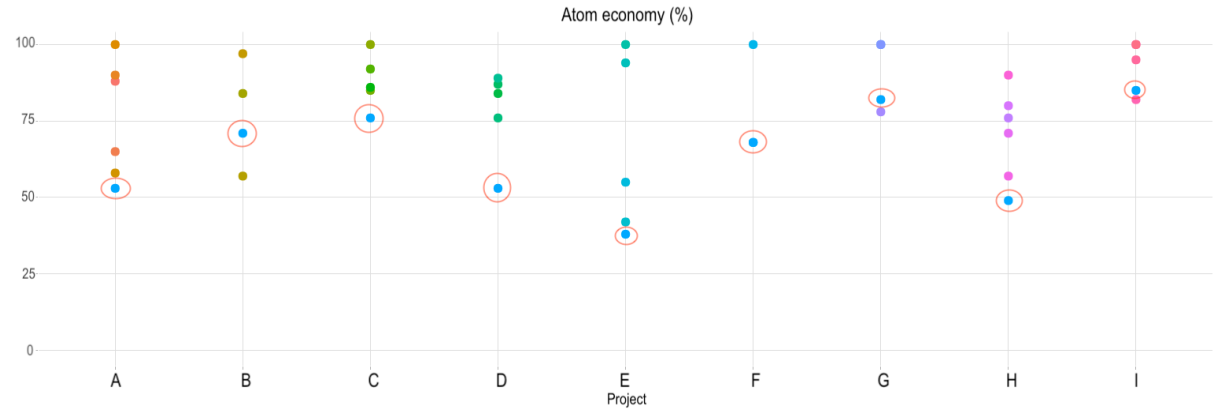


Figure 3.30: Data plot with atom economy values for each project evaluated with the knowledge-based assessment tool, provided by the user interface, including the overall process value, marked by a red circle.

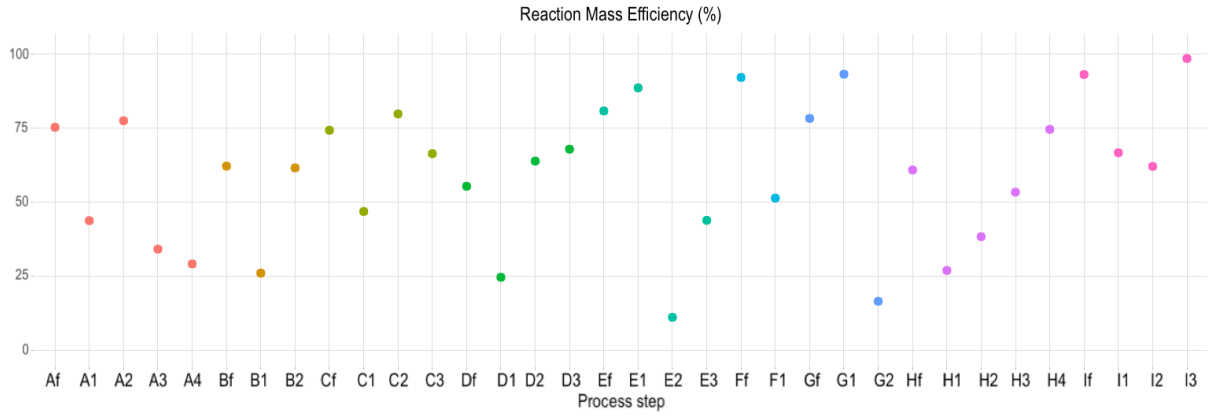


Figure 3.31: Data plot with reaction mass efficiency values for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

3.3.2.2 Reaction Mass Efficiency Results

Although the target ranges were given arbitrarily on a first trial basis (as explained in subsection 2.1.3), reaction mass efficiency (RME) had significantly low values, with just 18% of processes having an RME value of over 80% (see Figure 3.31). With such a big dispersion of data, it is difficult to assess exactly what range of values should the company aspire.

Since RME is not a theoretical value like AE, these values were consistently lower than AE, however, they did not follow the same trend (see Figure 3.32). As explained in subsection 1.2.2.4, RME also incorporates actual reaction yield and molar excess of reactants, and to understand the correlation between these features, Figures 3.33 and 3.34 were analysed, together with Figure 3.32. To include the influence of molar excesses, the green metric called stoichiometric factor (SF, see subsection 1.2.2.6) was calculated separately, through the assessment tool's database. This separate analysis also showed that only 18% of processes were run under stoichiometric proportions, corroborating the evidence concluded in the Constable et al. [32] studies.

While closely observing processes *E2* and *G2*, which had AE and laboratory MY values very similar to each other, one can see that, while both processes had high SF values, indicating far from stoichiometric reaction conditions, they also had the lowest RME values. Thus, the remarkable influence of nonstoichiometric conditions on a mass utilization efficiency metric. Additionally, the correlation between the four metrics is clearly evidenced with process *Ff*, which had an AE of 100% and stoichiometric proportions, resulting in an RME value equal to the laboratory MY.

Due to the low RME values obtained, the overall process RME values for each project were extremely low (see Figure 3.35), with 100% of projects having RME values below 30%. Project *F* was not included in this evaluation due to lack of information on corresponding process step's Demo Run experiment. Although an interesting green metric to evaluate, which provide much information on the reaction synthesis, RME does not seem to be easily interpreted, therefore, may not facilitate a future improvement strategy in drug development. Instead, perhaps the use of SF itself may prove more insightful than RME, on account of evaluating a relevant process parameter and being more intuitive.

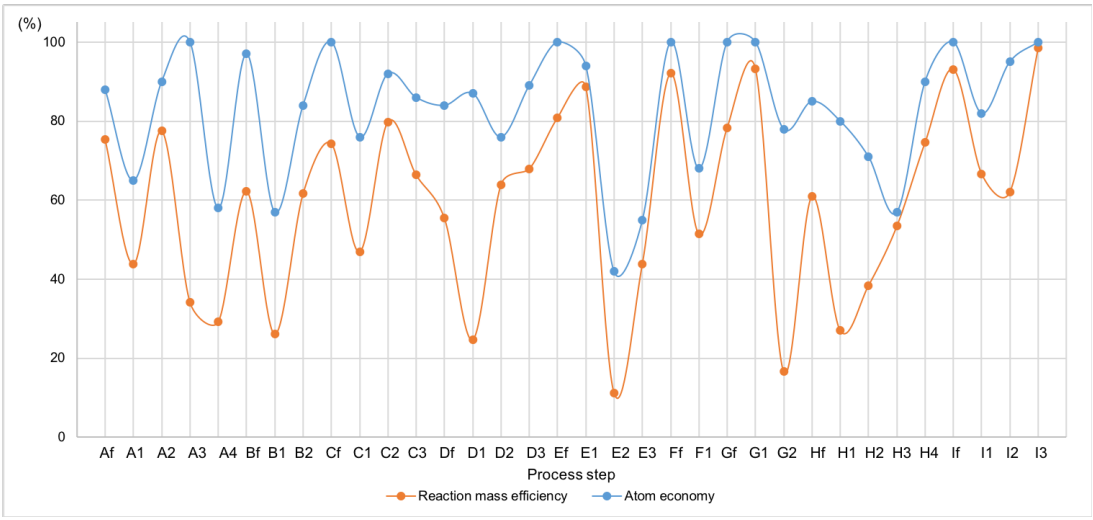


Figure 3.32: Data plot with reaction mass efficiency and atom economy values for each process step (in orange and blue, respectively).

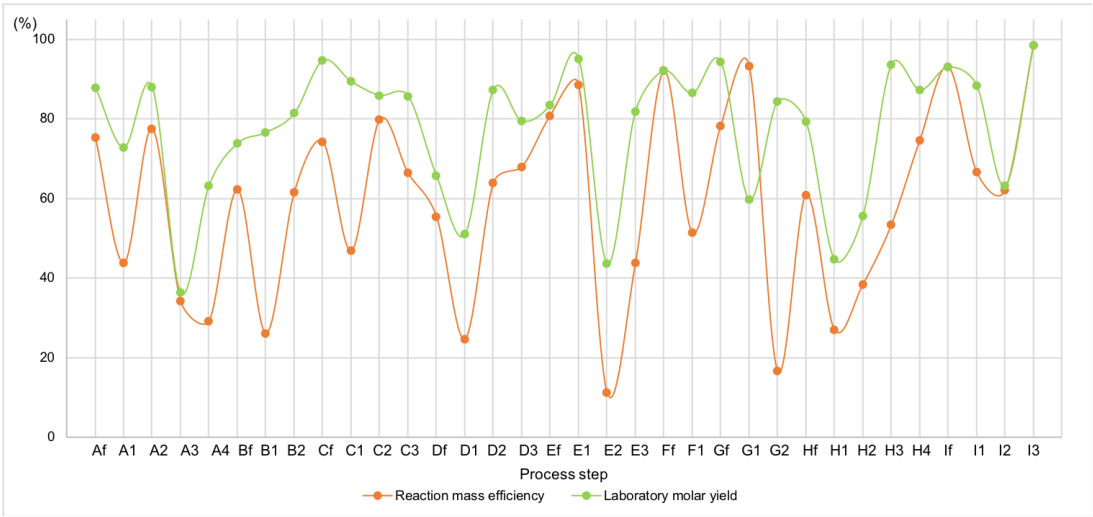


Figure 3.33: Data plot with reaction mass efficiency and laboratory molar yield values for each process step (in orange and green, respectively).

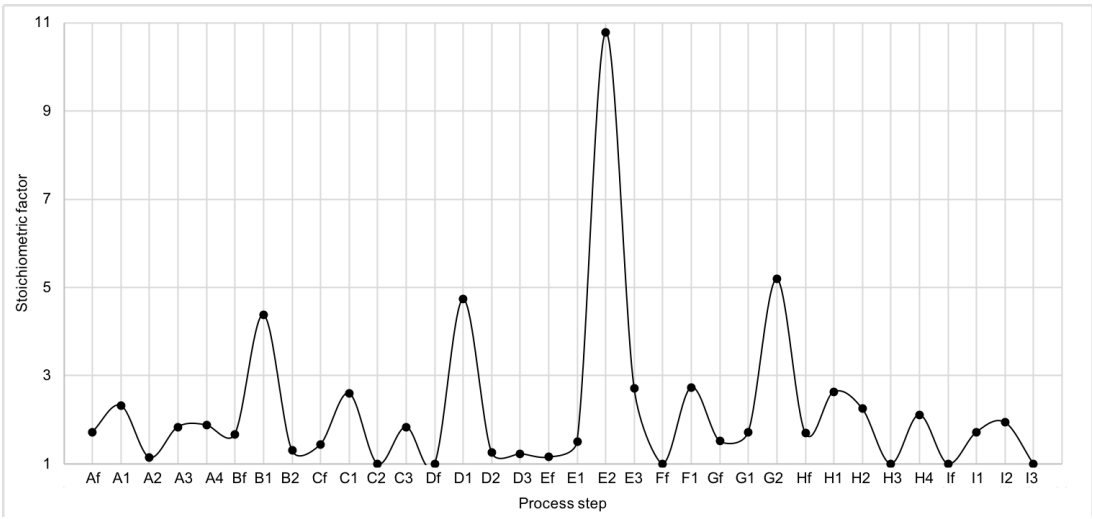


Figure 3.34: Data plot with stoichiometric factors for each process step.

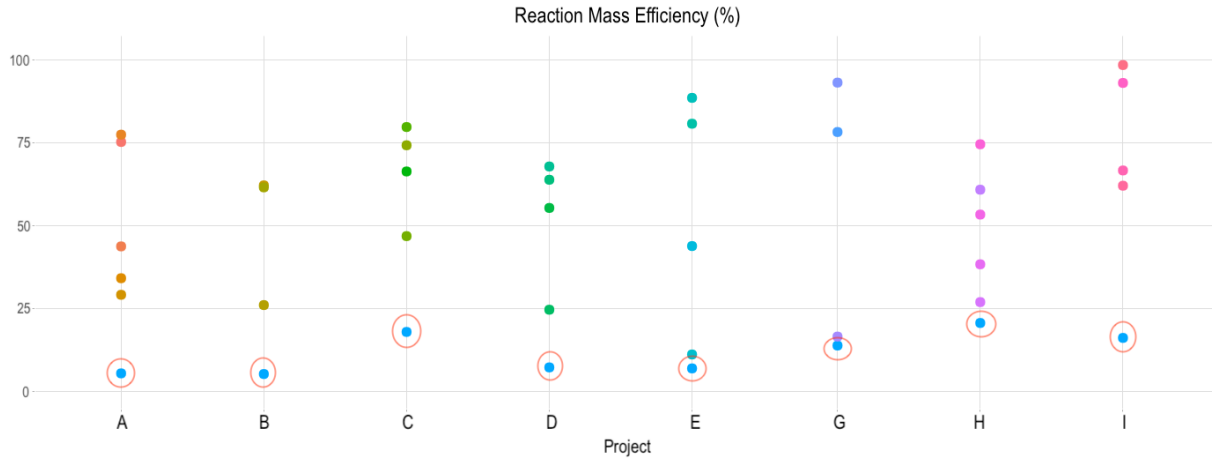


Figure 3.35: Data plot with reaction mass efficiency values for each project evaluated with the knowledge-based assessment tool, provided by the user interface, including the overall process value, marked by a red circle. Project *F* was not included in this evaluation due to lack of information on corresponding process step's Demo Run experiment.

3.3.2.3 Step Economy Results

Considering Figure 3.36, projects *C* and *I* were the only ones that had a step economy (SE) value within the minimum score range, due to the fact that they did not have a single telescoped synthesis in their processes. Projects *E* and *F* were the projects that had the most "degree" of one-pot synthesis, thus exhibiting the lowest SE values. These results show a clear tendency within the company to perform this type of production strategy, with 56% of projects integrating at least one telescoped synthesis. Additionally, as briefly discussed in subsection 3.3.2.1, there was a correlation between AE and SE values, evidenced in Figure 3.37, attributed to the impact of telescoped synthesis in the number of necessary reactants.

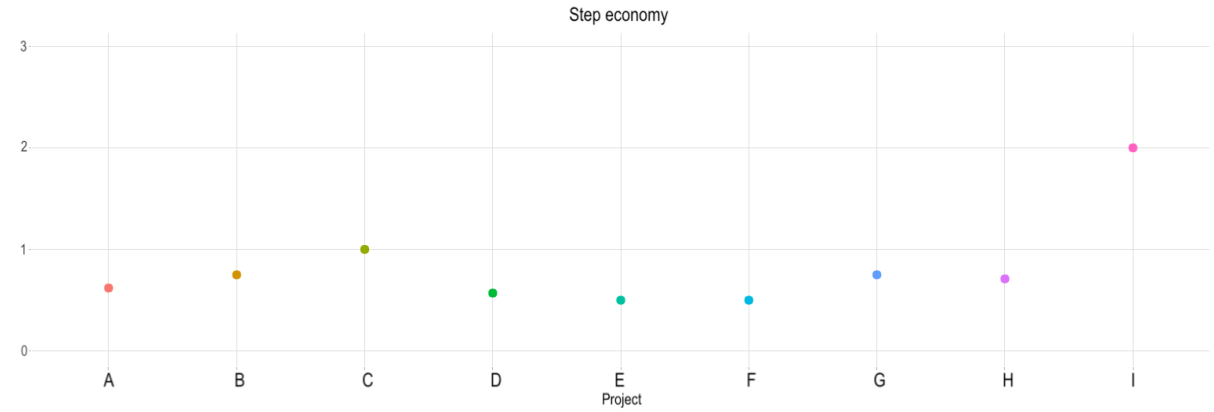


Figure 3.36: Data plot with step economy values for each project evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

3.3.2.4 Environmental Factor Results

Firstly, as seen in Table 3.2, the E-factor average and standard deviation values, for both laboratory and manufacturing classifications, did not have any physical meaning, since their deviation greatly surpassed

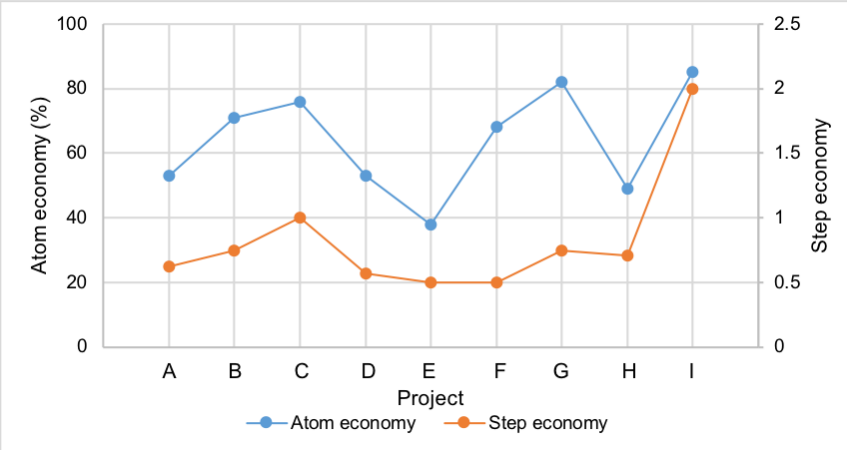


Figure 3.37: Data plot with step economy and atom economy values for each project (in orange and blue, respectively).

the average value. This evaluation does help the quantification of process's waste generation, however, a comparison analysis between significantly different processes does not prove to be adequate. In fact, Dach et al. [11] already expressed this difficulty in assigning a common aspiration value for E-factor, due to its dependency on process strategy and variations of complexity between different projects. A comparison evaluation per type of chemistry and type of target molecule, which can have identical process strategies, might be more suitable.

Nevertheless, regarding the laboratory scale (see Figure 3.38), 59% of processes achieved a good score, but still 18% of processes had very high E-factors (higher than 100 kg waste/kg product). Naturally, the same elevated E-factor values can be observed in each project's laboratory evaluation, in Table 3.3 and Figure 3.39. When evaluating projects still in process development phases, and with "time to market" constraints for waste focused optimization studies, these values are to be expected.

Process *Df* stood out with an enormous E-factor value, because of its process complexities – it incorporates a chromatography purification step, a charcoal filtration step, and other complex operations that were not discussed in the present work. One can conclude that these operations deeply impact waste generation, on account of their elution and regeneration processes (as explained in subsection 1.1.2.1), therefore this E-factor value should be regarded as an outlier in this evaluation.

Although telescoping strategies have the intention of minimizing overall process waste (see subsection 1.2.2.7), 70% of processes with telescoped reactions had high E-factor values (at least 40 kg waste/kg product). This is theoretically expected within each isolated step, due to the need for more workup solvents and reagents, and increase in workup/isolation constraints from growing by-product formation. However, comparing E-factor and SE values for overall processes (Figure 3.39), a correlation between more telescoped synthesis (i.e., lower SE value) and less waste generation (i.e., lower E-factor) was not quite achieved. Although project *F*, *G* and *H* corresponded to that expectation, project *E* had one of the lowest SE values and one of the highest E-factors, and vice versa for project *I*. Since E-factor varies greatly with project complexity, this correlation can only be truly assessed within the same type of process.

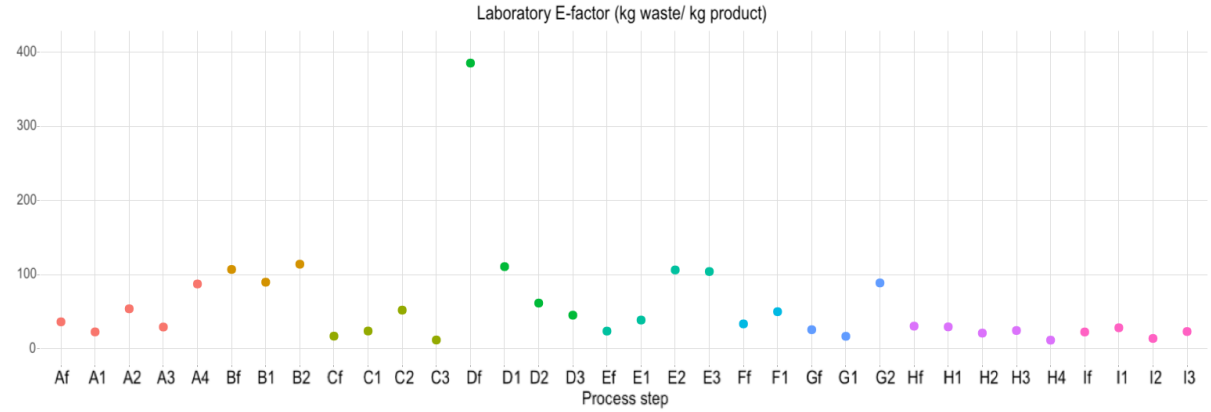


Figure 3.38: Data plot with laboratory E-factor values for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

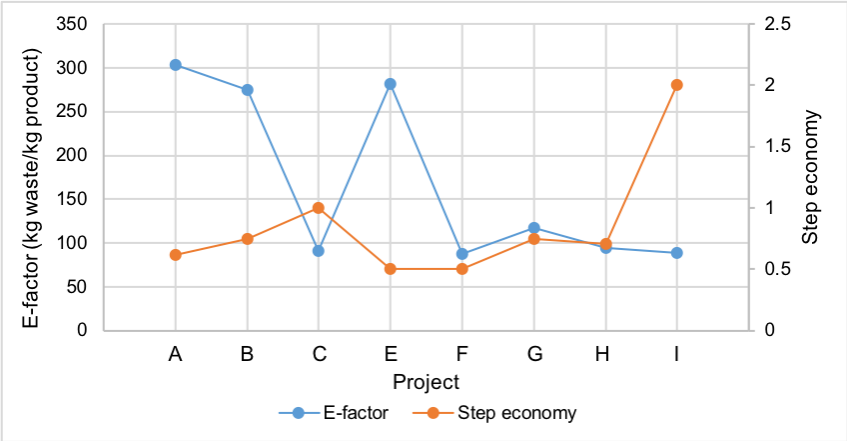


Figure 3.39: Data plot with E-factor and step economy values for each project (in blue and orange, respectively).

To assess the reason for this elevated waste generation, data from unit operations within each process, such as maximum occupied volumes in the main reactor (see Figure 3.14), distillation volumes (see Figure 3.16), and number of separation phases and pH adjustments (see Figure 3.20) were compared with E-factor values obtained for each laboratory process (see Figure 3.38).

Some examples expressed this correlation very clearly, such as processes *A2* and *A4*, which had the highest E-factor values within that project, and also exhibited higher number of phase separations and pH adjustments and distillation volumes; while process *A4* showed as much distillation volume as process *Af*, the first one had a greater maximum volume occupied in the main reactor, therefore also influencing the E-factor. Project *B*, which obtained very high E-factor values overall, also exhibited high maximum occupied volume, high distillation volume, and a large number of separation phases and pH adjustments. No step from project *C* had separation phases or pH adjustments, and the highest E-factor came from process *C2*, which also exhibited the highest distillation volume. From project *D*, with the exception of the already discussed process *Df*, this relation was also observed in process *D1*, which had the highest E-factor, highest distillation volumes, and elevated maximum volume occupied. Processes *E2* and *E3* had similar cases as processes *A4* and *A2*, respectively.

Table 3.4: Results of manufacturing E-factor values, in the form of each process's average, standard deviation, and absolute error between the manufacturing average and the E-factor value obtained in laboratory scale. The average and standard deviations were normalized at Hovione's request, in arbitrary units.

Code names	Average	Standard deviation	Absolute Error	Code names	Average	Standard deviation	Absolute Error
Af	20.7	9.4	84%	E1	14.0	1.0	17%
A1	7.0	0.8	1%	E2	46.9	0.6	42%
A2	22.5	5.2	35%	E3	64.9	3.5	101%
A3	9.5	1.1	5%	Ff	12.1	1.1	16%
A4	59.6	34.4	120%	F1	41.8	5.8	170%
Bf	57.3	7.7	73%	Gf	8.4	0.2	6%
B1	52.8	14.9	90%	G1	7.5	1.9	43%
B2	54.9	1.4	55%	G2	35.6	2.8	30%
Cf	5.6	0.1	6%	Hf	9.6	0.6	2%
C1	16.6	3.1	125%	H1	3.3	0.3	63%
C2	59.5	11.3	269%	H2	6.2	0.1	6%
C3	3.5	0.5	3%	H3	8.1	0.2	6%
Df	443.0	237.1	271%	H4	6.3	2.8	76%
D1	40.8	1.9	19%	If	7.8	1.3	11%
D2	20.0	1.1	5%	I1	15.1	4.2	72%
D3	15.4	1.0	10%	I2	5.6	0.7	30%
Ef	8.7	0.7	19%	I3	16.2	5.5	125%

However, E-factors from projects *F*, *G*, *H*, and *I* did not correlate so clearly as the others, most likely because of insufficient information from filtration operations, which was not properly implemented in the assessment tool, and would also influence the amount of waste produced in each process. Additionally, since E-factor depends on the amount of product obtained in each step, MY can also influence its value.

In terms of manufacturing assessment, E-factor values were averagely higher than laboratory values, which is not a good achievement, due to the greater implications of waste generation in such a big scale. As previously explained, it is best to compare these E-factor values within the same type of process, therefore a separate analysis was performed, comparing results from various batches with its corresponding laboratory E-factor (see Table 3.4). As observed in this table, most process's E-factor diverged greatly from its laboratory value, and, within the manufacturing scale, the data dispersion verified can also be linked to the development these processes are under.

While searching for possible issues that might have occurred that could explain this divergence from the laboratory values, some common situations turned up:

- More solvent added for phase separations than expected by the manufacturing technique
- Obtained lower yields compared with expected values
- More solvent added for filtration washes than expected by the manufacturing technique
- More solvent added for pH adjustments than expected by the manufacturing technique
- More solution added for reaction operations than expected by the manufacturing technique

This extensive analysis on the E-factor evaluation helps evidence the large impact that more workup/isolation operations can have on the environmental load of a process. Only process optimization studies focused on these operations, preferably resorting to simulation tools, can improve the process's performance.

3.3.2.5 Volume-Time-Output Results

As seen in Table 3.2, 48% of batches had volume-time-output (VTO) values within the maximum score range, with 54% of them having values in the range of 1–5 m^3h/kg. Firstly, the difference between the 1 m^3h/kg target value suggested by Boehringer Ingelheim (explained in subsection 2.1.3), and the VTO values obtained with the assessment tool, is clear. Besides this, similarly to the manufacturing E-factor, the values obtained for each process were not constant throughout their manufacturing batches, as can be seen by the overall elevated standard deviation values in Table 3.5. In addition, 71% of processes that had an average value higher than 30 m^3h/kg were telescoped synthesis, which was expected due to a higher cycle time for the same nominal volume. This parameter would only decrease for telescoped synthesis if an overall process value was obtained, where the use of less reactors would benefit the calculation (as discussed in subsection 1.2.2.8).

Straightforwardly, VTO depends on three factors: nominal volume, cycle time, and amount of product obtained (i.e., reaction yield) – all aspects that vary greatly, specially in processes still under development. For instance, with different campaign sizes that depend on the clinical trial phase and product demand, nominal volumes will change accordingly, having a huge impact on VTO. Additionally, in a CDMO context, VTO can also differ because of equipment constrains, when a production batch size is far below the available equipment's capacity, therefore the product obtained is not proportional to the nominal volume used.

Furthermore, cycle time is a parameter extremely prone to small variations, such as transfer of substances taking a bit longer, operator's shift change, lower visibility of the interface between phase separations requiring a more careful extraction, etc., with the added fact of having an unoptimized process that may require an extra unit operation that was not incorporated in the preceding batch – therefore, also greatly influencing VTO values. Molar yield remains a more constant parameter, although, in processes still being studied, issues can arise that will affect this value, therefore the batch's product output.

3.3.2.6 Process Excellence Index for Molar Yield and Cycle Time Results

Regarding reproducibility concerns in manufacturing scale, these two process excellence indexes focus on molar yield (PEIMY), and cycle time (PEICT) of the whole process up until the drying step. As seen in Table 3.2, 53% of processes had PEIMY values in the maximum score range, and only 38% achieving high scored PEICT values. These discrepancies in reproducibility are somewhat expected, since these processes are still under development, specially in manufacturing scale, which can require a lot of optimization studies for scale-up. Note that the PEIMY target values considered in the assessment tool were directed for commercial processes [11], therefore confirming process's variability during drug

Table 3.5: Results of manufacturing volume-time-output values, in the form of each process's average, and standard deviation.

Code names	Average (m^3h/kg)	Standard deviation (m^3h/kg)	Code names	Average (m^3h/kg)	Standard deviation (m^3h/kg)
Af	46.7	66.8 [1]	E1	21.2	6.0
A1	9.1	3.9	E2	65.9	8.1
A2	9.8	7.1	E3	90.3	8.9
A3	6.2	2.4	Ff	4.2	1.0
A4	47.0	39.6	F1	20.7	0.9
Bf	39.1	20.3	Gf	5.7	1.5
B1	20.0	4.2	G1	8.9	5.2
B2	27.0	13.3	G2	11.5	3.0
Cf	1.4	0.1	Hf	17.5	6.6
C1	2.9	1.1	H1	3.6	0.04
C2	21.5	2.6	H2	3.9	0.07
C3	3.8	1.5	H3	13.3	0.3
Df	142.9	60.1	H4	14.8	8.0
D1	22.6	1.0	If	8.4	3.8
D2	19.3	5.4	I1	31.7	33.7[1]
D3	18.7	2.8	I2	6.2	3.1
Ef	24.1	9.3	I3	9.7	8.2

[1] Here, the lower confidence limit drops below 0, therefore the limit considered is 0.

development phases.

PEICT has a significantly bigger data dispersion than PEIMY (see Table 3.2), as expected by the increase in variability regarding time schedules during manufacturing (as explained in subsection 3.3.2.5), and considering that often the objective of reaching a molar yield within the expected range can be made priority over the length of a batch's cycle time. Obtaining a low molar yield raises issues of low productivity, which can also be troublesome when considering intermediary products not manufactured in enough quantity for the next step's batch. Therefore, if an additional downstream operation can help achieve an improved molar yield, then more cycle time will be added to achieve this higher PEIMY.

This correlation between lower PEICT and higher PEIMY values is evidenced in Figure 3.40, although the two parameters did not follow a constant trend. Also, only 12% of processes had PEICT values reaching the target range for commercial manufacturing suggested by Dach et al. [11] (which was the same target as PEIMY), verifying these production differences between commercial and development projects.

Additionally, while observing Figure 3.40 and Table 3.5, one can see the correlation between the VTO values and PEIMY and/or PEICT, since these two parameters evaluate the reproducibility of two factors which VTO depends on, as explained in subsection 3.3.2.5. For example, process *Af* exhibited an elevated standard deviation for VTO, and simultaneously its PEICT value was significantly lower than most processes, revealing discrepancies in cycle time throughout the various production batches that influenced VTO. In contrast, process *A4* also exhibited an elevated standard deviation for VTO, but this time presented a low PEIMY value, thus discrepancies in product output. Not all processes exhibited this correlation correctly, because of the nominal volume aspect that also greatly influences VTO.

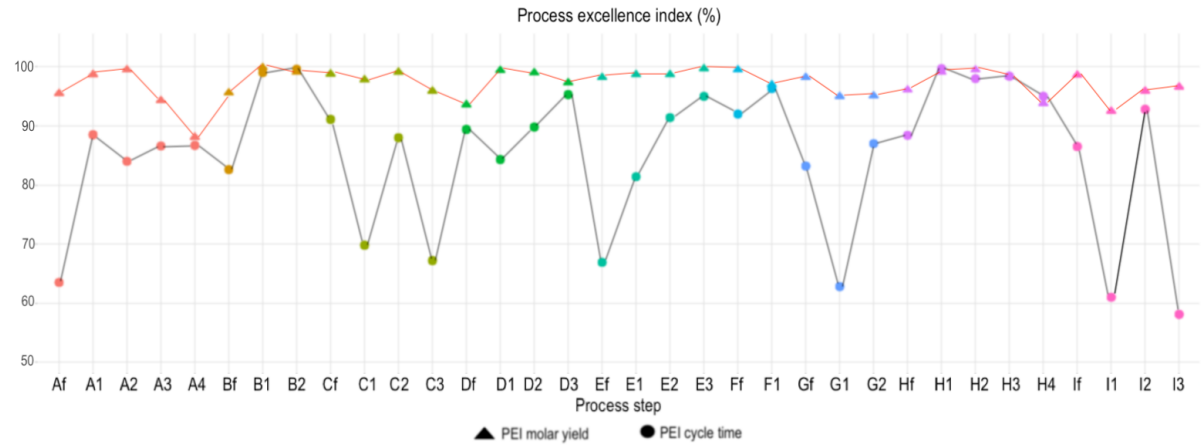


Figure 3.40: Data plot with process excellence index values for molar yield and cycle time (triangle/red line and dot/black line symbols, respectively) for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

3.3.2.7 Quality Service Level Results

In terms of quality assurance in production scale (see Table 3.2), 76% of processes did not have one single batch reprocessed or rejected, which is a good result regarding the robustness of the company's manufacturing processes. However, some of the reprocessed/rejected batches from the other 24% processes were mostly due to OOS events and contaminations from equipment.

3.3.3 Classification Results

After gathering all the data from each green metric and EcoScale criteria, a final classification was obtained by the assessment tool, attributed to each category evaluated. Figure 3.41 illustrates the laboratory classification results, which score ranges, as explained in subsection 2.1.3, were attributed arbitrarily for this assessment tool's first trial (see Appendix B). Given this, 53% of processes had a laboratory classification within the minimum score range, while none of the processes achieved maximum score range, with an average value of 43$\pm$8%. For the overall processes (see Figure 3.42), all projects, excluding project *F*, due to lack of information on RME overall process values, had final classifications within the middle score range, with an average value of 61$\pm$4%.

To understand these reasonably low values, one must analyse the weightings associated with each contributing parameter. Observing the processes with laboratory classification higher than 50%, particularly processes *A3*, *Ef*, *Ff*, *Gf*, *I3*, and *If*, all of them had an AE value of 100% (see Figure 3.29), and an E-factor within the maximum score range (see Figure 3.38). However, for each process value, the highest contributing factor is the EcoScale, both in terms of total sum of EcoScale points and an additional sum of the five lowest scored criteria, as explained in subsection 2.1.3.

These scores, in the form of percentages, were calculated separately, through the assessment tool's database, and Figure 3.43 shows the discrepancy between the total points and the points attributed to the critical aspects of each process. For example, process *E2*, which had the lowest laboratory classification, also had the lowest EcoScale total score, and the processes mentioned before, with the highest laboratory

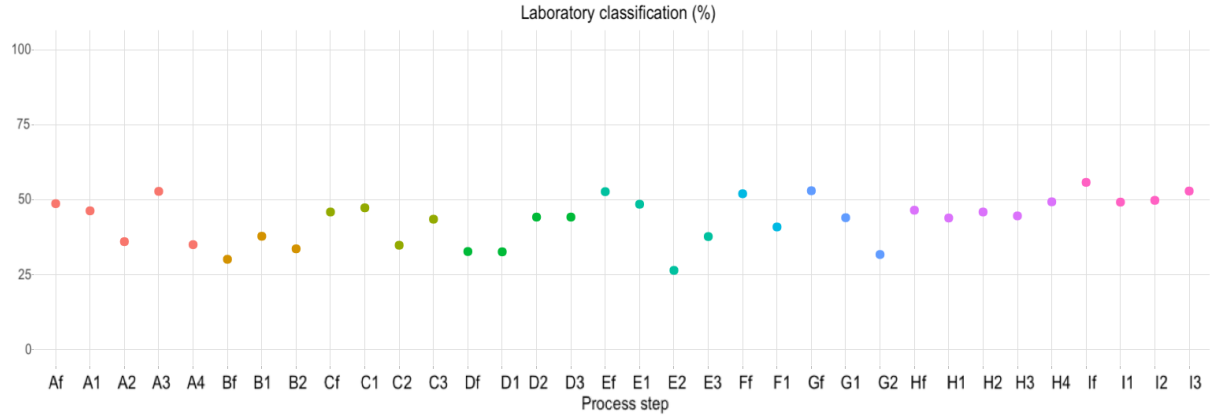


Figure 3.41: Data plot with laboratory classification values for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project.

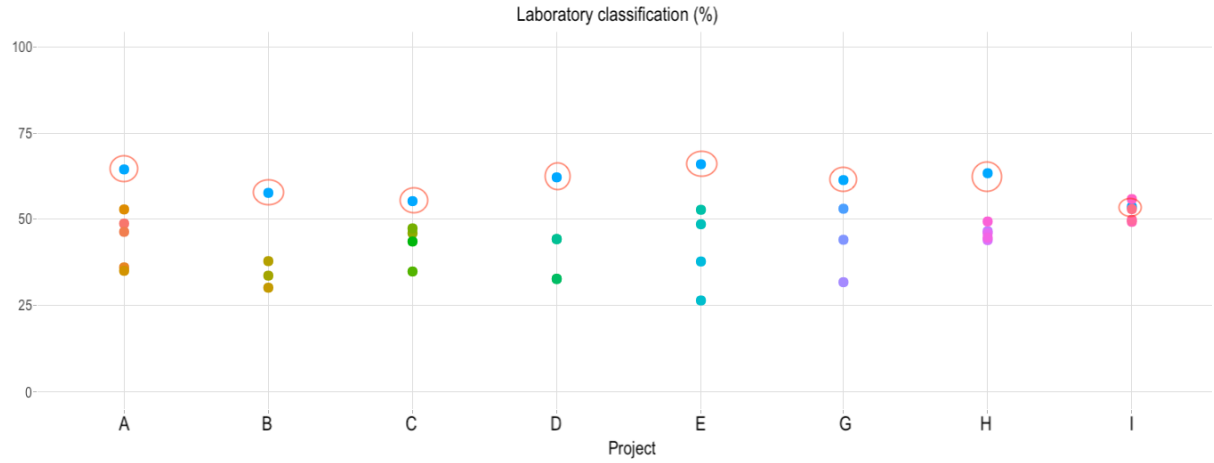


Figure 3.42: Data plot with laboratory classification values for each project evaluated with the knowledge-based assessment tool, provided by the user interface, including the overall process value, marked by a red circle. Project *F* was not included in this evaluation due to lack of information on RME overall process values.

classification, also had both the highest EcoScale total score and five lowest score sum.

Essentially, these low laboratory classifications are due to the addition of the five critical aspects scores (with an average of 9$\pm$0.03%), which were greatly below the maximum score they could add to the evaluation (i.e., 20% score). Although the EcoScale analysis exhibited an overall good final score (with an average of 77$\pm$0.07%), the five critical score sum, helped indicate various issues regarding aspects which were not exactly evaluated through the green chemistry metrics, such as equipment, process, raw materials, and HSE concerns. Besides their visualization (see Figure 3.8), it was also important to account for their score in the laboratory classification.

Additionally, the overall process laboratory classification exhibited higher values, most likely due to the strong contribution of SE, which generally had high scores associated with it (see Figure 3.36).

Regarding the manufacturing classification, as explained in subsection 2.1.3, this classification had no target values associated with it during this first trial, therefore only represented by its data (see Figure 3.44) and an average value of 87$\pm$6% per batch. On account of the arbitrarily given weighting percentage of

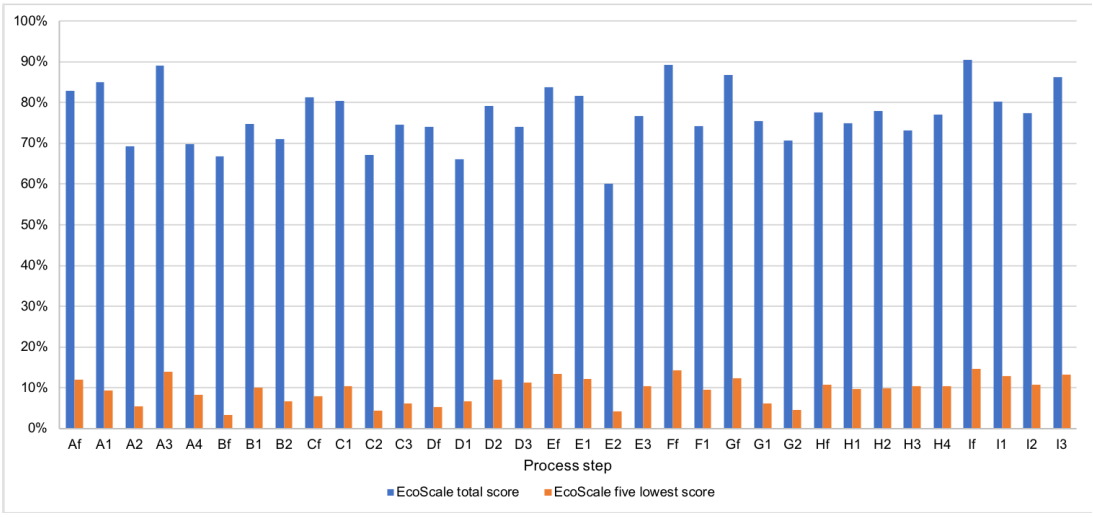


Figure 3.43: Score results, in percentage, from the EcoScale analysis for each process evaluated with the knowledge-based assessment tool, with both total sum of EcoScale points (in blue) and sum of its five lowest criteria (in orange).

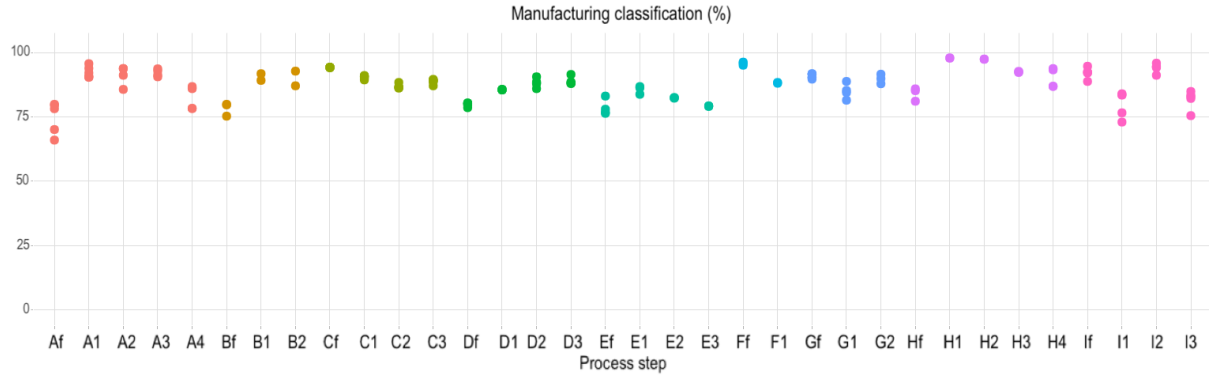


Figure 3.44: Data plot with manufacturing classification values for each process step evaluated with the knowledge-based assessment tool, provided by the user interface. Each colour designates one project, and each dot corresponds to one batch.

each manufacturing green metric (see Appendix B), the manufacturing classification exhibited high scores, which corresponded to the overall high scores obtained for PEIMY, PEICT, and QSL (see Table 3.2).

Finally, upon analysing the final classifications for both categories, specially for manufacturing, one comes to the conclusion that an optimization of the underlying model (i.e., what criteria contributes to each final classification, and their corresponding weightings) is still necessary to truly classify pharmaceutical processes using this knowledge-based assessment tool. 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.

3.3.3.1 Analysis per Type of Chemistry

One of the useful evaluations to be provided by the assessment tool was an analysis of all criteria (EcoScale and green metrics) 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., MY, 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, therefore a target value that the company can 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.

Unfortunately, this was not yet achieved in the present work, in spite of the collection of data regarding the type of chemistry for each process step, due to a lack of consensus between the given designations. Before a true analysis of this sort, a database with various established types of reactions must be constructed, and finally added to this assessment tool, once more enabling the growth of this knowledge network.

Chapter 4

Case Study Evaluation

In this chapter, another type of evaluation achieved by the knowledge-based assessment tool is demonstrated. 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.

It is important to note that, as with the previous chapter, the word ”project” designates the overall API process, while individual steps represent one process each. The project’s steps had code names attributed to them, where the first letter refers to the project name, the digit next to it refers to the step order, and the *f* character designates the final step of this project.

In this case, on account for the several process revisions, an additional code was added after the process code name, to represent its revision and laboratory lifecycle phase, in the form of a hyphen next to ”00” for the Assessment phase, and ”01” for the first process version in Demo Run phase (the incrementation of the last digit indicates which process revision it is). The Manufacturing lifecycle phase has the same codes as Demo Run. 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. To help understand these combinations, Table 4.1 exhibits a summary of these process codes, and their respective correspondence in the different project versions conducted over this API’s development.

As can be seen, a total of five different project versions, excluding the Assessment phase, were studied, therefore, to facilitate the data upload and organization in this software’s first trial, the data plots provided by the assessment tool are numbered per global project version. Also, it is worth noting that the final revisions of each process are integrated in project version 5, which was executed for the final validation campaign of this API.

As this evaluation was more focused on a validation study of both the project’s improvements over time and the assessment tool’s framework, not all criteria are thoroughly discussed here. Although chapter 3 demonstrated each criterion’s importance, some did not provide relevance in this particular study.

Table 4.1: Code names for the different steps, process revisions, and laboratory lifecycle phases of project *D*, including each process's combination into the global project version. The "x" symbol indicates in which project version each process belongs to. Manufacturing and Demo Run phases have the same process code name.

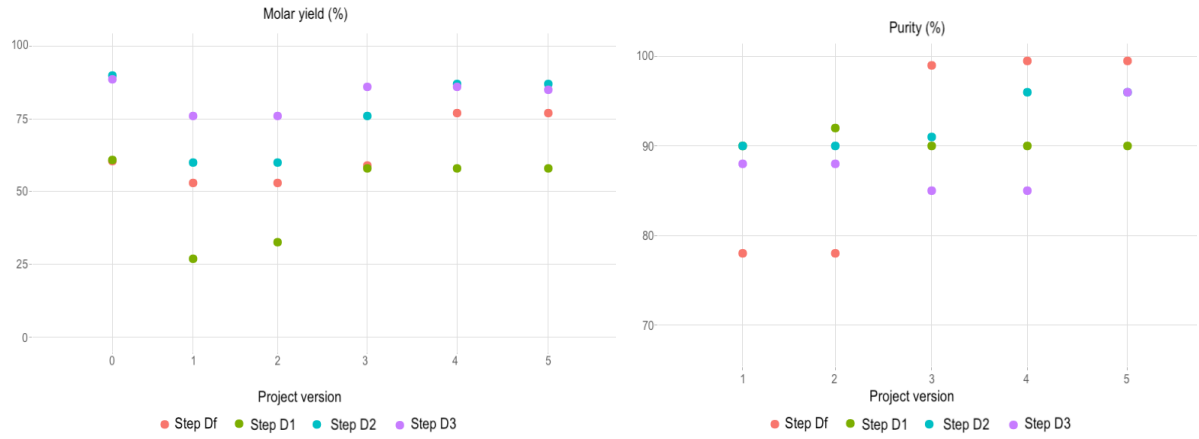
Process code name	Process revision	Laboratory lifecycle phase	Project version				
			1	2	3	4	5
D1-00	0	Assessment					
D2-00	0	Assessment					
D3-00	0	Assessment					
Df-00	0	Assessment					
D1-01	1	Demo Run	x				
D2-01	1	Demo Run	x	x			
D3-01	1	Demo Run	x	x			
Df-01	1	Demo Run	x	x			
D1-02	2	Demo Run		x			
D2-02	2	Demo Run			x		
D3-02	2	Demo Run			x	x	
Df-02	2	Demo Run			x		
D1-03	3	Demo Run			x	x	x
D2-03	3	Demo Run				x	x
D3-03	3	Demo Run					x
Df-03	3	Demo Run				x	x

4.1 EcoScale Criteria Analysis

In this section, the chosen and evaluated EcoScale criteria are analysed more closely. Some criteria were not discussed through this type of evaluation, whether for lack of information on past process revisions (specifically for the Assessment phase, where some data was not available for this evaluation, as explained in subsection 2.1.4), or for insufficient relevance to this study. These include #3 "Specification accomplishment", #8 "Distillation pressure conditions", #11 "Maximum number of samples per IPC", #13 "Columns needed?", #14 "Existing holding points?", #17 "Filtration of solid waste needed?", #18 "Drying conditions", #21 "All components are commodities?", #23 "Highly corrosive, toxic or hazardous for the environment material needed?", and #24 "Highly flammable or explosive material needed?".

4.1.1 Yield and Quality Results

In a first analysis of Figure 4.1(a), one can see that the expected molar yield (MY) for the Assessment phase was generally higher in every step of the project, however, there was a progressive improvement of this metric over the various process revisions within the company, achieving a final value very similar



(a) (b)

Figure 4.1: Data plots with expected molar yield values (a) and with purity degrees (b) (zoomed in) for each version of project *D*, which includes each revision of its process steps (described in Table 4.1). Project version 0 was not evaluated in terms of purity. These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.

to the Assessment's. This Assessment value can be regarded as almost theoretical, possibly already optimized by the client or even by other companies outsourced by them, thus making for a good goal to achieve. Process step *Df-03* succeeded with a MY for final validation higher than the client's proposal, this way enhancing this development work, specially because it is the key step of this API production.

Additionally, for the first project version, the MY for all steps exhibited a great drop from the Assessment MY, achieving their lowest value, which can be expected, on account of the usually necessary scale-down experiment as the client's technique arrives at the company, which can cause some issues in the beginning of the development.

In terms of quality, the purity achieved in the various Demo Run experiments (see Figure 4.1(b)) exhibited an improvement over each process revision, except for step *D1* which had a slight descent. The process with the greatest improvement was *Df-02*, maintaining it through process *Df-03*, this way achieving a higher purity in the final API for process validation.

4.1.2 Equipment Results

Regarding reaction temperature and pressure conditions (see Figure 4.2), steps *D2* and *D3* maintained their conditions, however, process *D1-03* exhibited an improvement by requiring room temperature conditions, and in contrast, process *Df-03* had an adjustment to conditions outside room temperature range. Nevertheless, this descent may actually be an optimization, by promoting a better reaction performance, and allowing for a higher MY (see Figure 4.1(a)). When comparing with the Assessment phase, one can notice that the first process revisions maintained the conditions proposed by the client, most certainly to ascertain their efficiency.

In terms of maximum volume occupied in the main reactor (see Figure 4.3(a)), no significant differences were demonstrated, except for process *D1-01*, which had an enormously heightened volume compared with *D1-00* (but quickly improved in the following revisions), and process *D2-03*, which achieved a

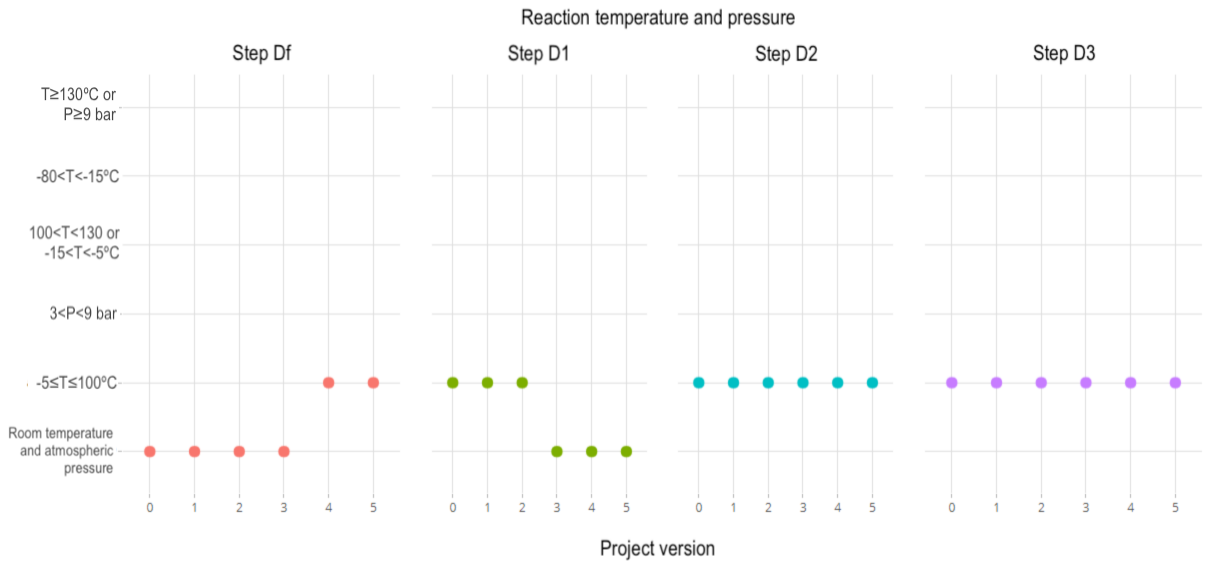


Figure 4.2: Data plots with reaction temperature and pressure answers for each version of project *D*, which includes each revision of its process steps (described in Table 4.1). These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.

noticeable improvement of its maximum volume occupied in the main reactor, therefore allowing for less waste generation during this phase.

The volume ratio aspect (see Figure 4.3(b)), as with the last criterion, remained somewhat constant, except for step *D1*, which presented a slight optimization alongside its process revisions, and process *D2-03*, which had a downfall on its improvement in this area. Interestingly, as this process achieved lower maximum volume occupied in the main reactor, it also started achieving an even lower minimum volume, possibly due to a higher distillation volume required with the process change (further explained in subsection 3.3.1.3).

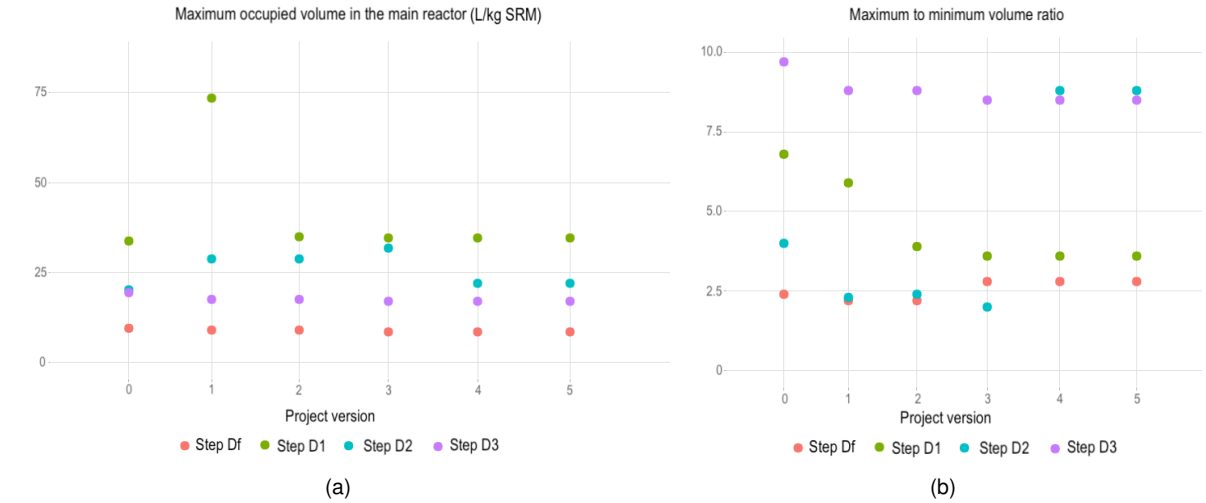


Figure 4.3: Data plots with maximum occupied volumes in the main reactor (a) and maximum to minimum volume ratios (b) for each version of project *D*, which includes each revision of its process steps (described in Table 4.1). These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.

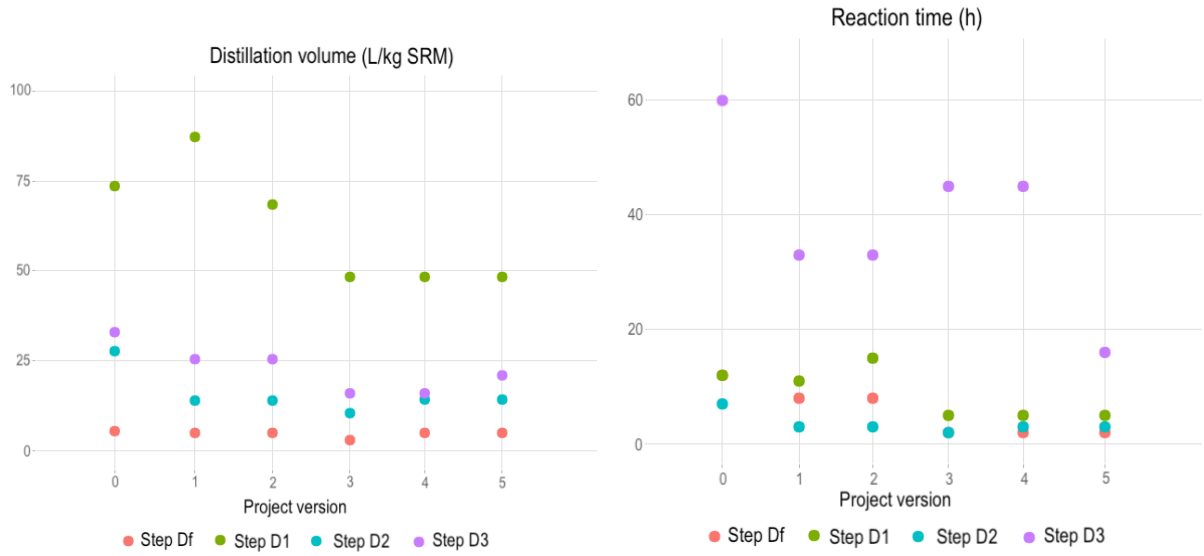


Figure 4.4: Data plots with distillation volumes (a) and reaction time values (b) for each version of project *D*, which includes each revision of its process steps (described in Table 4.1). These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.

4.1.3 Process Results

Concerning the distillation operation (see Figure 4.4(a)), the most significant changes were made to step *D1*, where process *D1-01* exhibited a higher distillation volume, consistent with its verified elevated maximum volume occupied in the main reactor (see Figure 4.3(a)), that would mean higher volumes of solvent to extract. With its last process revision (i.e., *D1-03*), a remarkable amount of distillation volume was reduced, due to an optimization in the number of distillations required. As described previously in subsection 4.1.2, process *D2-03* did exhibit a slight increase in distillation volume (about 4 L/kg), impacting its volume ratio. Besides this, all steps were able to either maintain or reduce their distillation volume, when compared with the Assessment phase.

In terms of reaction time (see Figure 4.4(b)), all final process revisions were optimized, when compared with the Assessment technique's requirement, particularly with step *D3*, which achieved the most reaction time reduction in its final process revision.

Concerning analytical load (see Figure 4.5), an overall increase in the number of IPC's required for each step was demonstrated, when compared with the Assessment phase, possibly due to a higher need for control to properly monitor these processes, and achieve a higher quality, which is one of the reasons most companies outsource their development processes to Hovione. Step *D1* seems to be the exception, with a remarkable reduction of IPC's needed, which certainly helped unburden its process.

Regarding the number of separation phases and pH adjustments, only step *Df* differed from its first process revisions, with an increase in the number of these operations since process *Df-02*. Additionally, in terms of filtration procedures, this process step *Df-02* suffered a replacement of its filtration stage for a more specific charcoal filter, thus also requiring a polish filtration to eliminate any activated carbon molecules that the previous revisions did not need (on account of the absence of a crystallization stage).

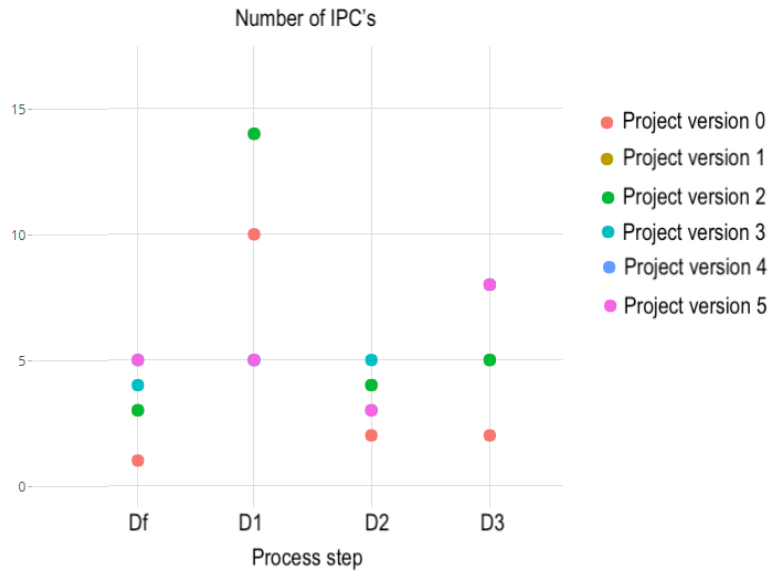


Figure 4.5: Data plot with number of IPC's for each step of project *D*, which includes each project version (described in Table 4.1). These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.

Possibly, these modifications to the final step of this API production, although process burdening, allowed for its overall optimization, specially in the form of higher values of MY and purity achieved (see Figure 4.1).

4.1.4 Raw Materials and Health, Safety, and Environment Results

In terms of Solvents ICH classification, the only modification verified was in step *D2*, with an alteration in the technique for process *D2-03* which replaced two class 3 solvents for other ICH class 2 solvents (i.e., methanol and dichloromethane). As discussed previously in subsection 3.3.1.4, these substances are very efficient organic solvents/reagents for several applications, thus perhaps this alteration allowed for this process's optimization with regard to workup procedures, that would translate itself in an improved MY (as seen in Figure 4.1(a)), as long as the purification procedures ensure the full removal of these toxic solvents from the product.

Regarding the REACH regulation, the only modification was in step *D1*, where process *D1-02* exhibited a change in the manufacturing technique to include a component in the candidate list for restrictive use (i.e., dimethylacetamide), however, properly replaced in the following and final process revision.

Concerning safety precautions for highly exothermic reactions, the only alteration made to this project was in step *D2*, which did not have a highly exothermic reaction at first, however, since process *D2-03*, a component was substituted for another that manifested an exothermic reaction whilst its addition to the reaction mixture (i.e., methanol replacing ethanol), therefore had to be manageable with a controlled addition.

4.2 Green Metrics Analysis

In this section, the chosen and evaluated green chemistry metrics are analysed more closely. No changes were introduced to step economy (SE) throughout each project version, therefore this criterion was not discussed through this type of evaluation. Additionally, due to lack of data from laboratory record sheets, project version's 1 and 2 were not analysed in terms of their laboratory E-factor, and, consequently, their laboratory classification was not considered. Reaction mass efficiency (RME) and quality service level (QSL) were not analysed through this type of evaluation for insufficient relevance to the study.

4.2.1 Atom Economy Results

As explained in section 3.1, atom economy (AE) is not expected to suffer modifications after the chemical development studies, however, as a project arrives at the outsourcing company, its chemists may have some creative freedom to optimize their processes. An experiment of this type is observed in Figure 4.6, where all steps from project *D* maintained their AE value, except for step *D1*. In process *D1-01*, AE decreased due to a change in the SRM of this process (particularly, a salt version was used instead of the freebase version of the SRM molecule); in process *D1-02*, the original freebase SRM was introduced once again, but another reactant was replaced by a higher-molecular weight one, thus still evidencing a slightly decreased AE; finally, in process *D1-03*, every reactant and SRM molecule was restored to the initial Assessment's proposal, this way demonstrating equal AE values, which were the highest.

Regarding the overall project (see Figure 4.6), the progression of AE values over the several project versions was consistent with the differences demonstrated by step *D1*.

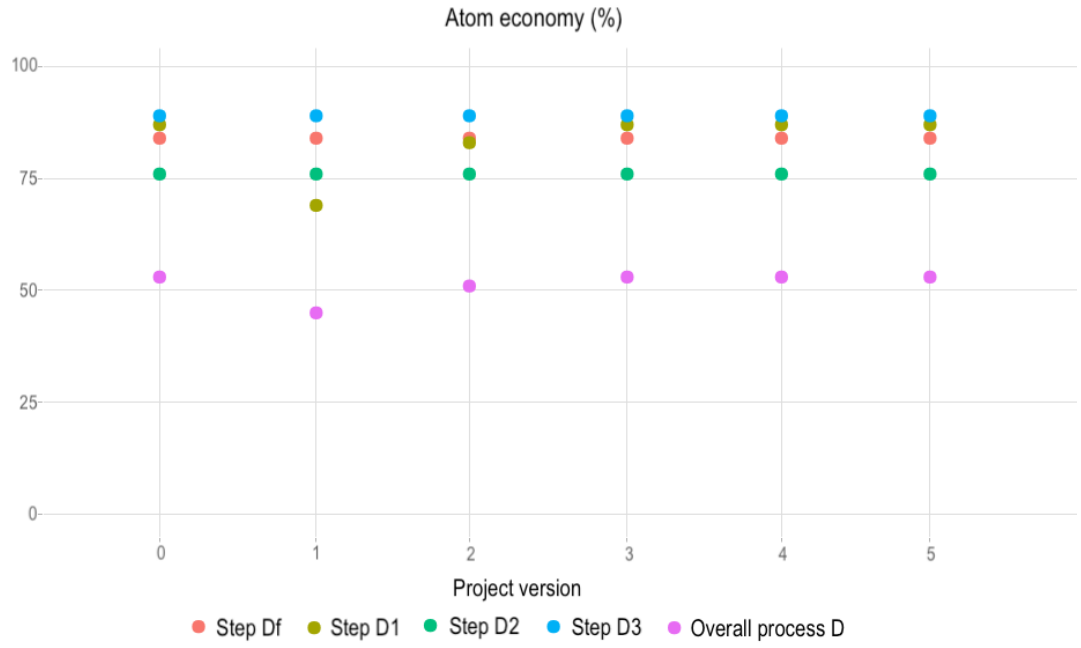
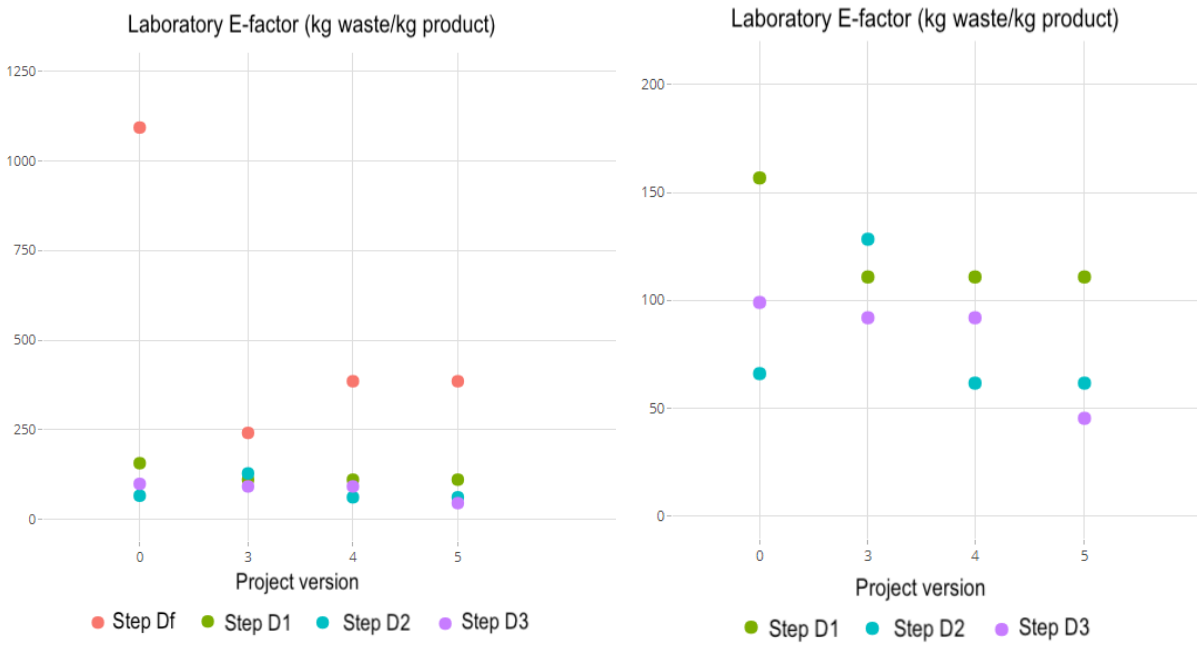


Figure 4.6: Data plot with atom economy values for each version of project *D*, which includes each revision of its process steps (described in Table 4.1) and overall project value. These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.



(a) (b) Zoomed in

Figure 4.7: Data plots with laboratory E-factor values for each version of project *D*, which includes each revision of its process steps (described in Table 4.1). This criterion was not evaluated for project versions 1 and 2. These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.

4.2.2 Environmental Factor Results

In terms of laboratory E-factor (see Figure 4.7), all steps, except for step *D2*, managed to reduce their Assessment phase's E-factor, on account of an optimization both in number and amount of solvents/solutions used. Furthermore, by analysing Figure 4.8, one can see the overall E-factor decreasing alongside the various project versions, evidencing a definitely more efficient process than the one proposed by the client.

Looking over the internal values from the different project versions, only step *Df*, ended up with a higher E-factor than the one achieved by process *Df-02*. Although no other components were added to the technique, and the MY from process *Df-03* even improved over the one obtained in *Df-02*, a higher volume of solvents was introduced to the process, specially due to an additional purification stage. This perhaps allowed for a better recovery of the API, although at the expense of its greenness's efficiency.

Regarding the manufacturing E-factor values (see Figure 4.9), a progressive decrease in the environmental load of each production batch was clearly demonstrated, with the exception of batch 5 from process *Df-03*, which showed an enormous increase when compared to its previous process revisions – as evidenced with its laboratory value. Nevertheless, in the final validation batches, this process's performance was optimized, and reached a somewhat constant level. In fact, all validation batches from each step achieved constant levels (with coefficients of variation of 3%, 2%, 2%, and 6% for steps *D1*, *D2*, *D3*, *Df*, respectively), which is quite good in order to demonstrate consistency between batches for the FDA's commercial approval.

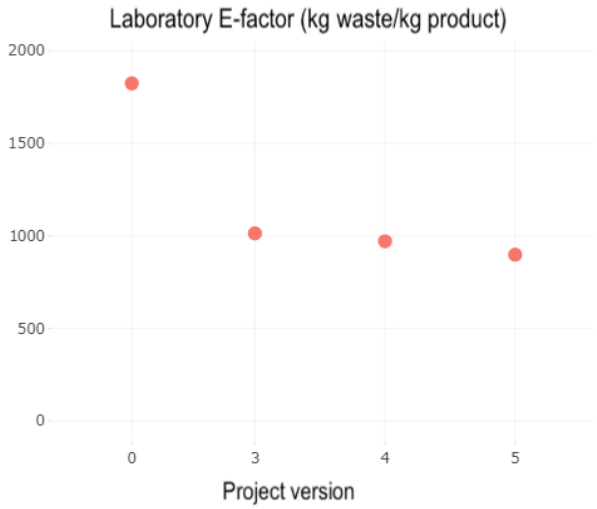
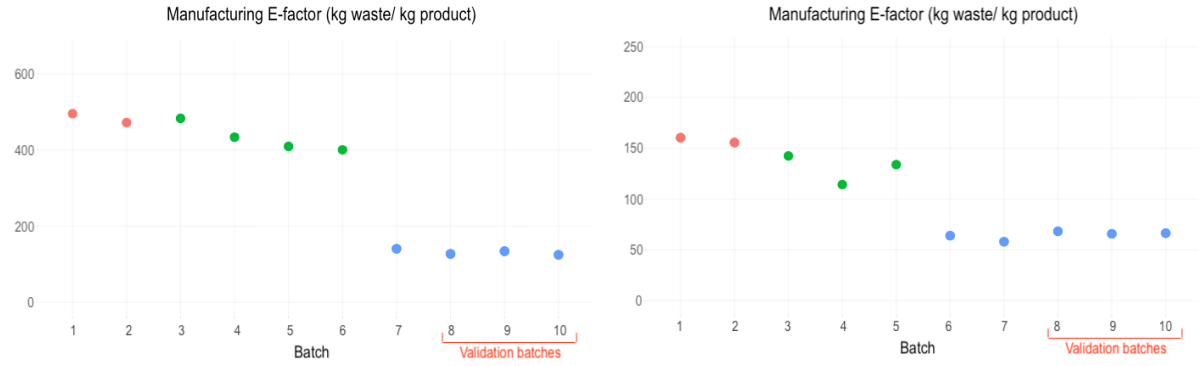
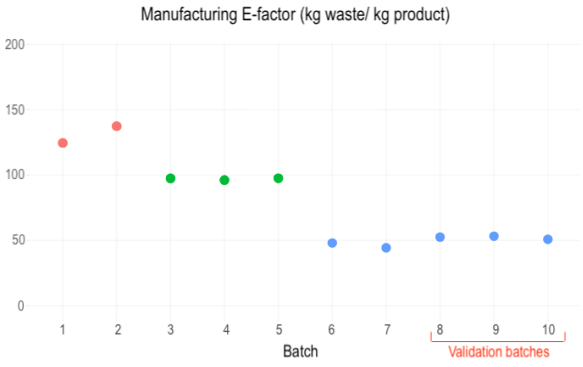


Figure 4.8: Data plot with overall laboratory E-factor values for each version of project *D*. This criterion was not evaluated for project versions 1 and 2. These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.



(a) Step D1

(b) Step D2



(c) Step D3

(d) Step Df

Figure 4.9: Data plots with manufacturing E-factor values for each production batch of project *D*'s steps, which includes process revisions 1, 2 and 3 (in red, green and blue colours, respectively). Batches 8,9 and 10 integrated the API validation campaign. These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.

4.2.3 Volume-Time-Output Results

Concerning the volume-time-output (VTO) values for each process step (see Figure 4.10), one can see an improvement over this metric alongside each process revision, 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 discussed in subsection 1.1.3.

While evaluating each process closely, step *D1* presented a clear development towards a more efficient manufacturing process, including great consistency between its validation batches (with a coefficient of variation of 4%). Step *D3* also exhibited improvements over time, with the final process revision achieving its lowest values, and a coefficient of variation of 4% for the validation batches.

Step *D2* presented a slightly increased VTO for the validation batches when compared to the previous process revision, however still demonstrating low data dispersion between them (with a coefficient of variation of 3%). The outlier value for batch 6 was due to a smaller batch size performed in the same nominal volume vessels as the following batch. Since VTO is scale-dependent, it can only be properly compared between batches with equal campaign sizes.

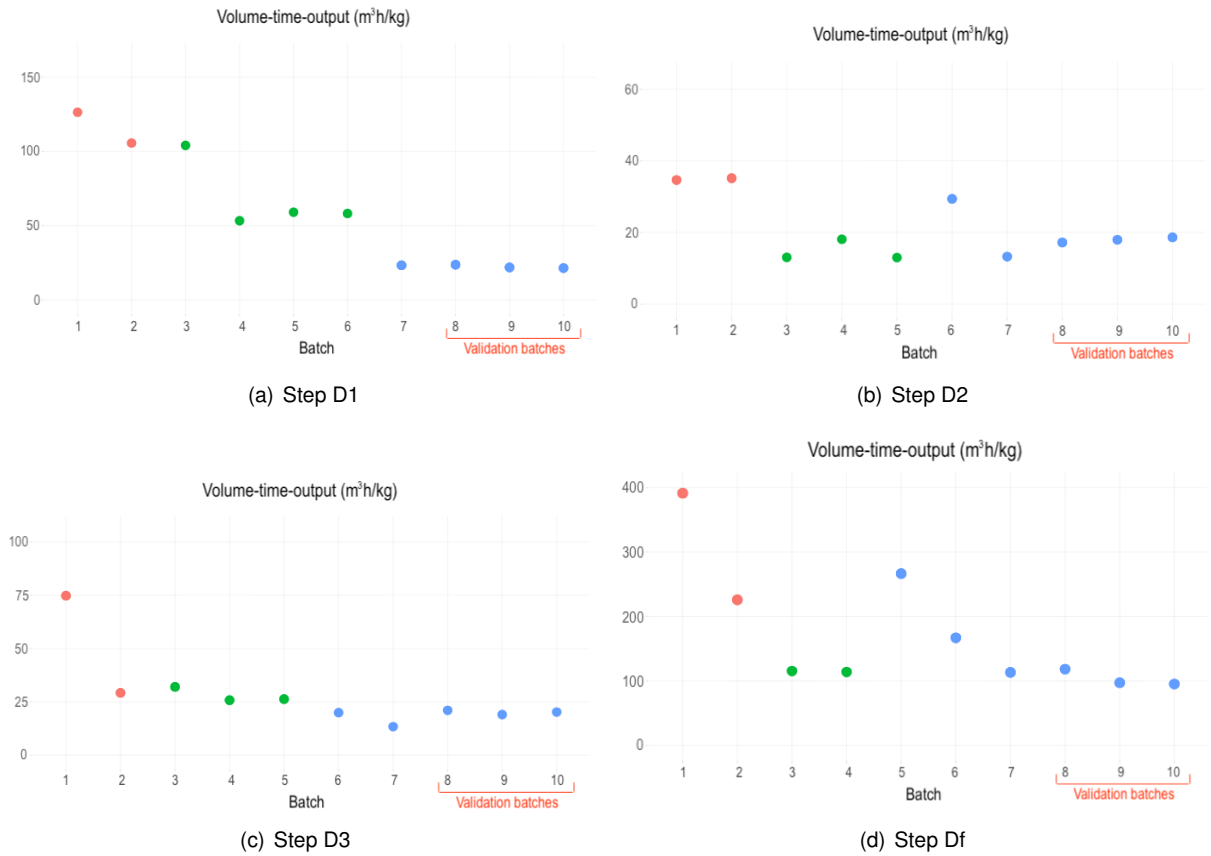
Finally, step *Df* also exhibited improvements alongside its process revisions, although some issues occurred with process *Df-03*. Batch 5 exhibited the lowest yield from that process revision, which led to a higher VTO (as with E-factor, in subsection 4.2.2). The following batches presented increasingly higher yields, however, the first validation batch ended up taking two more days than the scheduled time, which resulted in a higher VTO value than the other validation batches, thus allowed for a lower consistency between them (with a coefficient of variation of 10%).

Interestingly, when comparing VTO values for *D1-02* and *D1-03*, this last process revision provided lower values mainly because of a cycle time optimization, which could also be correlated with the far lower number of IPC's required for this step (see Figure 4.5).

4.2.4 Process Excellence Index for Molar Yield and Cycle Time Results

Process excellence indexes are very useful when targeting validation batches and already established commercial processes, due to their potential for reproducibility and robustness studies. In general, when analysing Figure 4.11, it is evident that the final process revision of each step did not present the higher reproducibility values, in terms of molar yield (PEIMY) and cycle time (PEICT). As seen in Figures 4.9 and 4.10, not all batches from process revision 3 were final validation ones, besides the fact that some of them even revealed production issues which might have affected these metrics.

Therefore, in a separate analysis (see Figure 4.12), one can see that much higher PEICT values were obtained when only considering the validation campaign of each step, demonstrating the necessary 3-batch consistency for commercial approval. For PEIMY values, this differentiation appears only significant with step *Df*, by excluding the low yield obtained in batch 5, as described in subsection 4.2.3.



(a) Step D1 (b) Step D2

(c) Step D3 (d) Step Df

Figure 4.10: Data plots with volume-time-output values for each production batch of project *D*'s steps, which includes process revisions 1, 2 and 3 (in red, green and blue colours, respectively). Batches 8,9 and 10 integrated the API validation campaign. These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.

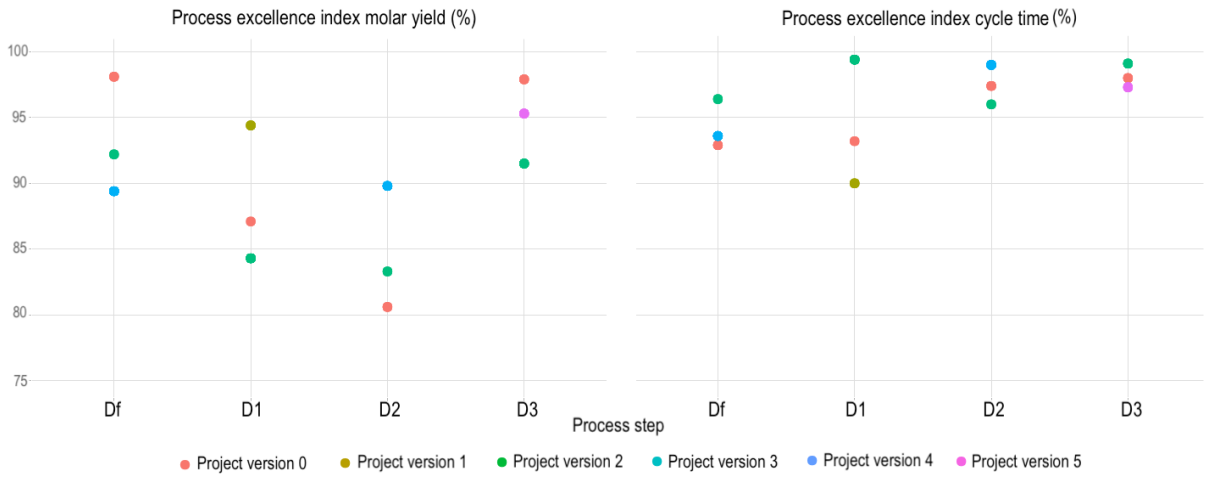


Figure 4.11: Data plots with process excellence index values for molar yield and cycle time (zoomed in) for each step of project *D*, which includes each project version (described in Table 4.1). These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.

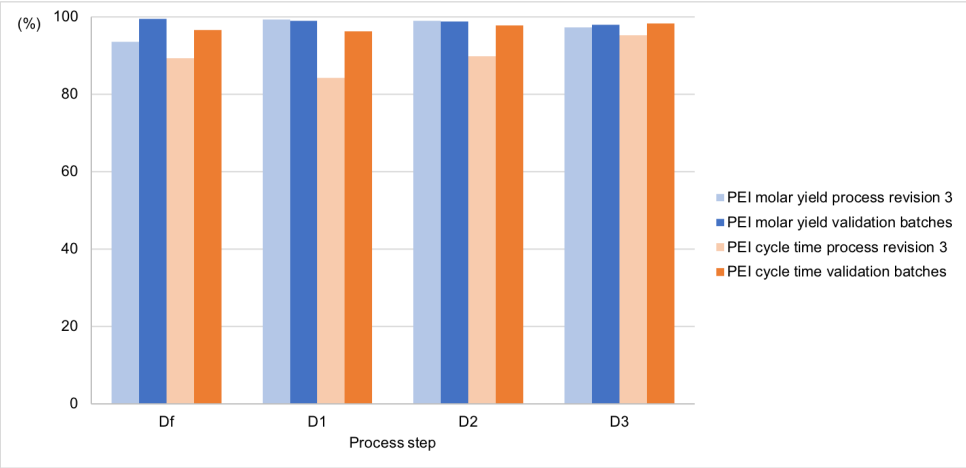


Figure 4.12: Graphic representation with results of process excellence index values for molar yield and cycle time (in blue and orange, respectively) for each step of project *D*, considering the results for all batches from process revision 3 and only final validation batches.

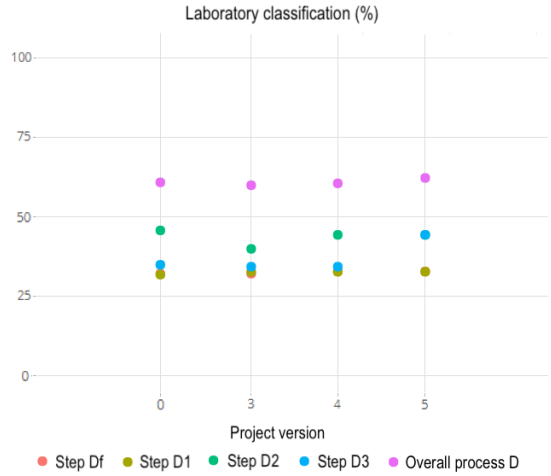
4.3 Classification Results

Regarding the laboratory classification for each project version evaluated (see Figure 4.13(a)), all steps, except for *D2*, demonstrated a slight improvement, when comparing the Assessment phase's with the final project version's classification. Looking over the company's internal progress, all steps exhibited improvements alongside each project version, except for step *D1*, on account of lack of information on project versions 1 and 2. In terms of EcoScale total score (see Figure 4.13(b)), it is indicated that step *D1* and *D3* achieved the best progression towards improvement, although step *D2* had the highest EcoScale score, regardless of its process revision. Step *Df* achieved a good EcoScale score, in spite of the fact that this step generally exhibited less efficient values for the rest of the evaluated metrics, namely E-factor and VTO – it is clear the positive contribution of several metrics on this holistic approach at evaluating processes, specially one as broadening as the EcoScale.

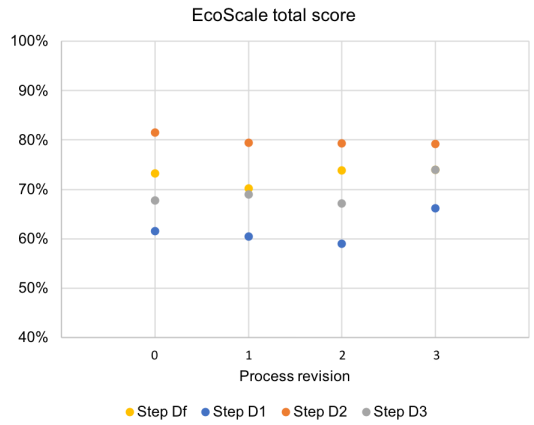
Along the course of this evaluation, some issues arouse from the comparison of projects with their respective client's technique, which might have happened due to an insufficient offer of hard data from their laboratory experiments, often only with typical process values available, making this evaluation exercise not fully accurate.

As with the laboratory classification, the manufacturing classification (see Figure 4.14) revealed almost constant values for all steps, with only slight differences between each process revision which, nevertheless, indicated an overall final improved process for each step.

To conclude, these final results by themselves did not demonstrate any relevant improvements over process revisions, although each criteria evaluated individually revealed these process modifications, and allowed for an adequate and useful evaluation. These final classifications for each process revision appeared to not be sensitive enough to detect the process modifications displayed and discussed in the previous sections, possibly due to an absence of a fully optimized model, as proposed in subsection 3.3.3.

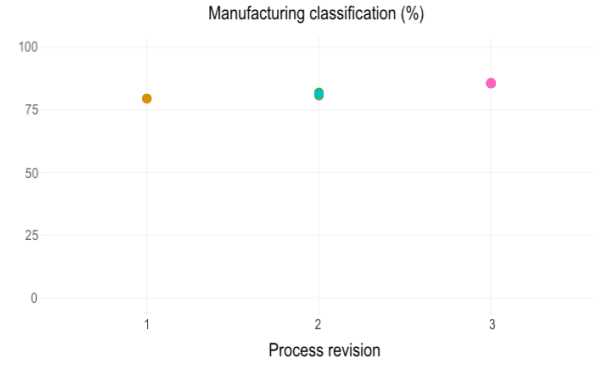


(a) This criterion was not evaluated for project versions 1 and 2. The values obtained by step *Df* are equal to the ones obtained by *D1*.

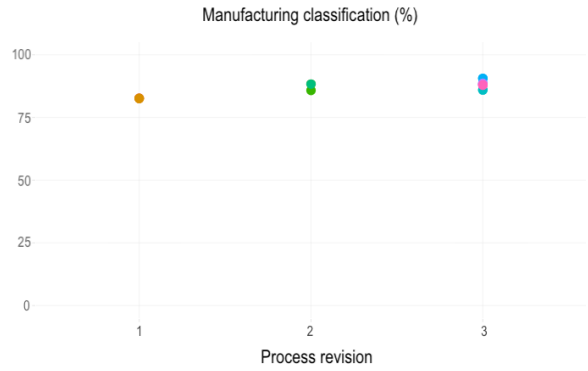


(b) The value obtained by process *D3-03* is equal to the one obtained by *Df-03*.

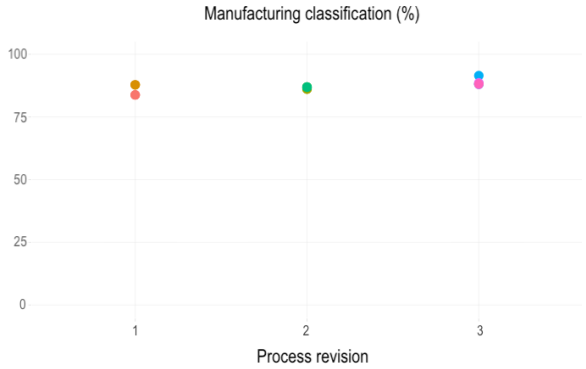
Figure 4.13: Data plots for laboratory classification values (a) and EcoScale total score values (b) (zoomed in) for each step of project *D*, per project version and process revision, respectively (described in Table 4.1).



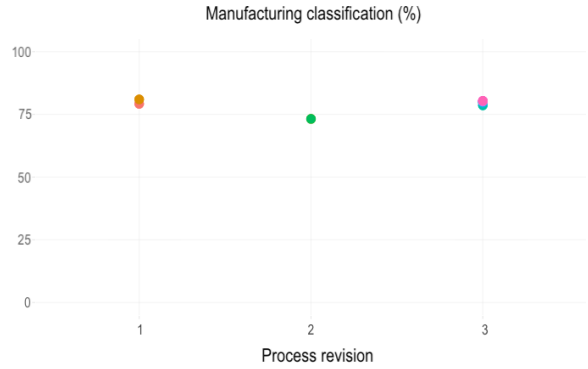
(a) Step D1



(b) Step D2



(c) Step D3



(d) Step Df

Figure 4.14: Data plots with manufacturing classification values for each production batch of project *D*'s steps. Each dot represents one production batch. These data were evaluated through the knowledge-based assessment tool, and this figure provided by its user interface.

Chapter 5

Conclusions

This final chapter presents a retrospective look over all the work put into the development of this knowledge-based assessment tool for pharmaceutical processes, including its implementation on several drug development projects at Hovione FarmaCiência S.A..

5.1 Achievements

With growing competition between pharmaceutical CDMO's, adding to the fact that this industry inherently presents various risks in succeeding (see subsection 1.1.1), these challenges must be overcome through a progression towards the Industry 4.0, with reliable access and management over the industry's knowledge across the lifecycle of a pharmaceutical product. Following this line of reasoning, two main objectives were proposed for this present work.

The first was the development of a data-driven tool that would allow for the quantification of chemical processes' efficiency, by embracing productivity, quality, greenness, and robustness, this way quantifying an otherwise subjective evaluation, particularly in the case of the EcoScale analysis. This objective was successfully achieved, as described in chapter 2, and the calculation of each metric brought additional value into understanding these chemical processes. Besides this measurement, the knowledge-based assessment tool allowed for the essential establishment of easily accessible databases with comprehensive knowledge gathered by this company over time.

The other central objective proposed was demonstrating the assessment tool's implementation in classifying chemical processes, with consequent comparison between them, which was also achieved. Various projects with different chemistries and processes were compared in section 3.3, that provided a global overview of the company on how it proceeds in drug development processes. The assignment of target ranges and score weightings to evaluate the relative importance of each metric was crucial for this classification approach, apart from the gained asset of being able to visualize what constitutes a good chemical manufacturing process, in terms of this company's priorities, as proposed by Dach et al. [11].

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 (in section 3.2); 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 (in chapter 4).

5.2 Future Work

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.

Firstly, as explained in subsection 3.3.3, the model designed for the calculation of final classifications (laboratory and manufacturing) must be optimized, namely what criteria contributes to each classification, and their corresponding weightings, since most of them were initial best guesses. The results provided by the overall project evaluation and the case study project were mostly inconclusive in terms of understanding if a given process is in fact ”good” or not, with lack of sensitivity to show process modifications, thus a validation of this assessment tool's model was not possible.

For this optimization to be possible , more projects must be evaluated, and more data from each of them has to be gathered, this way evaluating the company's reality before assessing target ranges and weightings. One potential approach could be dynamically assigning target ranges, depending on what type of process/chemistry to be evaluated. For example, as explained in subsection 3.3.1.1, process *A3* presented a low score for its molar yield evaluation, which is inherent in a chiral resolution, therefore, this type of reaction's molar yield should have a more realistic goal associated with it.

Additionally, the proposed analysis per type of reaction (discussed in subsection 3.3.3.1) still requires improvements for its implementation, namely a recognized database for types of chemistry. Regardless, this sort of evaluation would be deeply valued in understanding the influence of chemical synthesis on the various process criteria chosen for the assessment tool, and the possibility of assessing clusters of data would definitely guide the assignment of target values based of historical company knowledge.

To improve the assessment tool's evaluating skills, and enable the capture of as much process knowledge as possible, some upgrades can be performed. For instance, 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, as with 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), as well as having new company clients input their Assessment phase's data, to prevent lack of reliable information (as explained in section 4.3).

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 [56], integrating commonly calculated metrics as process mass intensity and volume-time-output, 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. It also presents an hierarchical data structure organized by projects, campaigns, steps, and batches, without neglecting the necessity for simple and user-friendly data entry frameworks. 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.

References

[1] P. Yegneswaran, M. P. Thien, and M. J. Lipa. Why Knowledge Management Is Good Business. In N. Calnan, M. J. Lipa, P. E. Kane, and J. C. Menezes, editors, *A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry*, chapter 1. CRC Press, 2017.

[2] N. Calnan, M. J. Lipa, P. E. Kane, and J. C. Menezes. Conclusion. In N. Calnan, M. J. Lipa, P. E. Kane, and J. C. Menezes, editors, *A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry*. CRC Press, 2017.

[3] D. Taylor. The Pharmaceutical Industry and the Future of Drug Development. In R. E. Hester and R. M. Harrison, editors, *Pharmaceuticals in the Environment*, chapter 1. The Royal Society of Chemistry, 2016.

[4] A. Daemmrich and M. E. Bowden. A Rising Drug Industry: Pharmaceuticals since 1870. *Chemical & Engineering News*, 83(25):28–42, 2005.

[5] The US Food and Drug Administration. The History of FDA's Fight for Consumer Protection and Public Health. `https://www.fda.gov/aboutfda/history/default.htm`, 2018. [Online; accessed: 2018-06-12].

[6] *ICH Topic Q7: Good Manufacturing Practice for Active Pharmaceutical Ingredients*. European Medicines Agency, 2000.

[7] G. A. V. Norman. Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs. *JACC: Basic to Translational Science*, 1(3):170–179, 2016.

[8] The US Food and Drug Administration. The Drug Development Process. `https://www.fda.gov/ForPatients/Approvals/Drugs/default.htm`, 2018. [Online; accessed: 2018-06-12].

[9] A. D. Braem, J. T. Sweeney, and J. W. Tom. Process Scale-up and Assessment. In D. J. am Ende, editor, *Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing*, chapter 20. John Wiley & Sons, Inc., 2011.

[10] J. C. Hamm, M. M. Miller, T. Ramsey, R. L. Schild, A. Stewart, and J. W. Tom. Kilo Lab and Pilot Plant Manufacturing. In D. J. am Ende, editor, *Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing*, chapter 22. John Wiley & Sons, Inc., 2011.

[11] R. Dach, J. J. Song, F. Roschangar, W. Samstag, and C. H. Senanayake. The Eight Criteria Defining a Good Chemical Manufacturing Process. *Organic Process Research & Development*, 16(11): 1697–1706, 2012.

[12] *Guidance for Industry on Process Validation: General Principles and Practices*. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research and Center for Veterinary Medicine, 2011.

[13] S. Pommeranz. Recent Statement by FDA on Process Validation - 3-Batch Validation Obsolete? https://www.gmp-compliance.org/gmp-news/recent-statement-by-fda-on-process-validation-3-batch-validation-obsolete, 2010. [Online; accessed: 2018-07-04].

[14] H. Yang. How Many Batches Are Needed for Process Validation under the New FDA Guidance? *PDA Journal of Pharmaceutical Science and Technology*, 67(1):53–62, 2013.

[15] K. D. Tait. Pharmaceutical Industry. In J. M. Stellman, editor, *Encyclopaedia of Occupational Health and Safety*, chapter 79. International Labour Organization, 1998.

[16] Taylor, Phil. Outsourcing of production gaining pace in big pharma. https://www.in-pharmatechnologist.com/Article/2008/05/27/Outsourcing-of-production-gaining-pace-in-big-pharma, 2008. [Online; accessed: 2018-07-10].

[17] E. M. Cordi. Design of Distillation and Extraction Operations. In D. J. am Ende, editor, *Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing*, chapter 12. John Wiley & Sons, Inc., 2011.

[18] R. R. McKeown, J. T. Wertman, and P. C. Dell'Orco. Crystallization Design and Scale-Up. In D. J. am Ende, editor, *Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing*, chapter 13. John Wiley & Sons, Inc., 2011.

[19] F. X. McConville. Scale-Up Dos and Dont's. In D. J. am Ende, editor, *Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing*, chapter 21. John Wiley & Sons, Inc., 2011.

[20] US Environmental Protection Agency. Granular Activated Carbon. https://web.archive.org/web/20140710160845/http://iaspub.epa.gov/tdb/pages/treatment/treatmentOverview.do?treatmentProcessId=2074826383, 2017. [Online; accessed: 2018-09-11].

[21] F. D. Antia. The Design and Economics of Large-Scale Chromatographic Separations. In D. J. am Ende, editor, *Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing*, chapter 18. John Wiley & Sons, Inc., 2011.

[22] Y. Wang. Extracting Knowledge from Failed Development Programmes. *Pharmaceutical Medicine*, 26(2):91–96, 2012.

[23] T. Buclin, M. Nicod, and S. Kellenberger. Dosage regimen - Pharmacokinetics (online resource for students from the Faculté de biologie et de médecine, Université de Lausanne). https://sepia.unil.ch/pharmacology/index.php?id=76, 2009. [Online; accessed: 2018-07-09].

[24] D. J. am Ende. Chemical Engineering in the Pharmaceutical Industry: An Introduction. In D. J. am Ende, editor, *Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing*, chapter 1. John Wiley & Sons, Inc., 2011.

[25] Industry Standard Research. Two-thirds of pharmaceutical manufacturing is outsourced; preferred providers pick up largest share. https://www.isrreports.com/outsourced-pharmaceutical-manufacturing/, 2016. [Online; accessed: 2018-07-10].

[26] P. T. Anastas and J. C. Warner. *Green Chemistry: Theory and Practice*, volume 30. Oxford University Press, 2000.

[27] J. L. Tucker. Green Chemistry, a Pharmaceutical Perspective. *Organic Process Research & Development*, 10(2):315–319, 2006.

[28] A. D. Curzons, D. J. C. Constable, D. N. Mortimer, and V. L. Cunningham. So you think your process is green, how do you know? – Using principles of sustainability to determine what is green – a corporate perspective. *Green Chemistry*, 3(1):1–6, 2001.

[29] F. Roschangar, R. A. Sheldon, and C. H. Senanayake. Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level ^{TM} concept. *Green Chemistry*, 17(2): 752–768, 2015.

[30] M. Tobiszewski, M. Marć, A. Galuszka, and J. Namieśnik. Green Chemistry Metrics with Special Reference to Green Analytical Chemistry. *Molecules*, 20(6):10928–10946, 2015.

[31] B. M. Trost. The atom economy – a search for synthetic efficiency. *Science*, 254(5037):1471–1477, 1991.

[32] D. J. C. Constable, A. D. Curzons, and V. L. Cunningham. Metrics to 'green' chemistry – which are the best? *Green Chemistry*, 4(6):521–527, 2002.

[33] F. Calvo-Flores. Sustainable Chemistry Metrics. *ChemSusChem: Chemistry & Sustainability Energy & Materials*, 2(10):905–919, 2009.

[34] R. A. Sheldon. Organic Synthesis - Past, Present and Future. *Chemistry and Industry*, (23):903–906, 1992.

[35] R. A. Sheldon. The E Factor: fifteen years on. *Green Chemistry*, 9(12):1273–1283, 2007.

[36] R. A. Sheldon. The E factor 25 years on: the rise of green chemistry and sustainability. *Green Chemistry*, 19(1):18–43, 2017.

[37] R. A. Sheldon. Consider the environmental quotient. *CHEMTECH*, 24(3), 1994.

[38] T. Hudlickly, D. Frey, C. Claeboe, L. Brammer Jr, et al. Toward a 'reagent-free' synthesis. *Green Chemistry*, 1(2):57–59, 1999.

[39] C. Jiménez-González, C. Ollech, W. Pyrz, D. Hughes, Q. B. Broxterman, and N. Bhathela. Expanding the Boundaries: Developing a Streamlined Tool for Eco-Footprinting of Pharmaceuticals. *Organic Process Research & Development*, 17(2):239–246, 2013.

[40] J. Andraos. Unification of reaction metrics for green chemistry: Applications to reaction analysis. *Organic Process Research & Development*, 9(2):149–163, 2005.

[41] P. A. Wender, M. P. Croatt, and B. Witulski. New reactions and step economy: The total synthesis of (±)-salsolene oxide based on the type II transition metal-catalyzed intramolecular [4+4] cycloaddition. *Tetrahedron*, 62(32):7505–7511, 2006.

[42] P. A. Clarke, S. Santos, and W. H. Martin. Combining pot, atom and step economy (PASE) in organic synthesis. Synthesis of tetrahydropyran-4-ones. *Green Chemistry*, 9(5):438–440, 2007.

[43] K. Van Aken, L. Strekowski, and L. Patiny. Ecoscale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters. *Beilstein journal of organic chemistry*, 2:3, 2006.

[44] T. T. Phan, C. Gallardo, and J. Mane. GREEN MOTION: a new and easy to use green chemistry metric from laboratories to industry. *Green Chemistry*, 17(5):2846–2852, 2015.

[45] P. T. Anastas and R. L. Lankey. Life cycle assessment and green chemistry: the yin and yang of industrial ecology. *Green Chemistry*, 2(6):289–295, 2000.

[46] F. Roschangar, Y. Zhou, D. J. Constable, J. Colberg, D. P. Dickson, P. J. Dunn, M. D. Eastgate, F. Gallou, J. D. Hayler, S. G. Koenig, et al. Inspiring process innovation via an improved green manufacturing metric: iGAL. *Green Chemistry*, 20(10):2206–2211, 2018.

[47] *Impurities: Guideline for Residual Solvents Q3C(R6)*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2016.

[48] European Chemicals Agency. Substances of very high concern identification. `https://echa.europa.eu/substances-of-very-high-concern-identification-explained`, 2018. [Online; accessed: 2018-09-11].

[49] European Commission. REACH Implementation. `http://ec.europa.eu/environment/chemicals/reach/implementation_en.htm`, 2017. [Online; accessed: 2018-09-11].

[50] M. Tokunaga, J. F. Larrow, F. Kakiuchi, and E. N. Jacobsen. Asymmetric catalysis with water: efficient kinetic resolution of terminal epoxides by means of catalytic hydrolysis. *Science*, 277(5328): 936–938, 1997.

[51] M. Rossberg, W. Lendle, G. Pfleiderer, A. Tögel, T. R. Torkelson, and K. K. Beutel. *Chloromethanes*, pages 15–39. American Cancer Society, 2011.

[52] J. Ott, V. Gronemann, F. Pontzen, E. Fiedler, G. Grossmann, D. B. Kersebohm, G. Weiss, and C. Witte. *Methanol*, pages 2–23. American Cancer Society, 2012.

[53] I. F. McConvey, D. Woods, M. Lewis, Q. Gan, and P. Nancarrow. The importance of acetonitrile in the pharmaceutical industry and opportunities for its recovery from waste. *Organic Process Research & Development*, 16(4):612–624, 2012.

[54] D. Bormett. High-potency APIs: containment and handling issues. `http://www.pharmtech.com/high-potency-apis-containment-and-handling-issues?id=&sk=&date=&pageID=4`, 2008. [Online; accessed: 2018-09-30].

[55] Y. Hayashi. Pot economy and one-pot synthesis. *Chemical science*, 7(2):866–880, 2016.

[56] D. Kaiser, J. Yang, and G. Wuitschik. Using data analysis to evaluate and compare chemical syntheses. *Organic Process Research & Development*, 22(9):1222–1235, 2018.

Appendix A

EcoScale Framework

The EcoScale presented in this section was implemented in the knowledge-based assessment tool developed and presented in this work. Its calculation is fully explained in subsection 2.1.2.

Due to confidentiality constraints, this appendix could not be disclosed for this document's public version.

Appendix B

Multipoint Analysis System

This appendix contains a comprehensive list of each green metric applied in the knowledge-based assessment tool, with corresponding target values, colour codes and score system associated with each target, and weighting contribution of each metric that allows for a global evaluation of both classification categories, i.e., laboratory and manufacturing.

Due to confidentiality constraints, this appendix could not be disclosed for this document's public version.

Appendix C

Functional Requirements Specification

This appendix exhibits the answering template for the knowledge-based assessment tool (a Microsoft Excel file) which is uploaded to the software that will automatically calculate each evaluating criterion, and quantify the classification for both laboratory and manufacturing categories for a certain API project. The template presented here is randomly filled out, just for its visual demonstration, and is composed of three pages, an EcoScale answer sheet (section C.1), a materials data sheet (section C.2), and a manufacturing data sheet (section C.3).

Due to confidentiality constraints, this appendix could not be disclosed for this document's public version.