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INDEX

1 EXECUTIVE SUMMARY 6

2 INTRODUCTION 7

3 LEGISLATION THAT APPLIES TO HUMAN MEDICINES WITHIN EU FRAMEWORK... 8

3.1 CURRENT REGULATORY EU FRAMEWORK FOR HUMAN MEDICINES 8

3.2 REVISION OF THE EU GENERAL PHARMACEUTICALS LEGISLATION 12

4 INPUTS FOR GREENER APPROACHES FOR PHARMACEUTICALS 15

4.1 FIRST INPUT – THE PHARMACEUTICAL SUPPLY CHAIN 15

4.2 SECOND INPUT – ENVIRONMENTAL RISK ASSESSMENT 16

4.3 THIRD INPUT – THE MEDICINES ARE VITAL FOR HUMAN BEINGS 17

5 REGULATORY STATE OF ART FOR PHARMACEUTICAL DEVELOPMENT 18

6 ETERNAL STAKEHOLDERS CASE STUDIES 21

6.1 CASE STUDY SELECTED FOR A GQTPP 22

6.2 CASE STUDIES OVERVIEW AND PROGRESS STATUS 22

7 FROM QTPP TO GQTPP IN CONTROL STRATEGY 27

7.1 QTPP, CQAS AND MANUFACTURING PROCESS SCHEME 27

7.2 PROMOTION OF QTPP TO GQTPP 33

8 CONCLUSION 35

REFERENCES 37

INDEX of tables

Table 1. Overview of ETERNAL stakeholders case studies 23

Table 2 – QTPP elements (Case study 1) 28

Table 3 – CQAs and justification (Case study 1) 29

Table 4. Relation of the manufacturing process and the CQAs (1/2) 31

Table 5. Relation of the manufacturing process and the CQAs (2/2) 32

Table 6. gQTPP proposal – Case 1 33

INDEX of figures

Figure 1. ETERNAL objectives mapping of how the ETERNAL objectives are pertinent to the work programme 6

Figure 2. Concept diagram for pharmaceutical development 19

Figure 3. ETERNAL case studies objectives 22

Figure 4. Process scheme for establishing the CQAs (ICH Q8 guideline) 27

INDEX of abbreviations

AMR	Antimicrobial Resistance
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
ATMP	Advanced Therapy Medicinal Products
BREF	Best Available Technique Reference Document
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CQA	Critical Quality Attributes
CMC	Chemistry, Manufacturing and Controls
CPP	Critical Process Parameters
CTD	Common Technical Document
CU	Content Uniformity
DMF	Drug Master File
EC	European Commission
EMA	European Medicines Agency

EU	European Union
EPR	Extended Producer Responsibility
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
gBbD	Greener Compliant by Design
gQTPP	Greener Quality Target Product Profile
HCWH	Health Care without Harm
ICH	International Council for Harmonisation
IED	Industrial Emissions Directive
ICP	In-Process Parameter
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NHS	National Health Service
NMT	Not More Than
OTC	Over the Counter
PAT	Process Analytical Technology
PCS	Producer Compliance Scheme
PEC	Predicted Environmental Concentration
Ph. Eur.	European Phamacopoeia
PMDA	Pharmaceuticals and Medical Devices Agency
PRN	Packaging Recovery Notes
PSD	Particle Size Distribution
QbD	Quality by Design
QP	Qualified Person
QTPP	Quality Target Product Profile
SIGRE	Sistema Integrado de Gestión de Residuos de Envases
SWP	Safety Working Party
TAMC	Total Aerobic Microbial Count
TPP	Target Product Profile
TYMC	Total Yeast and Mold Count
UDI	Unique Device Identification
US	United States
USP	United States Pharmacopeia

WHO World Health Organization

1 Summary

The ETERNAL project is a four-year HORIZON Research and Innovation Action with the overall purpose of contributing to sustainable development of pharmaceutical manufacture, use and disposal, by using and promoting full life cycle approaches covering design, manufacture, use, and disposal. This includes assessing the environmental risks of active pharmaceutical ingredients, residues, metabolites, and other chemicals and by-products of the production process. The project consists of four working groups: green manufacturing, digitalization transformation, social awareness and safe use and disposal (Figure 1).

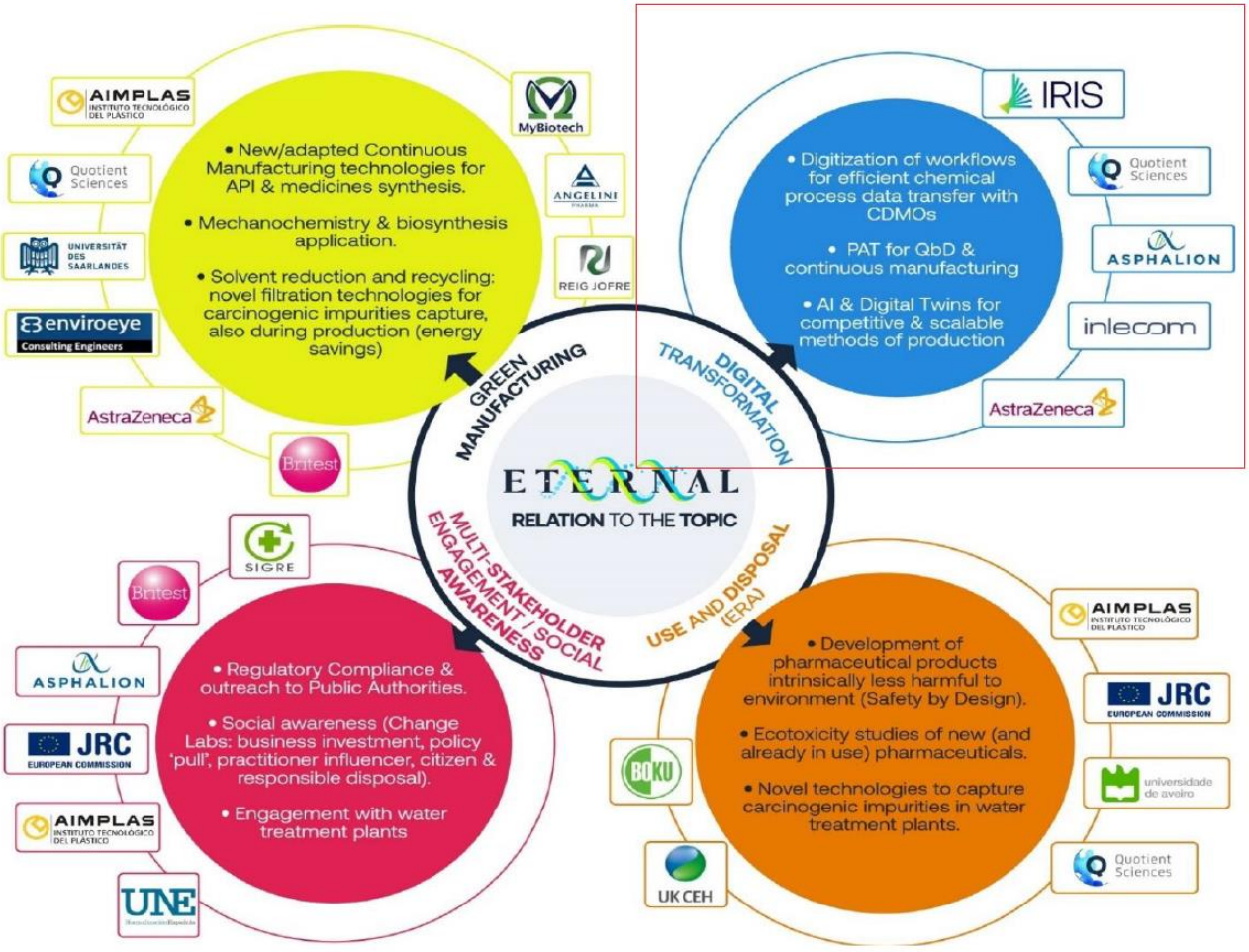

Figure 1. ETERNAL objectives mapping of how the ETERNAL objectives are pertinent to the work programme

Within the scope of the ETERNAL project digitalisation transformation activities, it is expected to prepare, argue and discuss the relation to the regulatory compliance implications regards future pharmaceutical live production and as such ensure that a compliant-by-design approach to the development work is adopted in a cocreation process related not only to the digitalization

innovations of this work package. In this sense, a proposal of the relevant key-drivers and a roadmap of the possible regulatory pathways or relevant regulatory frameworks for the required "compliant-by-design" strategies applying the concepts of "greener design" in Europe is expected to be delivered and the current document is the outcome of such deliverable exercise.

2 Introduction

This document corresponds to deliverable D2.2, which discusses the regulatory framework possibilities, flexibilities, hurdles and pitfalls to implement environmental-oriented compliance by design strategies, in order to support the development of sustainable medicines and/or processes considered green-by-design or greener-by-design.

This deliverable was supposed to be upload on August 31st, 2023. However, in order to maximize the potential application of the concepts discussed throughout this document on the case studies under development within ETERNAL project, it was agreed to postpone with the Project Officer approval the delivery date, allowing the progress of the case studies and thus have more information about them.

The present document presents an overview the current legislation within EU framework for human medicines that has a direct impact in the initial development of any pharmaceutical product, and other legislation that impacts on direct inputs or requirements to care about during the development, clinical trials, marketing authorization and post-commercialization phase, including those that are being revised or under consultation.

The document is focused on the initial approach of design and planification of a pharmaceutical compound that pertains to the research, diagnosis, prevention, and treatment of diseases in human beings.

Possible first steps to implement relevant trends and potential greener approaches that may be useful to incorporate green-by-design or greener-by-design approaches into the development of new medicines and potential regulatory pathways to market are discussed. Potential key factors in the development of a human medicinal product are outlined within the framework of the content requirements in a Pharmaceutical dossier for human use.

The document is structured as follow:

1. An overview of the current, and proposed changes for the legislation for human medicines.
2. The discussion on different inputs for greener approaches to minimize pharmaceutical residues.
3. Overview of the most overarching guidelines for the pharmaceutical development.
4. An overview of the ETERNAL stakeholder case studies, and the selection of a candidate to implement the key-drivers.
5. An implementation of the previous concepts in a real case study.
6. Conclusions of the concept paper "compliant-by-design"

3 Legislation that applies to human medicines within EU framework.

3.1 Current regulatory EU framework for Human medicines

The current legislation that applies to human medicines within the European framework covers several phases of a medicine's lifecycle, including development, initial marketing authorization, post-marketing changes, and disposal. The EU can regulate not only through legally binding instruments such as treaties, regulations, and directives—or "hard law"—but also through the various recommendations, opinions, communications, notices, and guidelines issued by the European Commission, known as "soft law."

Key pieces of applicable "hard law" are provided hereafter:

- **Regulation (EC) No 726/2004 (1)**: Establishes the European Medicines Agency (EMA) and sets out procedures for the authorization and supervision of medicinal products for human and veterinary use within the EU. It introduces a centralized procedure for authorizing certain medicines, which must be followed before they can be marketed in the EU. It also covers pharmacovigilance, transparency, information provision, and procedures for post-authorization changes.
- **Directive 2001/83/EC (2)**: This Directive is the central EU legislation governing the marketing authorization, manufacturing and importation, classification, labelling and packaging, safety monitoring, distribution and advertising of medicinal products for human use. Its purpose is to ensure safety, efficacy, and quality of these products within the EU.
- **Regulation (EC) No 1394/2007 (3)**: This Regulation is an EU law which amends Directive 2001/83/EC and Regulation (EC) No 726/2004 regarding Advanced Therapy Medicinal Products (ATMPs). It regulates the approval, distribution, and safety measures for these innovative gene, cell, and tissue-based medicines across the EU. Key features include centralized marketing authorization via EMA, creation of the Committee for Advanced Therapies (CAT), specific technical requirements for ATMPs, and incentives for small and medium-sized enterprises
- **Regulation (EU) 2017/745 (4)**: This law amends Directive 2001/83/EC regarding medical devices. It sets safety standards and transparency requirements for medical devices, introduces Unique Device Identification (UDI), mandates a regulatory compliance officer in organizations, and increases scrutiny for high-risk devices.
- **Clinical Trials Regulation (EU) No 536/2014 (5)**: Governs the conduct of clinical trials on medicinal products for human use in the EU. It simplifies the application process, enhances transparency, improves safety reporting, promotes a risk-proportionate approach, and includes rules for participant protection and environmental safety.
- **Directive 2010/84/EU (6)**: This Directive amends Directive 2001/83/EC and pertains to the pharmacovigilance of medicinal products for human use in the EU. It aims to enhance monitoring of safety, improve data collection, promote transparency, and requires risk management plans and post-authorization safety studies.
- **Regulation (EU) No 1235/2010) (7)** : Governs the monitoring and reporting of adverse reactions to human medicines, defines the role of the European Medicines Agency in coordinating these activities, and promotes transparency, risk management, and the use of a Pharmacovigilance System Master File.
- **Directive 2004/27/EC (8)**: Amends Directive 2001/83/EC focusing on public health protection, pharmacovigilance, herbal medicines, advertising rules, patient information, and manufacturing/importing guidelines. In what specifically concerns to the disposal of medicines, the Directive 2004/27/EC (8) indicates that Member States should take

appropriate measures to ensure that unused or expired medicines are collected and disposed of in a safe manner.

As there are many specific technical requirements that are not covered in detail in the above set of Directives and Regulations, "soft law" documents, namely those guidelines issued by the International Council for Harmonisation (ICH), which are recognized by European Health Authorities, must be considered when it comes to technical requirements for pharmaceuticals for human use.

The ICH is a global organization that brings together regulatory authorities and the pharmaceutical industry to develop and promote harmonized standards and guidelines to ensure that safe, effective, and high-quality medicines are developed and registered in an efficient and cost-effective manner. ICH guidelines are designed to promote harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, and thus, reduce or obviate duplication of testing carried out during the research and development of new medicines. The process of adoption of these guidelines is described below:

- Drafting (Steps 1 and 2): The first step in the process is the drafting of the ICH guidelines. This is done by expert working groups that consist of representatives from the ICH members, which include the EMA, the US Food and Drug Administration (FDA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), among others.
- Consultation (Step 3): Once a draft guideline is prepared, it's released for public consultation. In Europe, this process is managed by the EMA. The draft is published on the EMA website, and comments are invited from the public.
- Finalization (Step 4): After the consultation period, the working group reviews the comments received and makes any necessary revisions to the guideline. The final guideline is then endorsed by the ICH Assembly.
- Implementation (Step 5): After endorsement, the guideline is implemented in the regulatory framework of the ICH members. In Europe, this is done through a notice to applicants and guideline document published by the European Commission.

Some ICH guidelines applicable to the scope of this concept paper are listed below:

- ICH Q1A (R2) - Stability Testing of New Drug Substances and Products (9).
- ICH Q2 (R1) - Validation of Analytical Procedures: Text and Methodology (10).
- ICH Q3 – Impurities (Q3A (R2) (11), Q3B (R2) (12), Q3C (R8) (13), Q3D (R2) (14)).
- ICH Q7 - Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (15).
- ICH Q8 (R2) - Pharmaceutical Development (16).
- ICH Q9 (R1) - Quality Risk Management (17).
- ICH Q10 - Pharmaceutical Quality System (18).
- ICH Q11 - Development and Manufacture of Drug Substances (19).
- ICH Q12 - Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (20).
- ICH E6 (R2) - Good Clinical Practice (21).
- ICH M4 (R4) - Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (22).

All the information related to a Human Medicines should be compiled and packaged in a concrete manner. The dossier of a human medicine is a comprehensive collection of data and documents about a medicinal product. It is submitted to health authorities for the purpose of obtaining marketing authorization for the product. The format of this dossier is standardized across many

countries through the Common Technical Document (CTD) format, which was developed by the ICH.

The CTD dossier is divided into five modules:

- Module 1 - Administrative and Prescribing Information: This module contains region-specific information, such as application forms, product labelling, and patient information.
- Module 2 - Summaries: This module provides overviews and summaries of the data presented in Modules 3 to 5. It includes an introduction, quality overall summary, nonclinical overview and summary, clinical overview and summary, and a literature review.
- Module 3 - Quality: This module provides detailed information about the drug substance and product, including its manufacturing, characterization, control strategy, reference standards, packaging, and stability.
- Module 4 - Nonclinical Study Reports: This module contains all the nonclinical (animal) study reports, including pharmacology, pharmacokinetics, and toxicology studies.
- Module 5 - Clinical Study Reports: This module contains all the clinical (human) study reports, including reports on pharmacokinetics, pharmacodynamics, efficacy, and safety.

The content of the dossier should demonstrate that the medicinal product is safe, effective, and of high quality. It should provide sufficient information for the health authority to assess the benefits and risks of the medicinal product and make an informed decision about its approval for marketing.

According to the existent EU framework, namely Directive 2001/83/EC (2), human medicinal products under registration or to be registered in the Union are required to have a scientific evaluation of their potential impact within the environment. This evaluation is known as Environmental Risk Assessment (ERA) and shall be included as part any registration dossier in the EU, as detailed hereafter:

- In accordance with article 8(3) of Directive 2001/83/EC (2), as amended, the evaluation of the potential environmental risks posed by medicinal products should be submitted, their environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit the impact should be considered. In any event, this impact should not constitute a criterion for refusal of a marketing authorisation.
- The aim of the ERA is to identify, characterize, and assess the potential risks posed by the medicinal product to the environment. The ERA should also propose measures to limit these risks.
- ERA should be an integral part of the planning and development of a medicinal product, and provide information on:
    - The physicochemical properties of the active pharmaceutical ingredient (API)
    - Estimation of the amount of the API that will be introduced into the environment.
    - Calculation of the concentration of the API that is expected to enter the environment.
    - Further details and fate and behavior in the environment and on living organisms.
- The detailed guidance on how to conduct an ERA is provided in the guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447/00 corr 2 (23).
- The conclusion of an ERA for medicinal products involves a synthesis of all the information gathered during the assessment to determine whether the medicinal product poses a risk to the environment. The conclusion may include the following outcomes:

  - No Risk: If the Predicted Environmental Concentration (PEC) of the API is below the action limit, the ERA may conclude that the medicinal product is unlikely to pose a risk to the environment.
  - Potential Risk: If the PEC is above the action limit, or if the risk characterization indicates a potential risk, the ERA may conclude that the medicinal product could pose a risk to the environment. In this case, further investigation or risk management measures may be recommended.
  - Risk Unclear: If the ERA cannot conclusively determine whether there is a risk due to insufficient data or other uncertainties, the conclusion may state that the potential environmental risk of the medicinal product is unclear. Further data may be needed to clarify the risk.
  - Risk Management Measures: The conclusion should also include any proposed risk management measures to mitigate potential environmental risks. This could include recommendations for changes in manufacturing, use, or disposal of the medicinal product.
- The results of the ERA can impact the information provided in the labelling and precautions for the medicinal product. For example, if the ERA identifies a significant environmental risk associated with the product, this information may need to be included in the product's labelling. The precautions might also include instructions for the proper disposal of the product to minimize environmental impact.

As above-mentioned, until today, a negative outcome of the ERA shall not constitute a criterion for refusal of a marketing authorisation. Recognizing this pitfall and the global environmental challenges the World is living, the regulatory mindset of the Health Authorities is changing and new legislation is expected with stricter requirements. Recently, there was a review from the European Commission related to the Revision of the EU general pharmaceuticals legislation that may impact the scope of the greener perspective. Further details are discussed in the following header (see "Revision of the EU general pharmaceuticals legislation**¡Error! No se encuentra el origen de la referencia.**").

3.2 Revision of the EU general pharmaceuticals legislation

As part of the EU pharmaceuticals strategy, and drawing lessons from the COVID-19 pandemic, the Commission plans to evaluate and revise the EU's general legislation on medicines for human use to ensure a future-proof and crisis-resistant medicines regulatory system.

Scientific evidence shows that pharmaceuticals are present in the environment because of manufacture, patient use, and improper disposal of unused or expired products. The fact that antimicrobials have been detected in wastewater treatment, manufacturing effluent, surface and ground waters is of particular concern, as their presence boosts antimicrobial resistance. In addition, if pharmaceuticals enter the water cycle or the food chain, they also affect human health directly. In order to face these challenges, the proposed reform of pharmaceutical legislation strengthens the ERA of medicines to ensure a better evaluation and limit the potential adverse impacts of medicines on the environment and public health. Some approaches to strength ERAs are listed below:

- Introducing a refusal ground for the marketing authorization where companies do not provide adequate evidence for the evaluation of the environmental risks or if the proposed risk mitigation measures are not sufficient to address the identified risks.
- Setting clearer ERA requirements, including compliance with scientific guidelines, regular ERA updates, and post-authorization obligation for additional ERA studies.
- Extending the ERA scope to cover the risks to the environment from the manufacturing of antibiotics.
- Extending ERA to all products already in the market and potentially harmful to the environment.

In parallel, EMA guideline on ERA is under revision (EMEA/CHMP/SWP/4447/00 corr 2 (23)). This revision aims to provide harmonized ERA requirements and testing up-to-date with current scientific knowledge, as well as an ERA stepwise approach optimized to the use of human medicines.

In this context, non-governmental organizations such as Health Care without Harm (HCWH) has already published recommendations in line with European Commission initiative.

The pharmaceutical industry tends not to prioritize ERAs during the development of new drugs as environmental risks are not considered in the benefit-risk assessment for human medicines. For the same reason, environmental risks are not considered in the pharmacovigilance system, which means that environmental effects are not reported after use and referral procedures are not possible in case of environmental risks. On the other hand, EMA committees for human medicines do not include ERA experts and there is no permanent working party for environmental issues for human medicines. Referring to ERAs itself, these reports do not consider the risks that manufacturing discharges and their cumulative impact can have on the environment and human health, the risks of antimicrobial resistance development from production, use and disposal, nor the risks that degradation products, metabolites and combination effects can pose (24).

Finally, ERA data are not fully publicly available, which is in conflict with the Aarhus Convention. Only main ERA studies are published in (European) Public Assessment Reports, where they are categorised by products rather than by substances, making environmental information on APIs difficult to research. It is also common that ERA studies submitted post-approval are not reflected in (European) Public Assessment Reports.

Considering the above mentioned, HCWH raise the following recommendations to approach these challenges (24):

- Include ERA in the benefit-risk assessment for human medicines.
- Include environmental issues in the pharmacovigilance system to monitor real-world data.
- Establish a catch-up procedure for pharmaceuticals that have been authorized on the market before 1 December 2006 without ERA.
- Make it compulsory for pharmaceutical companies to provide comprehensive and reliable environmental data at the time of marketing authorization.
- Make ERA data publicly accessible in an online database under supervision of the EMA.
- Replace the current product-based environmental assessment system with a substance-based review system, for which marketing authorization holders would share responsibility, to reduce administrative burden, increase transparency, and reduce animal testing.
- Broaden the scope of ERAs to also address environmental risks during the production and formulation process, risks of antimicrobial resistance development and maintenance in the environment from production, use, and disposal for antimicrobials, as well as environmental risks of degradation products, metabolites, and combinations effects, in view of the growing evidence that mixtures of pharmaceuticals can have a greater joint toxicity.
- Require a regular review of ERAs.
- Ensure a better link between ERA data and other regulatory frameworks such as relevant EU water and soil legislation.

HCWH also foresees other areas different to ERAs where a greener vision might be applicable regarding human medicines. Drug manufacturing can be a source of pharmaceutical discharges into the environment in concentrations that can be significantly higher than toxic thresholds. These emissions can have devastating impacts on ecosystems and can contribute to the development of antimicrobial resistance, which threatens local populations and global health. Despite Directive 2008/105/EC (amended by Directive 2013/39/EU) obliges the European Commission to develop a strategic approach to water pollution from pharmaceutical substances, currently there are no specific rules in the EU regulating the emissions from pharmaceutical production into the environment. Many pharmaceutical plants supplying the EU market are located outside Europe in countries with weaker environmental and regulatory systems, particularly in the case of antibiotics (24).

There are several industry-led initiatives that seek to promote responsible supply chain management in the pharmaceutical sector. However, these initiatives often lack effective action or transparency.

HCWH propose the following recommendations related to the supply chain (24):

- Make it compulsory for pharmaceutical companies to publicly disclose supply chain information, including names and locations of suppliers, production units, and processing facilities, in an online public database to ensure the traceability of all pharmaceutical products.
- Include mandatory environmental criteria that address discharges of pharmaceutical residues into the environment, e.g., emission limit values, in the EU Good Manufacturing Practice (GMP) legislation.
- Develop environmental standards for drug production that will create a level playing field for drug manufacturers. Such standards would also support pricing and reimbursement

agencies and procurers, who could use them as a benchmark to reward companies that have invested in greening their supply chain.
- Develop guidelines to help purchasing authorities use procurement policy to promote greener pharmaceuticals and sustainable production with clear environmental criteria and performance indicators based on the Public Procurement Directive.
- Advocate for a revision of the WHO GMP framework that includes mandatory environmental criteria addressing the discharges of pharmaceutical residues into the environment.
- Strengthen international cooperation and dialogue with manufacturing countries, develop a global research agenda, and advocate for global solutions.

Another approach that HCWH raises is to encourage the use of greener medicines, promotion its responsible use and reduction of waste. Pharmaceuticals are biologically active and not readily biodegradable in the environment, having a high carbon footprint. In this context, recommendations from HCWH are listed below (24):

- Make pharmaceuticals that can cause a harm to the environment prescription-only, based on environmental risk thresholds.
- Support the training of healthcare professionals on the environmental impact of medicines and the exchange of best practice to promote responsible use and proper disposal.
- Incentivise the research and development of environmentally sustainable and climate-neutral pharmaceuticals throughout the value chain through funding schemes.
- Make pharmaceutical companies contribute to financing post-registration monitoring and water treatment costs due to pharmaceutical pollution.
- Develop guidance for healthcare institutions to reduce the discharges of pharmaceutical residues from use and disposal to municipal wastewater.
- Promote the separate collection of urine of patients administered with X-ray or magnetic resonance imaging (MRI) contrast agents.
- Make it compulsory for pharmaceutical companies to measure and consistently report (both in terms of comparability and quality) the greenhouse gas emissions of their products throughout the value chain.
- Ban advertising for OTC medicines that can pose a risk to the environment
- Adopt stronger market conditions for medicines with high environmental risk, e.g., marketing limitations when greener alternatives exist, risk management measures to prevent environmental releases, or limitation of use in healthcare institutions with effective on-site wastewater treatment facilities.
- Classify pharmaceutical substances based on environmental criteria and create a label for OTC products that meet high environmental standards to reward and incentivise green production and development as well as to allow patients to make informed purchasing decisions.
- Develop implementation guidelines on pharmaceutical collection schemes that harmonise take-back systems across the EU and collaborate with Member States to properly enforce the current regulation.
- Make it compulsory to feature disposal information for patients on the outer drug packaging and in pharmacies (in addition to patient information leaflets) to prevent disposal via the toilet or sink.

- Compel pharmaceutical companies to propose different packaging sizes and forms for their products, in particular for liquid drugs, to reduce the amount of pharmaceutical waste.
- Compel pharmaceutical companies to contribute to financing pharmaceutical collection schemes under the Extended Producer Responsibility (EPR) principle of the Waste Framework Directive.
- Regulate the management of human medicinal waste beyond cytostatic and cytotoxic substances, which are the only pharmaceuticals explicitly classified as hazardous waste under the Waste Framework Directive currently.

4 Inputs for greener approaches for pharmaceuticals

The European Commission is presently undertaking a comprehensive revision of the European Union's general legislation pertaining to medicinal products intended for human consumption. The objective of this revision is to establish a regulatory system for medicinal products that is resilient, adaptive, and prepared for future challenges. This undertaking also provides an opportunity to reflect upon and learn from the experiences of the COVID-19 pandemic, which has exerted considerable pressure on Europe's healthcare infrastructure. (See the section - Revision of the EU general pharmaceuticals legislation for the proposed changes in the legislation).

The European Commission published the Pharmaceutical Strategy for Europe on November 25, 2020, which has laid the foundation for the current revision process. Within this strategy, the subsection titled "High quality, safe and environmentally sustainable medicines" enumerates a series of measures designed to enhance the quality and environmental sustainability of medicinal products for human use within the European Union.

The Pharmaceutical strategy introduces two key initiatives: enhancing supply chain transparency and bolstering environmental risk assessments for human medicine. It also outlines additional measures, particularly focusing on producing quality, sustainable medicines and reducing carbon emissions in value chains. It is worth to mention some initiatives already studied in the field of clinical trials. While there is not yet a specific framework for green drivers in the pharmaceutical industry, the potential impact of digital adoption in clinical trials could have a beneficial sustainability impact, primarily through the reduction of CO_2 emissions (25).

To minimize pharmaceutical residues impact on human, animal, and environmental health, it is crucial to implement robust measures, both legislative and non-legislative, across a medicine's lifecycle. Different inputs for greener approaches are provided hereafter.

4.1 First input – The pharmaceutical supply chain

Pharmaceutical manufacturing can significantly contribute to environmental pollution, with emissions exceeding toxic thresholds and potentially leading to ecosystem damage and antimicrobial resistance (AMR). Despite these risks, there are no specific EU regulations governing pharmaceutical production emissions, including APIs.

While the pharmaceutical industry falls under the Industrial Emissions Directive (IED) and its corresponding Best Available Technique Reference Documents (BREFs), these do not set emission limits for APIs. Furthermore, many pharmaceutical factories serving the EU market are based outside Europe, often in countries with less stringent environmental regulations, especially for antibiotics.

Therefore, alongside enhanced EU regulation, a global approach involving international cooperation and dialogue is required to address these issues across all supply chains.

The pharmaceutical supply chain's opacity complicates the task of tracing the origins of APIs. The absence of readily available supply chain data hinders the enforcement of accountability within the pharmaceutical industry regarding potential emissions of pharmaceutical residues during the manufacturing process.

4.2 Second input – Environmental risk assessment

ERAs are designed to assess and mitigate potential negative impacts of medicinal products on the environment. They ensure that potential effects are scrutinized and appropriate preventative actions are taken when risks are identified. Pharmaceutical companies are required to conduct ERAs and present them to the EMA during the marketing authorization process.

The guideline concerning ERAs for human medicines was implemented on December 1, 2006. However, it was not enforced retroactively. Consequently, many medicinal products for human use that were introduced to the EU market via the centralized procedure prior to this date often lack a comprehensive ERA. For many of these products, data pertaining to potential environmental impacts are not available.

The pharmaceutical industry often places less emphasis on ERAs during the development of new drugs, as environmental risks are not factored into the benefit-risk assessment for human medicines.

Similarly, environmental risks are not taken into account in the pharmacovigilance system. This implies that environmental effects are not reported post-use, and referral procedures in case of environmental risks are not applicable.

Another challenge is the limited purview of ERAs. These assessments do not account for the potential risks that manufacturing discharges, along with their cumulative impact, may pose to the environment and human health. Moreover, ERAs do not take into consideration the risks related to the development of AMR from production, usage, and disposal. Similarly, the risks associated with degradation products, metabolites, and combination effects are not encompassed within ERAs.

Lastly, the full spectrum of ERA data is not publicly accessible, a circumstance that is at odds with the principles of the Aarhus Convention.

The Aarhus Convention, officially known as the United Nations Economic Commission for Europe (UNECE) on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters, is an international legal agreement on environmental democracy. The Aarhus Convention is a unique instrument in environmental law and governance that links environmental rights and human rights, demonstrating that sustainable development can only be achieved through the involvement of all stakeholders.

Only the primary ERA studies are published in (European) Public Assessment Reports, where they are classified by products rather than by substances. This classification system makes it challenging to conduct research on the environmental information pertaining to APIs. Additionally, it is not uncommon for ERA studies submitted after approval to be omitted from (European) Public Assessment Reports.

4.3 Third input – The medicines are vital for Human beings

It may seem obvious, but medicines play an indispensable role in safeguarding human health and well-being. They serve as crucial tools for preventing, diagnosing, and treating a wide array of illnesses and health conditions. By alleviating symptoms, curing diseases, or slowing the progression of chronic conditions, medicines enhance the quality of life and extend longevity. Furthermore, they are instrumental in public health strategies to combat global health threats, such as pandemics and antibiotic resistance. Hence, medicines are not merely beneficial, but absolutely vital for human beings in maintaining and improving health outcomes on a global scale.

Pharmaceuticals, due to their biologically active nature, mobility (especially metabolites), and resistance to biodegradation, can have significant environmental impacts, even at low concentrations. They are specifically designed to interact with living systems, which can result in adverse effects on non-target species and ecosystems.

In addition, pharmaceuticals contribute significantly to carbon emissions, exacerbating the global climate crisis. For instance, in 2020, England's National Health Service (NHS) reported that 20% of its carbon emissions stemmed from medicines and chemicals in supply chains, highlighting a substantial opportunity for carbon reduction (26).

Waste from unused medication constitutes a significant issue, accounting for 10% of wastewater pollution. Directive 2004/27/EC (8) mandates Member States to devise suitable collection systems for unused or expired drugs. However, it does not offer implementation guidelines, leading to considerable variations in the systems and their usage across Member States.

There are additional concerns that pharmacies in some EU countries are required to independently finance disposal and collection schemes. To fund these collection systems, certain Member States, including France and Spain, have introduced EPR schemes for expired pharmaceutical products. Countries with the highest collection rates typically have such schemes in place.

In the EU, the principle of EPR applies. This means that producers are required to finance the collection, treatment, and disposal of waste from their products. This principle is established under the EU's Waste Framework Directive 2008/98/EC (27).

Several EU countries have implemented EPR schemes for various waste streams, including packaging waste, electronic waste, and end-of-life vehicles. Here are a few examples:

- **France**: The country has EPR schemes for various waste streams. For packaging waste, organizations such as Citeo are responsible for implementing the scheme. Producers pay fees based on the type and weight of packaging they put on the market. These fees are then used to finance the collection and recycling of packaging waste.
- **Germany**: The country operates a dual system where manufacturers and distributors finance the collection and recycling of sales packaging that typically ends up with the consumer. The Green Dot system is a well-known symbol of this scheme. Small businesses can also take advantage of a centralized registration portal, which simplifies the administrative process.
- **Sweden:** The country has a Packaging and Newspaper Collection Service financed by producers. The fees are based on the type and weight of packaging or newspapers put on the market.

- **Netherlands:** In the Netherlands, producers and importers of packaged goods are responsible for the collection and recycling of packaging. They pay a waste management contribution, which is used to finance the system.
- **Spain:** The country has an Integrated Management System for Packaging Waste. SIGRE (Sistema Integrado de Gestión de Residuos de Envases) It is a non-profit entity created in 2001 by the Spanish pharmaceutical industry to ensure the correct environmental management of packaging waste and expired or unused medications.
- **United Kingdom:** The UK operates a Producer Compliance Scheme (PCS) where producers finance the recovery and recycling of packaging waste by buying Packaging Recovery Notes (PRNs) from accredited reprocessors.

These models vary greatly from country to country due to differences in national legislation, market dynamics, and waste management infrastructure. In general, though, they all follow the same principle: producers should bear the costs of managing the waste generated by their products.

5 Regulatory state of Art for pharmaceutical development

The pharmaceutical industry is heavily regulated and guided by a plethora of guidelines at both national and international levels. As addressed in Legislation that applies to human medicines within EU framework.

Current regulatory EU framework, these guidelines are set to ensure the safety, efficacy, and quality of the pharmaceutical products. Below are summarized the most overarching guidelines for the pharmaceutical development:

ICH Q8 (R2) Pharmaceutical Development provides a framework for the design, development, and presentation of information for pharmaceutical products. It promotes the concept of QbD, which is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Based on this concept, a complete pharmaceutical development should include the following elements (see Figure 2**¡Error! No se encuentra el origen de la referencia.**):

- Definition of specific Quality Target Product Profile (QTPP) which is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product.
- Identification of potential Critical Quality Attributes (CQAs) of drug substance, excipients and drug product, being the physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
- Definition of the formulation selecting the type and the quantity of excipients to properly deliver drug product.
- Selection of an appropriate manufacturing process.
- Definition of a control strategy that covers a planned set of controls, derived from current product and process understanding that ensures process performance and product quality.
- Performance of a systematic evaluation, understanding, and refining of the formulation and manufacturing process by identification of material attributes and process parameters that can have an effect on product CQAs and determining the functional relationships that link material attributes and process parameters to product CQAs.

- Use of ICH Q9 principles of quality risk management to establish an appropriate control strategy.

Practical considerations within the concepts of ICH Q8 (R2) (16):

- The term TPP stands for Target Product Profile, while QTPP stands for Quality Target Product Profile.
    - The concept of a TPP originated in the field of drug development, particularly in the context of clinical research. A TPP is essentially a strategic development process tool that provides a format for a team to translate their strategy into a comprehensive, concise, and clear document that describes a drug product's desired properties and current knowledge collected during the R&D process.
    - The TPP includes information regarding the intended use in patients, the route of administration, dosage form, dosing regimen, and the safety and efficacy goals.
- The QTPP, on the other hand, is a term introduced by the ICH in its Q8 (R2) (16) guideline on pharmaceutical development.
- A QTPP is an extension of the TPP. It includes all the characteristics that a drug product should have to meet the desired quality, safety, and efficacy requirements. It includes not only clinical properties but also pharmaceutical quality aspects.
- In the QTPP, the focus is on parameters or characteristics of the drug product, which may include aspects like dosage form, dosage strength, release profile, container closure system, drug product quality criteria (e.g., sterility and purity), and stability.
- In essence, a TPP is developed first to define the general product profile and then it is extended into a more comprehensive QTPP that includes the quality considerations.

A scheme of pharmaceutical development following ICH Q8 (R2) principles is provided in Figure 2.

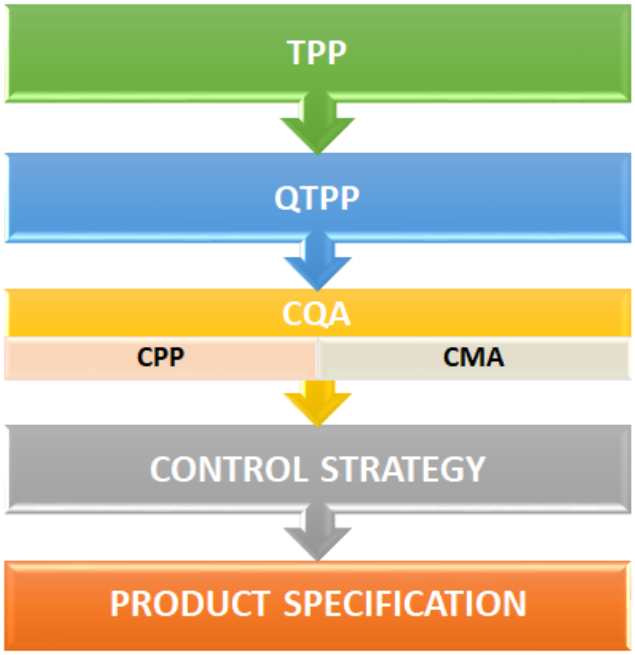

Figure 2. Concept diagram for pharmaceutical development

In order to use a systematic approach and methodology, the concepts and tools of ICH Q9 (R1) (17) are used.

ICH Q9 (R1) Quality Risk Management (17) provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality covering all stages of product lifecycle. Quality risk management is based on the following two principles:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

ICH Q9 (R1) (17) complements ICH Q8 (R2) (16) by providing a structured framework for the management of risks to the quality of the pharmaceutical product. It is an integral part of QbD as it allows for informed decision-making, resource allocation, and risk mitigation in the product development process.

These two guidelines interconnect as described below:

1. Informed Decision-Making: ICH Q8 (R2) (16) encourages understanding the product and process, which forms the basis of decision-making. On the other hand, ICH Q9 (R1) (17) provides the tools to assess and mitigate the risks associated with these decisions.
2. Risk-Based Approach: both guidelines promote a risk-based approach. ICH Q8 (R2) (16) does this through the QbD concept, where risks are identified and mitigated during the product development phase and ICH Q9 (R1) (17) provides the framework for managing these risks.
3. Product Lifecycle Management: both guidelines emphasize the importance of considering the entire product lifecycle. ICH Q8 (R2) (16) focuses on the development phase, while ICH Q9 (R1) stresses the importance of risk management throughout the product's lifecycle.
4. Process Control: ICH Q8 (R2) (16) promotes the use of Process Analytical Technology (PAT) and robust control strategies to ensure process performance and product quality and ICH Q9 (R1) (17) complements this by providing a risk management framework that can help in the development of these control strategies.

In summary, ICH Q8 (R2) (16) and ICH Q9 (R1) (17) work together to promote a comprehensive, scientifically sound approach to pharmaceutical development and quality risk management. ICH encourages a deep understanding of the product, process, and associated risks, leading to better decision-making, improved product quality, and ultimately, enhanced patient safety.

In addition, other ICH guidelines are considered to be connected with the guidelines described above. These guidelines are described below.

ICH Q10 Pharmaceutical Quality System (18) describes a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. The model is based on ISO quality concepts, includes applicable GMP regulations and complements ICH Q8 (R2) (16) and ICH Q9 (R1) (17). These three guidelines are interconnected, forming a triad that aims to design quality into products. These three guidelines together ensures that a product is fit for its intended use, is effective and safe, and can be consistently manufactured.

ICH Q11 Development and Manufacture of Drug Substances (19) provides guidance on development, manufacturing process and control strategy of drug substances, including both chemical entities and biotechnological/biological entities. This guideline applies ICH Q8 (R2) (16) and ICH Q9 (R1) (17) concepts to the development and manufacture of APIs. It guides the identification of critical quality attributes, process parameters, and sources of variability, and the establishment of an effective control strategy for manufacturing. This is achieved by

integrating the QbD and Quality Risk Management principles from ICH Q8 (R2) (16) and ICH Q9 (R1) (17).

ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (20) provides a framework to manage post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle. This guideline is designed to enhance the clarity, transparency, and flexibility of post-approval changes and to promote innovation and continual improvement

In summary, ICH Q11 (19) and ICH Q12 (20) take the principles outlined in ICH Q8 (16), ICH Q9 (17), and ICH Q10 (18) and apply them to specific stages of the product lifecycle, from the development and manufacture of drug substances to the management of post-approval changes.

Despite the fact that ICH guidelines are not explicitly 'green-oriented', their principles can indeed be applied to drive sustainable efforts within the industry. As of today, there isn't a specific framework for green drivers in the pharmaceutical industry. However, the concepts and tools described in the ICH guidelines provide a comprehensive approach that can be leveraged to promote sustainability being conscious of their natural limitations due to the lack of specificity and regulatory authority endorsement for this purpose. In this context, ICH guidelines offer a wide range of strategies and methods that can be used to optimize processes, reduce waste, and increase efficiency, and using them as a basis for green initiatives can be a proactive and innovative approach to reducing environmental impact.

A starting point might be the update of concepts described in ICH guidelines like QTPP and CQA to a greener perspective. This will allow to obtain an updated concept of QbD which includes green drivers. These concepts are detailed in From QTPP to gQTPP in Control strategy.

6 ETERNAL stakeholders case studies

In the previous sections Asphalion summarised the core concepts and tools for the pharmaceutical development, the trends of the pharmaceutical regulation and the inputs and ideas for developing greener pharmaceutics. The next content is focused in the screening of the Eternal stakeholder studies (Figure 3) and its potential in their current state to be selected to represent an exemplary proposal to “green-quality-by-design” (gQbD).

The key driver to be a potential case study for a gQbD approach is the development stage, and the time needed to be commercialized, whether as a technology or as a component of a registration dossier.

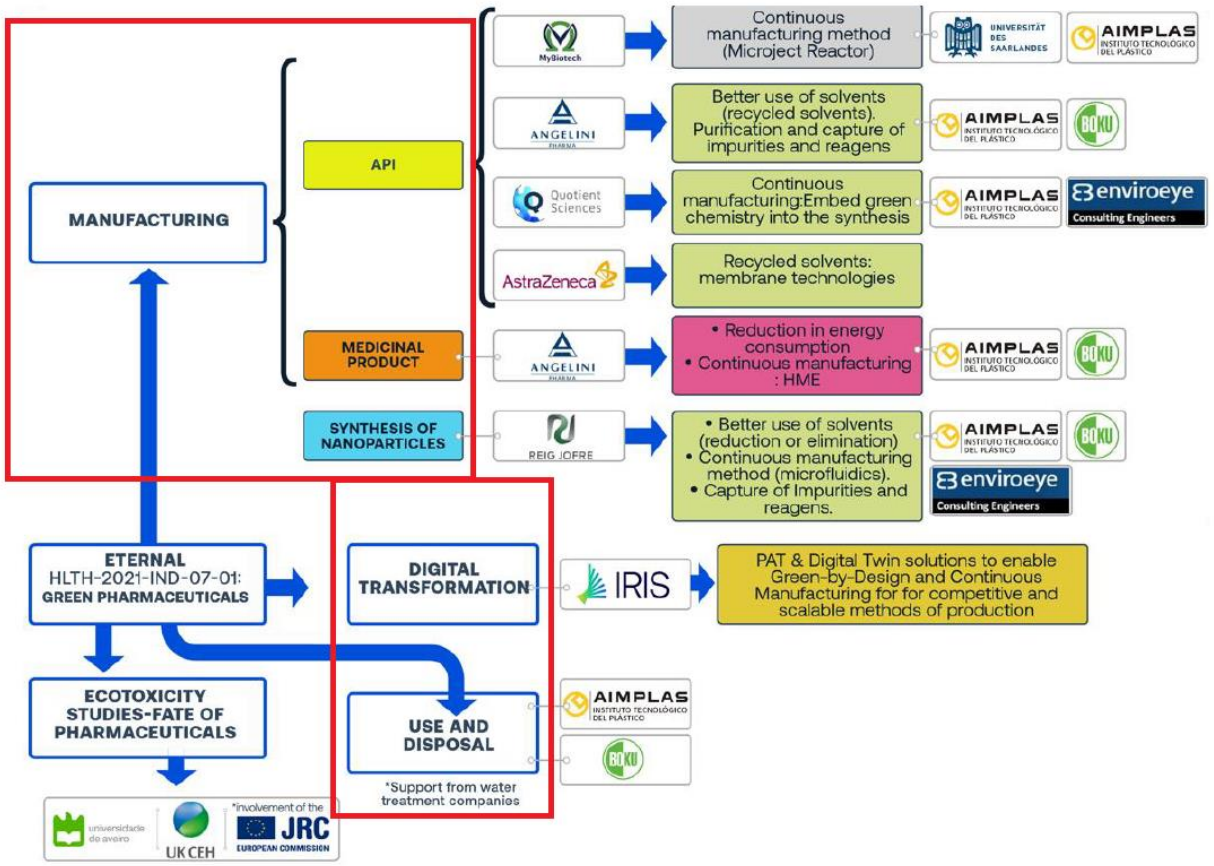

Figure 3. ETERNAL case studies objectives

6.1 Case study selected for a gQTPP

The case study 1 from Angelini Pharma is embedded within an advanced pharmaceutical development with a structured QTPP and CQAs that convert the case study in a suitable candidate for the greener approach gQTPP.

6.2 Case studies overview and progress status

All case studies fall within the scope of the green manufacturing activities in the ETERNAL project (Figure 1). An overview table of the relevant case studies performed within the scope of the Eternal initiative is provided in Table 1. This table summarized the concepts, scope, current status and potential regulatory pathway to market within the current pharmaceutical regulation for each case study. Currently, all the case studies are on-going.

Table 1. Overview of ETERNAL stakeholders case studies

Case Studies	Sponsor	Scope	Current Status	Potential Regulatory Pathway to market	Industrial/Commercial Implementation
Case Study 1	Angelini Pharma	Development of a generalized method for continuous DP manufacturing process with the intention of: - Reducing environmental impact of the drug product formulation process in terms of energy and materials consumption. - Reducing operating costs. - Potential improvement of quality process and/or consistency of the DP by CM investigating real-time monitoring - Potentially reducing time to market to the benefit of both patients and the business by simplifying formulation.	Status: On-going Two drug product manufacturing processes have been investigated so far in the manufacture of immediate release tablets of a selected API, both involving the use of a CM technology. These new processes consist of less production steps and smaller places to be conditioned thanks to the smaller dimension of the equipment train utilized. . Several trials have been performed (also by using DoE) obtaining a good prototype with the desired quality and functional attributes. It has been submitted to a pre-industrialization stage stability study.	The traditional manufacturing process involves numerous phases and equipment in various production rooms, leading to high energy consumption. The fewer steps a manufacturing process has, the less source of risks might be faced and, therefore, preferred by regulators. Despite in both manufacturing processes some issues have been identified, they are considered as potentially reachable and therefore, with a potential regulatory pathway.	The manufacturing processes under development might be implemented by: - Submission of related post-approval change. - Submission of new marketing authorization application.
Case Study 2	Angelini Pharma	Development of an improved distillation process for API manufacturing process which allows the recycling of solvents used during the process. This new technology might allow to switch to greener and/or bio-based solvents obtaining a more sustainable process and potentially, reduce the manufacturing costs.	Status: On-going The study is ongoing searching the best way to optimize the recycling system.	Use of recycled solvents is not typically accepted by regulators, mainly for the risk of impurities carryover. However, the study suggests that the process under development might be considered as a great opportunity to implement a more sustainable process and be accepted by regulators. Quality controls and number of cycles of recycling/purifying	The distillation process under development might be implemented by: - Submission of new ASMF/DMF - In cases where a finished product is currently based in this ASMF, subsequent related post-approval change should be submitted. - Submission of new marketing authorization application.

Case Studies	Sponsor	Scope	Current Status	Potential Regulatory Pathway to market	Industrial/Commercial Implementation
				solvents should be validated, justified and enclosed in the Drug Master File (DMF).	
Case Study 3	Reig Jofre	The development of greener manufacturing processes using liposomes increase the efficacy of API encapsulation and the use of recycled solvents. The benefits of this proposal are: - Energy consumption reduction. - Waste reduction; higher encapsulation efficiency and recovery of API from waste stream means less active ingredient lost to waste stream. - Recycle of solvent and unencapsulated active back into the process. - Use of less harmful solvents. - Product nanoparticles are greener (less drug excreted by patients due to enhanced bioavailability and absorption).	<u>Status: On-going</u> Several trials of API manufactured with liposomes has been performed. However, diafiltration issues with API loss has been observed. Regarding the recovery and purification of solvents, trials with ethanol using fractional distillation have been performed obtaining positive results: - Similar characteristics obtained with the recycled ethanol. - Successful separation of API from the waste using an ion exchange resin after 24 hours.	More progress is needed on the project to determine its regulatory potential.	More progress is needed on the project to determine its industrial/commercial implementation.
Case Study 4	Quotient Sciences	Greener-by-design synthesis methods through development and optimization of API manufacturing processes for reduced environmental impact. The project consists of: - Process development & production with high	<u>Status: On-going</u> Continuous stirred tank reactor and plug flow system are under development. A continuous stirred tank reactor can have higher productivity for the same footprint as a batch reactor.	The premise of "greener-by-design" synthesis methods is to gain a greater level of process understanding early on in process development to allow optimization algorithms to be used to minimize the environmental impact. By its nature this means that relationships between CQAs and CPPs will be understood as this is	More progress is needed on the project to determine its industrial/commercial implementation. If this project demonstrates that through the application of optimization algorithms and flow technology we can deliver "greener-by-design" synthesis methods the intention would be to market this as an additional service for our existing PR&D activities. As

Case Studies	Sponsor	Scope	Current Status	Potential Regulatory Pathway to market	Industrial/Commercial Implementation
		process mass intensity from flow processing. - Integrate acquisition of process safety data to minimise experiments. - Ability to make a market "claim" about greener chemistry benefits. - Demonstrate a practical approach to greener process design and development as a marketplace differentiator - Linking the data to cost and impact analysis to deliver further value and drive KPIs for the approach.	Plug flow reactors can operate at elevated temperatures and pressure, expanding the window of operation for processes, better control of residence time and temperature, and reduce volatile organic compounds emissions. Characterization experiments and with the continuous stirred tank reactor have been performed.	needed for process optimization. If a process that Quotient Sciences developed for a customer were to be taken forward for regulatory filing, QbD experimental data needed for the file would be readily accessible in an organised digital format.	Quotient Sciences perform contract R&D and manufacturing, we would not be submitting the regulatory file ourselves for successful drug candidates but may also author it on a customer's behalf.
Case Study 5	MyBiotech GmbH	This case study concerns development of greener approaches in biologics manufacturing. In particular, the case study is related to the optimization by genome engineering of the strain used in Rapamycin manufacture. Fermentation from natural producers generates a wide range of undesired co-products (toxic, carcinogenic etc.) in addition to the desired product. Upstream re-design of the producer strains can prevent the production of the impurities and hence avoid the environmental impacts from the purification steps. The project seeks:	<u>Status: On-going</u> Successful substitution of the current strain used and gen deletion has been achieved. The new rapamycin extraction, storage, and analysis have been established. However, low rapamycin yield and worse stability results have been observed compared to the current process.	The project is considered relevant and with potential for future implementation. However, the project is still in the development phase and more progress is needed to determine its regulatory potential.	More progress is needed on the project to determine its industrial/commercial implementation.

Case Studies	Sponsor	Scope	Current Status	Potential Regulatory Pathway to market	Industrial/Commercial Implementation
		- Resource efficiency = cost efficiency (less solvent). - Process intensity increase - lower cost/energy. - Reduction of environmental impact (release of co-products into ecosystem). - Simpler process with less steps. - Process integration – linking extraction with fermentation. - More robust, so less risk of quality problems. - Possibly yield enhancement.			
Case Study 6	AstraZeneca	Use of membranes to simplify manufacturing process. The characteristics of membranes allow: - Energy efficient recovery and purification of solvents. - Applying membrane purification to remove potential mutagenic impurities. - Recovery of product from waste streams reducing ecotoxicity.	<u>Status: On-going</u> So far, it has generated understanding to support the case study and solvent swaps for a range of solvents without substrate have been assessed.	More progress is needed on the project to determine its regulatory potential.	More progress is needed on the project to determine its industrial/commercial implementation.

7 From QTPP to gQTPP in Control strategy

As mentioned in previous section concerning the pharmaceutical development guidelines (see Regulatory state of Art for pharmaceutical development), the main concepts described throughout the present document will be applied to the Eternal case study 1 as an illustrative example. The selection of case study 1 was mainly based on its stage of development which allows a more detailed and concrete discussion of the approach that can be implemented. However, the same approach could be applied to the other case studies.

The details are covered in the next sub-sections:

- 7.1 - QTPP, CQAs and manufacturing process scheme
- 7.2 - Promotion of QTPP to gQTPP

All the concept processes are able to be replicated and applied in the development and manufacturing of medicines to enhance the understanding and control of the process, leading to a consistent quality of the end product.

7.1 QTPP, CQAs and manufacturing process scheme

Upon design and decide a TPP to initiate a potential business according to the know-how and scientific experience, an initial QTPP should be designed, the CQAs should be identify for the drug product, and the impacts of the process and materials should be assessed (see Figure 4).

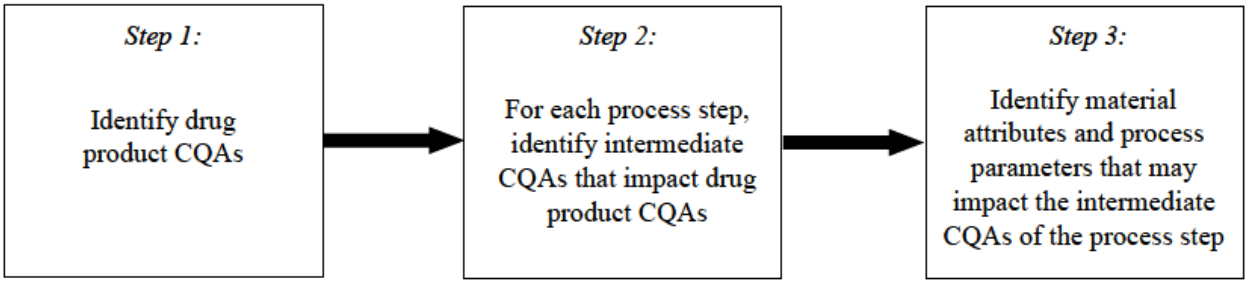

Figure 4. Process scheme for establishing the CQAs (ICH Q8 guideline)

Below, the Case study 1 is described as follows:

1. QTPP is enclosed Table 2
2. CQAs are outlined in Table 3
3. Relation of the manufacturing process and the CQAs is showed in Table 4 and Table 5*
   **Each relation and potential impact should be studied in subsequent design of experiments and trials. These studies will not be shown as they are strictly confidential.*

Table 2 – QTPP elements (Case study 1)

QTPP Elements		Target	Justification
Dosage Form		Tablet	Suitable form for the disease treatment
Dosage Design		Rounded tablet without score line	Improve compliance of patients thanks to its easier swallability
Route of Administration		Oral	Suitable route for the disease treatment and patient compliance
Dosage Strength		Established strength	Dose required for the therapeutic action
Pharmacokinetics		Immediate release	Assure a suitable onset of action and efficacy
Stability		2 years	Sustain the supply chain and to avoid waste
Drug Product Quality Attributes	**Appearance (Physical Attribute)**	Suitable appearance	Guarantee acceptability of patients
	Hardness (Physical Attribute)	Suitable hardness	Avoid any breakage during production and packaging process
	Identification	Compliant	ICH Q6A
	Assay	95-105%	ICH Q6A
	Uniformity of Dosage Units by mass variation	AV <15	Ph. Eur. current edition
	Dissolution	Q80 in 60 min.	USP monograph
	Degradation Products	Below limits calculated following ICH Q3b	ICHQ3B
	Residual Solvents	No solvents	Reduce safety and environmental issues
	Water Content	NMT a selected percentage	Internal specification
	Microbiological Quality	TAMC <1000 UFC/g; TYMC< 100 UFC/g; *E.coli* = Absent/g	Ph.Eu. current edition
	Disintegration	< 15 min.	Ph. Eur. current edition
Container Closure System		Able to guarantee the stability over time of the drug product	Achieve 2 years of drug product shelf-life period

Table 3 – CQAs and justification (Case study 1)

Quality Attributes of the Drug Product		Target	Is it a CQA?	Justification
Physical Attributes	**Appearance (color/shape)**	white to off-white rounded tablet, acceptable by patient	NO	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	no odor	NO	Odor does not impact the safety and efficacy of the product.
	Size	minimized size	NO	Size does not impact the safety and efficacy of the product.
	Friability	Not applicable	NA	NA
Identification		Compliant	**YES**	Identification is critical for safety and efficacy. However, formulation and process variables are unlikely to impact this CQA.
Assay		95-105 %	**YES**	Fundamental for the safety and efficacy of the product.
CU - Uniformity of Dosage Units by mass variation		AV <15	**YES**	Fundamental for the safety and efficacy of the product.
Dissolution		Q80 in 60min	**YES**	Fundamental for the efficacy of the product. Failure to meet the dissolution specification can impact bioavailability.
Degradation Products		below limits calculated following ICH Q3b	**YES**	Fundamental for the safety of the product.
Residual Solvents		no solvents	NA	Residual solvents can impact safety. However, no solvent is used in the drug product manufacturing process. Therefore, formulation and process variables are unlikely to impact this CQA.
Water Content		NMT a selected percentage (Internal specification)	NO	Generally, water content may affect degradation and microbial growth of the drug product and can be a potential CQA. However, in this case, the API is not sensitive to hydrolysis and moisture will not impact stability. Moreover, since it is a solid product the risk of microbial growth is very low. However, water content is monitored in the pre-industrialization stage stability to check if it could affect any other attributes.

Quality Attributes of the Drug Product	Target	Is it a CQA?	Justification
Microbiological Quality	Ph. Eur. current edition	**YES**	Non-compliance with microbial limits will impact patient safety. However, in this case, the risk of microbiological growth is very low because melt granulation is utilized for this product (no water is added during all the process).

Table 4. Relation of the manufacturing process and the CQAs (1/2)

Drug Product CQAs	Manufacturing process stages			
	[1] Sieving of materials	**[2] Dry blending**	**[3] Continuous Melt Granulation**	**[4] Milling**
Assay	Presence of lumps could affect the subsequent blend uniformity. CPP could be screen size.	Suboptimal blending may cause variable flowability and variable API distribution in the blend. CPP could be the time of blending. However, the risk is low because materials are further mixed in the subsequent granulation phase and the drug loading is high.	Granulation is useful to improve flow, minimize segregation and enhance CU. However, the PSD of granules is an important characteristic to guarantee a not variable tablet weight (potentially affecting the assay). That's why a milling step to control the final PSD is introduced to lower the risk.	The milling step controls the final granule size distribution. A suboptimal distribution may affect flow, causing variable tablet weight during compression affecting the assay. CPP could be screen size (Measuring the weight of the tablets is an IPC during compression)
CU - Uniformity of Dosage Units by mass variation	The presence of lumps could affect the subsequent blend uniformity. CPP could be screen size.	Suboptimal blending may cause variable flowability and variable API distribution in the blend. CPP could be the time of blending. However, the risk is low because materials are further mixed in the subsequent granulation phase and the drug loading is high.	-	If milling generates excessive fines, both bulk density and flowability of the blend may be impacted. This may impact CU. CPP could be screen size.
Dissolution	-	-	-	A large number of big granules may impact dissolution. CPP could be screen size.
Degradation Products	-	-	The temperature selected for the granulation process is below the temperature at which API starts the degradation process. The risk linked to process temperature is thus low.	-
Microbiological Quality	-	-	-	-

Table 5. Relation of the manufacturing process and the CQAs (2/2)

Drug Product CQAs	Manufacturing process stages			
	[5] Sieving of materials	[6] Mixture blending	[7] Compression	[8] Blistering/Packaging
Assay	Presence of lumps could affect the subsequent blend uniformity. CPP could be screen size.	Suboptimal blending could lead to lack of homogeneity impacting the assay. CPP could be the time of blending. However, the API is in high percentage in the product.	Tablet weight variability can impact the assay. CPP could be the press speed. (->Weight of the tablets is an IPC)	-
CU - Uniformity of Dosage Units by mass variation	Presence of lumps could affect the subsequent blend uniformity. CPP could be screen size.	Suboptimal blending could lead to lack of homogeneity impacting the assay and CU. CPP could be the time of blending. However, the API is in high percentage in the product.	Tablet weight variability can impact the assay and CU. CPP could be the press speed. (->Weight of the tablets is an IPC)	-
Dissolution	-	Suboptimal blending may impact the distribution of the excipients in the blend which could impact disintegration and dissolution of the tablets. CPP could be the time of blending.	In general, a potential CPP could be the compression force that could potentially impact the tablet hardness and DT.	-
Degradation Products	-	-	-	Defects in blisters may impact the chemical stability of the product. However, the API is not particularly sensitive to humidity/temperature, thus the risk is low.
Microbiological Quality	-	-	-	Defects in blisters may impact on the microbiological stability of the product. However, the formulation is solid and contamination risk is reduced. Moreover, the raw materials are previously evaluated in terms of microbiological purity. Thus, the risk is low.

7.2 Promotion of QTPP to gQTPP

The established QTPP, CQA, design of experiments, formula optimizations, manufacturing optimization phases, and analytical methods development and justification, in the product should be included in the dossier the section 3.2.P.2 (Pharmaceutical development), in several sub-headings.

As part of the concept of the ICH Q8 (R2) (16), a control strategy should be planned. Therefore, as part of such a strategy, it could be considered the inclusion of a detailed control strategy of the product that the includes the environmental sustainability of the product towards this new concept of the gQTPP.

An example of the gQTPP according to the environmental sustainability inputs is proposed is provided in Table 6. New environmental sustainability or green(er) variables could be enhanced, improved, as well as include new technologies leading to new shipping validated methods that will encompass a lower carbon-footprint in the supply chain.

Table 6. gQTPP proposal – Case 1

gQTPP Elements		Target	Justification/Reference
Formula		Minimal number of excipients, simple recipe, no water in formula	Decrease negative environmental impact of the production of medicine
Manufacturing Facilities Related to the Manufacturing Process	**Water Usage**	The use of water is only limited to washing equipment pieces.	Decrease negative environmental impact of the production of medicine.
	Energy Consumption	Minimal number of production steps, small dimension of equipment, suitable for continuous manufacturing, to get a low energy consumption process either for the equipment and for air conditioning of the rooms (HVAC – Heating, Ventilation and Air Conditioning)	Decrease negative environmental impact of the production of medicine.
	Building Construction	In relation to the process, the spaces to be air conditioned are minimized, thanks to the smaller dimension of the equipment train utilized, and optimized	Decrease negative environmental impact of the production of medicine.
	Waste Treatment	*The waste is reduced at maximum. The waste treatment is under the local laws.*	*Local law*
Drug Substance Manufacturing Site(s)	**Water Usage**	*Global water usage in the API manufacturing is included as a variable in the process of the selection of qualified drug substance supplier* *Internal audits, and QP inspections also covers this variable*	*QP declaration API manufacturer statement – Water, energy usage and sustainability commitment*
	Process Mass Intensity	*Efficiency of the synthesis steps is to be calculated as a Process Mass Intensity (PMI). Use of reagents and process parameters are to be optimised to minimise the PMI for a given processing step.*	*API manufacturer statement – PMI*

gQTPP Elements		Target	Justification/Reference
	Energy Consumption	*Energy usage in the API manufacturing is included as a variable in the process of the selection of qualified drug substance supplier* *Internal audits, and QP inspections also covers this variable*	*API manufacturer statement – Water, energy usage and sustainability commitment*
	Building Construction	*Building construction of the API manufacturing is included as a variable in the process of the selection of qualified drug substance supplier*	*API manufacturer statement – Water, energy usage and sustainability commitment*
Drug Product Quality Attributes	**Residual Solvents**	No solvents	Reduce safety and environmental issues
Container Closure System	**Material of Construction**	*Material of construction and environment impact of manufacturing of the packaging materials is included as a variable in the process of the selection of container closure system suppliers*	*Energy usage and sustainability commitment – supplier[1]* *Energy usage and sustainability commitment – supplier[n]*
Validated Shipping Methods	**Carbon Foot-Print**	*The shipping transportation methods have been qualified and selected taking into account the total carbon foot-print along with the quality controls*	*Carbon foot-print – land[1]* *Carbon foot-print – land[n]* *Carbon foot-print – air[1]* *Carbon foot-print – air[n]* *Carbon foot-print – ship[1]*

- *Notes: the text in cursive means a hypothetical approach*

8 Conclusion

The current pharmaceutical regulatory landscape only contemplates the inclusion of an ERA in the registration dossier. However, in any case the presence of an ERA or its content do not constitute a barrier to the MAA approval. The current regulatory environment for pharmaceutical products is being updated to incorporate stricter criteria for analyzing and validating environmental impact. However, these updates are not happening fast enough to encompass all aspects of effectively managing the entire supply chain under the principle of "sustainability" to reduce the carbon footprint.

As of today, there is not a specific framework for green drivers in the pharmaceutical industry. However, by using current principles and ideas of pharmaceutical development and updating them to a "greener" perspective (gQTPP, and gControl Strategy), we can apply, from the start of a project, an argument line to construct a control strategy to achieve a "greener" development of pharmaceutical products.

This approach has been applied to case study 1 within the six case studies of ETERNAL project due to its stage of development. However, the key-drivers proposed are applicable for all the case studies and the sponsors are encouraged to incorporate these concepts in the development of any kind of human medicine taking into account the approach of quality-by-design applicable for the European framework for the development of pharmaceutical products.

With the new proposal of gQTPP, the principles of pharmaceutical development based on QTPP and CQAs can be leveraged to enable, control and ensure sustainable developments with less impact on the environment.

This new proposal must go hand in hand with new regulatory requirements for the content of the drug dossier, as well as new requirements at the level of pharmaceutical inspection for finished product and for active substances that will activate new requirements for the minimum information for drug substances/active ingredients dossiers (DMF/ASMF) and technical documentation of manufacturing facilities, (e.g. SMF).

Key points:

- The regulatory environment for pharmaceuticals is evolving to include stricter environmental impact criteria.
- Current pharmaceutical development principles can be used to create strategies for "greener" product development.
- The new gQTPP proposal links pharmaceutical development principles to control and ensure less environmentally impactful development.
- This proposal requires new regulatory requirements for drug dossier content and pharmaceutical inspection.
    - The absence of specific requirements permits the use of arbitrary methods, which may not necessarily conform to a harmonized strategy through the globe.
    - In the absence of explicit requirements, the data generated could be viewed by regulatory bodies as information that shouldn't be included in a registration dossier. This could complicate the evaluation process and lead to inconsistencies, meaning that, despite its presence, authorities might not deem it as relevant or as providing added/differentiating value.
    - In today's global context, marked by pressing environmental challenges, it is imperative to incorporate environmental sustainability into pharmaceutical practices. This includes minimizing the ecological footprint of medicinal products and considering these factors during the approval process. This approach should

not be seen as discretionary, but rather as a fundamental aspect of contemporary pharmaceutical development and regulation.

- These new requirements will lead to additional requirements for active substance, finished products and manufacturing facility documentation.

Therefore, with this new approach different perspectives of the same target will be interconnected allowing the Health Authorities to assess the drug product with enhanced information and pursuing the same goal, manufacture and market affordable medicines with a less impact in the environment.

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