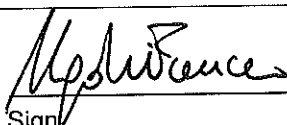


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Updating history

REV.	UPDATING DESCRIPTION
1.0	First issue

SIGNING AND APPROVAL		
Paolo Chiesi	PARMA 2'6 FEB. 2019	
RESEARCH & DEVELOPMENT	Date	Sign
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CHIEF EXECUTIVE OFFICER	Date	Sign

مجلس

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1 REVISIONS RATIONALE

Rev 1.0 First issuance.

2 AIM

2.1 INTRODUCTION

The pharmaceutical industry involves the use of many chemicals both during the production phase and during the research and development of new therapeutic solutions. Indeed, chemicals are fundamental in many parts of the industry.

The types of chemicals used include reagents, catalysts, solvents, salts, acids and bases, intermediates, Active Pharmaceutical Ingredients (APIs), propellants, surfactants, and a variety of excipients.

Both people and the environment can be significantly affected by the use of chemicals. Over the years, many regulations (e.g. REACH) have introduced restrictions on the use of hazardous chemicals in order to protect people and the environment from the adverse effects of exposure.

Chiesi is committed to the responsible use of chemicals, recognizing the importance of minimizing their use or selecting those that are minimally hazardous so that their potential effects on human health and the environment can be reduced or prevented. The company is also aware that this commitment must be considered during the acquisition of new products developed by third parties.

To eliminate or minimize the potential effects of hazardous chemicals, Chiesi is committed to designing enclosed processes using effective containment strategies based on the best available practices and closed systems to avoid any potential environmental emissions. To limit emissions into the environment as much as possible, Chiesi is also engaged in designing abatement systems using the best applicable technologies.

Chemicals used in our research and development activities are handled by trained researchers using the lowest possible quantities needed under controlled conditions to minimize environmental emissions and workplace exposure.

It is important to underscore that the pharmaceutical sector is unique in that there are very strict and binding regulatory and quality requirements to ensure that any changes to manufacturing processes do not adversely affect the quality, safety, or efficacy of medicines on the market. This means that, before changing an existing manufacturing process, we must conduct an appropriate validation and ensure that the new process is able to produce essentially the same quality medicine that was

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originally approved for the market, and that the new process does not affect drug efficacy or safety profiles. Consequently, it is not always technically feasible to substitute chemicals in many existing manufacturing processes and, even if it were possible, the cost of making these changes could be prohibitive.

Notwithstanding the above, Chiesi is in any case committed to minimizing – as much as possible and through any reasonable mean available – any adverse impact related to the use of chemicals during the manufacturing process.

3 CONTENT

3.1 SUBSTANCES RESPONSIBLE FOR CLIMATE CHANGE

Chiesi's approach has always been in line with European policies on the emissions control of fluorinated greenhouse gases, including hydrofluorocarbons (F-gases, HFCs). In fact, in addition to sustainable chemistry initiatives, alternative propellant gases with lower environmental impact are currently under evaluation, even though our currently commercialised drug products have a Global Warming Potential (GWP) lower than the propellant gases used by competitors (e.g. HFA 134).

To underscore its commitment, in 2016 Chiesi had the Carbon Footprint certified for its main pharmaceutical drug product dedicated to asthma treatment (pMDI and DPI inhaler).

Chiesi is aware of the importance of making a positive impact on the lives of patients and of operating sustainably at the same time. Chiesi's goal is to contribute to a healthy environment and demonstrate leadership in doing whatever is necessary to prevent climate disruption.

Chiesi believes that we all need to ensure that the impact of climate change on health is better understood so that we can formulate and carry out our responses through the optimal inter-relationships between people, health, and the environment. More specifically, Chiesi is resolved to contributing responsibly to the progress towards science-based reduction targets for CO₂ equivalents.

For these reasons Chiesi is strongly committed to:

- Developing actions that support science-based CO₂ eq reduction targets.
- Using substances with lower CO₂ eq. whenever possible.
- Scouting for the best available technologies to minimize emissions and avoid leakage during development and manufacturing processes.
- Contributing to increased energy efficiency and using energy from renewable sources.
- Providing Greenhouse Gases (GHG) emissions reporting based on well-established calculation methodologies and publicly disclosing CO₂ eq. performance regarding its main products.

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3.2 MANAGEMENT OF SUBSTANCES-OF-CONCERN

MAIN PRINCIPLES

Responsible management of the “chemicals-of-concern” listed below is essential for Chiesi to reach its sustainability objectives:

- Carcinogenic, mutagenic and reproductive (CMR) hazardous substances are controlled by Chiesi’s Management System and use is limited as much as possible. When alternatives are not available (e.g. for pharmacopoeia tests), CMRs are managed following rigorous procedures applied from the purchasing phase, though strictly controlled handling, to disposal.
- Environmentally Persistent, Bio-accumulative and Toxic or Very Persistent and Very Bio-accumulative molecules are avoided.
- Ozone depleting chemicals are avoided.
- Endocrine disruptors or suspected endocrine disruptors are avoided (in anticipation of European regulatory requirements).
- In line with EU regulations, the use of Substance of Very High Concern (SVHCs) is avoided as soon as they are identified.

3.3 MANAGEMENT ASPECTS

Based on the principles listed above, Chiesi implements a range of actions in order to ensure that the chemicals and materials we produce or use are not adversely affecting health or the environment.

- **Communication to employees and stakeholders**

A deep understanding of the intrinsic danger of molecules and new chemical entities is the basis for the sound management of chemicals.

For these reasons Chiesi is committed to:

- Using risk assessment-based approaches on our proprietary APIs to identify the key workplace health and safety hazards and to identify appropriate control strategies to protect people’s health and the environment.
- Implementing robust processes through sound procedures to obtain updated relevant safety information on chemicals from our suppliers, toxicological studies, and published literature.
- Communicating information to our employees about chemical risk management and control strategies via dedicated programs (procedures, periodical documentation review, e-room repository, intranet communication, protocols, forms for external communication, etc.).
- Providing all chemical hazard information to relevant stakeholders (e.g. contract manufacturers/key suppliers, partners) in order to facilitate the implementation of appropriate control strategies through risk management.
- Adopting a management strategy based on banding categorization for New Chemical Entities when a full toxicological characterization is not available.

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- Encouraging responsible management of hazardous chemicals by applying consistent standards to our contract manufacturing operations. This is achieved by requiring that our suppliers comply with all legal and regulatory requirements and defining minimum HSE standard requirements. And conducting for key suppliers, pre-HSE evaluations and periodical audits; providing encouragement and assistance to help improvement in HSE matters whenever necessary.
- Committing to openness and transparency with regard to hazardous chemicals management.
- **Substitution of "Chemicals-of-Concern"**
 - Identifying "substances-of-concern" currently in use and applying, wherever possible, the substitution principle as the first alternative.
 - Assessing the feasibility of less hazardous chemicals as a second step: referring to selection guides available in the literature in order to choose more sustainable solvents and reagents. Where elimination or substitution is not technically possible, adopting appropriate and responsible risk management approaches.
 - Ensuring that choices relating to substitution of hazardous chemicals and process optimization are documented in the relevant Research and Development Report
 - During the development of a new drug product, evaluating the environmental impact of excipients and APIs, as well as of the major metabolites and impurities/degradation products (e.g. ecotoxicology - environmental fate and degradation, general toxicology, ecology).
 - Paying particular attention to devices and packaging components. For drug products under development, the selection and development of the device and packaging components will be performed with the aim of avoiding or minimizing the use of substances-of-concern.
 - For products already on the market, evaluating the possibility of replacing these substances with ones that have lower impact.
 - Whenever possible, limiting the scale of API and drug product manufacturing processes during development to reduce the use of chemicals, waste, and emissions.
 - Exploring the possibility of using flow chemistry for the API manufacturing continuous process.
 - Reducing solvent consumption whenever possible by using appropriate analytical equipment (e.g. UPLC systems) or sample preparation.
 - Increasing the use of modelling tools to optimize experimental and statistical approaches (e.g. Design of Experiment) in order to minimize handling and consumption of chemicals, as well as waste and emissions.
 - With specific procedures and processes, ensuring appropriate communications to the appropriate European authorities (e.g. CLP notification to ECHA).
 - Enforcing the principles of "green chemistry" and process efficiency in process optimization to minimize the use of chemicals and reduce associated waste and emissions.
 - Exploring opportunities for the use of bio-transformation (e.g. bio-catalysis).

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- **Life cycle perspective (LCP) studies**

LCP is a systematic approach to environmental management that provides information to build knowledge about the life cycle of research, development and production processes.

This approach contributes to sustainable development by controlling or influencing the way the organization's products and processes are designed, manufactured, distributed, consumed and disposed of by using a life cycle perspective that can prevent environmental impacts from being unintentionally shifted elsewhere within the life cycle.

LCP considers consecutive and interlinked stages of products and processes starting from raw materials and natural resources (including water, energy, etc.) and ending with final disposal. Life cycle stages include the acquisition of raw materials, design, production, transportation/delivery, use, end-of-life treatment and final disposal.

Chiesi is committed to studying its drug products under development and on the market along their entire life cycle in order to decrease their impact on health, safety and the environment.

