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REVIEW ON REGULATORY INSIGHTS OF GREEN CHEMISTRY AND SUSTAINABILITY

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ABSTRACT

This article illustrates the importance and implementation of green chemistry practices in the pharma industry. The current climate interrelated to impending Global crises shows the impact on green chemistry, which provides unique opportunities for innovations via product substitution, new feedstock generation, catalysis in aqueous media, utilization of microwaves, the scope for alternatives, or natural solvents. This paper summarizes the environmental protocols for the synthesis of some FDA-approved drugs which possess high volume demand coupled with their requirement of high chemical and optical purity, utilization of green chemistry. Various innovations in green chemistry such as the use of catalysts in experiments, safer chemicals and auxiliaries, design for degradation with the more efficient synthetic formulation. This conceptual paper demonstrates how the principles and metrics influence the life cycle chemicals from design to disposal and steps taken for sustainability development. It is driven by a desire to reduce costs and increase the sustainability of the manufacturing process. The Regulatory restrictions and self-impositions in adopting green chemistry by this pharmaceutical industry have made a significant impact. The concept in the new act was to adopt a process that generates no pollutants rather than treating pollutants after products. It states that the cost-effective modernization of the regulatory process will protect human health and the environment while also reducing the burden to the industry. This article defines how pharmaceutical manufacturers change methods into "greener methods to use less toxic reagents and solvents to minimize their effluents and solid waste.

Green chemistry is not just a catchphrase. It is an essential principle of chemical research that will sustain our society in the 21st century and further into the future. This core concept described a research success from the last 20 years, including advances in synthetic efficiency application, of alternative synthetic methods, use of less hazardous solvents and Reagents, and development of renewable feedstock. Further green chemistry will depend on innovations that consolidate and integrate these achievements made using principles as a framework for design for sustainability and reduce hazards should be eliminated as contrasting but provide freedom to explore and invent scientific disciplines to create new solutions.

Keywords: Green chemistry, sustainability, alternative assessment, harmful chemicals

INTRODUCTION:

Half of the 20th century led to a significant economic edge and increased living standards in developed parts of the world. As a result of the last two decades, awareness of the need for environmental protection has increased through Green and viable technologies. Laws and regulations to protect the ecosystem from harmful chemicals. Green chemistry indulges things in the form of medicine, dyes, cosmetics, polymers, food products, biomolecules, agrochemicals, paints, nanoparticles, liquid crystals. Green Chemistry concepts stand for two most important components **[2]**:

1. First, Green chemistry depicts the dilemma of efficient usage of starting materials for synthetics and the associated reduction of waste due to then use.
2. Second, if accords with the safety, environmental issues, and health-related to the manufacturing usage of chemicals and their disposals **[16]**.

Green chemistry provides a new approach to the synthesis, processing, and Application of chemical substances in such a manner as to reduce threats to health and the environment. This new approach is also known as **[2]**:

1. Environmentally benign chemistry
2. Clean chemistry
3. Atom economy
4. Benign-by-design chemistry

Principles of Green Chemistry:

Paul Anastas, United States of environmental protection Agency and John c. warner developed twelve principles that cover such concepts as below **[15]**:

1. **Prevention:** It's better to prevent waste than to clean up waste after it is formed.
2. **Atom Economic:** Synthetic methods should be designed to maximize all materials used in the process into the final product.
3. **Less Hazardous Chemical Syntheses:** Whenever practicable,

Synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. **Designing safer chemicals:** Chemical products should be designed to preserve the efficacy of function while reducing toxicity.
5. **Safer Solvents and auxiliaries:** The use of auxiliary substances (ex: solvents, separation agents, etc.) should be made unnecessary whenever possible and innocuous when used.
6. **Design for Energy Efficiency:** Energy requirements should be recognized for their environmental and economic impacts and minimized; synthetic methods should be conducted at ambient temperature and pressure.
7. **7. Use of Renewable Feedstock:** A material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. **Reduce Derivatives:** Reduce derivatives – Unnecessary derivation (blocking group, protection, and de-protection temporary modification) should be avoided whenever possible.
9. **Catalysis:** Catalysis reagents (selective as possible) are superior Stoichiometric reagents.
10. **Design for Degradation:** Chemical Products should be designed to not persist in the environment and break down into innocuous degradation products at the end of their function.
11. **Real-time Analysis for pollution prevention:** Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control before the formation of hazardous substances.
12. **Inherently safer chemistry for accident prevention:** Substances and the formation of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires **[1-5]**.

Ex: Synthesis of ibuprofen

History:

Racheal Carlson published "silent spring" in 1962, creating awareness related to pesticides and their ties to environmental pollution. RyojNovori selected three points for the development of green chemistry in 2005

- Employ green solvents like supercritical CO_2.
- For green solvent oxidations, the use of aqueous hydrogen peroxide
- Application of Hydrogen in asymmetric production.

Chemical Disasters:

1956: Mina Mata disease was first discovered in Mina Mata city in Japan. It was caused by the release of Methylmercury in the industrial wastewater from a chemical factory.

1961: Itai-Itai disease was caused by cadmium poisoning due to mining in Toyama prefecture in Japan.

1976: The Servo disaster was an industrial accident in a small chemical manufacturing plant near Milan in Italy. It has resulted in the highest known exposure to 2,3,7,8 tetrachloro-dibenzo P-dioxin in medical pollution.

1984: The Bhopal disaster was an industrial catastrophe at a pesticide plant owned and operated by union carbide (UCIL) in Bhopal, India, resulting in the exposure of over five people. It was caused by methylcynate (MIC) gas.

1986: The Chernobyl disaster was a nuclear accident at the Chernobyl nuclear plant in Ukraine, resulting in the release of radioactive materials. Most fatalities from the accident were caused by radiation poisoning **[4]**.

1989: Exxon Valdez, an oil tanker, hit a reed and spilled an estimated minimum of 10.8 million us gallows (40.9 million liters) of crude oil. It has been recorded as one of the largest spills in U.S. history and one of the most significant ecological disasters **[3]**.

Problems with currently used solvents:

In the U.S. in the early 1990s: Solvent production was 26 million tons p.a of tracked chemicals; many of the top chemicals released or disposed of were solvents (MeOH, toluene, Xylene, CS_2, MEK, and CH_2CL_2)

Organic Solvent Hazards:

- Flammable – (almost all except chlorinated solvents)
- Carcinogenic – (Chlorinated Solvents are aromatics)
- High vapor pressure – (i.e., inhalation Route)
- Narcotic – (ether, chloroform)
- Toxic – (MEOH, CS_2)
- Mutagen/tetragons – (toluene)
- Peroxides (ethers)
- Smog formation

Applications of Green chemistry:

1. Green dry cleaning of clothes
2. Bleaching of paper

Emerging Green chemistry tools in organic chemistry:

For organic synthesis, the challenges for chemists include the discovery and development of new synthetic pathways using green chemistry tools such as;

- Green solvents
- Green catalysis in organic chemistry
- Dry media synthesis
- Catalyst free reactions in organic synthesis

It requires a new approach to minimize materials, the energy requirement of chemical processes and products, eliminate the dispersion of hazardous chemicals to use renewable resources **[8]**.

Solvents:

Green chemistry aims to reduce solvent use. Solvent selection is a critical priority in generating chemistry because solvents are used in high volumes, and many of them are flammable and toxic compounds. New green solvents, e.g: ethyl lactate, -2- methyl tetrahydrofuran, cyclopentylmethylether **[19, 1]**.

Simple solvent selection guide developed by Pfizer:

Solvents are assessed based on safety, health, and regulatory criteria and categorized as preferred usable and undesirable solvents; consider using the suggested alternatives **[12]**.

Preferred	Usable
Water	Cyclohexane
Acetone	Heptane
Ethanol	Toluene
2-propanol	Methyl cyclohexane
1-propanol	Methyl t- butane
Ethyl Acetate	Isooctane
Isopropyl Acetate	Acetonitrile
Methanol	2-MethylTHF
1-butanol	Xylenes

GSK, Sanofi, and AstraZeneca developed some solvent selection guides and unified solvent selection guides for the common solvent used in Medicinal chemistry **[3]**. Murphy's Law of solvents states that "the best solvent for any process step is terrible for the subsequent step. "No solvent is perfectly green. The non-conventional solvents are more exciting, but it's the conventional ones that are greening the industry.

Alternative Assessment:

Six broad steps in conducting the alternative assessment are as follows;

1. Scoping, problem formulation, identifying alternatives for considering actions **[9]**.
2. Hazard/ comparative exposure assessment
3. Technical feasibility Assessment
4. Economic feasibility Assessment
5. Other life cycle considerations
6. Decision making

Alternative assessment emerged in the late 1990s as the FDA's (EPA) comparative process to evaluate substitutes to toxic chemicals used in specific industry sectors. It is the step defined and solutions-oriented process for identifying and comparing

potential chemical and non-chemical alternatives that could replace chemicals of concern based on their health hazard, performance, and economic viability **[10]**. Regulatory and non-regulatory programs with alternative assessment or substitution provisions **[10]**. Government Or regulatory authorities play an essential role in establishing tandem for alternative assessment and substitution, including developing criteria for chemicals and materials to avoid substitution (e.g., less safe and safer chemicals), establishing clear guidance and requirement for the alternative assessment process, and developing metrics to monitor the substitution process inform for noncompliance.

Regulatory Actions	**Alternative assessment-specific regulatory provisions** **− European Commission's 2006 Registration, Evaluation, Authorization, and Restriction of Chemicals** **− E.U. Biocidal Products Regulation [(E.U.)528/2012]** **Classification-based substitution requirements** **− European Commission's 2004 Carcinogens or Mutagens at Work Directive** **− European Commission's 2008 Classification, Labelling, and Packaging of Substances and Mixtures (CLP Regulation)** **Requirements for the use of safer alternatives in procurement** **− U.S. Federal Executive Order 13514, 2009 Federal Leadership in Environmental, Energy and Economic Performance** **Single or multiple chemical restrictions with alternative assessment requirements** **− European Commission's 2002 Restriction of Hazardous Substances Directive** **− Japan's 1991 Law for Promotion of Effective Utilization of Resources in Japan and2008 mandatory industry standard JIS C 0950 the marking for the presence of the specific chemical substances for electrical and electronic equipment** **− Norwegian Environmental Agency's 1976 Norwegian Product Control Act, Section 3A Pollution prevention** **− China's 2002 Law of the People's Republic of China on the Promotion of Clean Production** **− European Commission's 2008 Integrated Pollution Prevention Control Directive.**
Non-regulatory programs	**China's State Recommended Catalogue of Alternatives Materials for Toxic and Hazardous Substances and Products** **European Commission's D.G. Environment's Non-Toxic Environment Initiative – 7th Environmental Action Programme** **− Swedish Chemicals Agency (KEMI) Environmental Quality Objectives, "A Non-Toxic Environment"** **− U.S. EPA Safer Choice Program** **− U.S. OSHA Transitioning to Safer Chemicals**

Regulatory system overviews the following:

- Restrictions/ limitation chemicals and classes of concern. Requirements for alternative assessment with clear guidance and enforcement.
- Information collection requirement – on chemical toxicity, uses/functions, and classification.

Food and Drug Administration:

FDA encouragement of green chemistry can enable more excellent public safety, public health, and enhanced process efficiency, potentially reducing the cost of

medicines and spurs the innovations required to evolve industrial practices towards ultimate sustainability. A good example of broad green chemistry impact that FDA encouragement can achieve is seen via Q-11: development and manufacture of substance. By enabling and defining advanced GMP starting materials as a significant structural fragmented substance of defined chemical properties. Pre- GMP can be easily optimized without additional regulatory filing, and equivalence and control are ensured through rigors specifications at GMP starting materials.

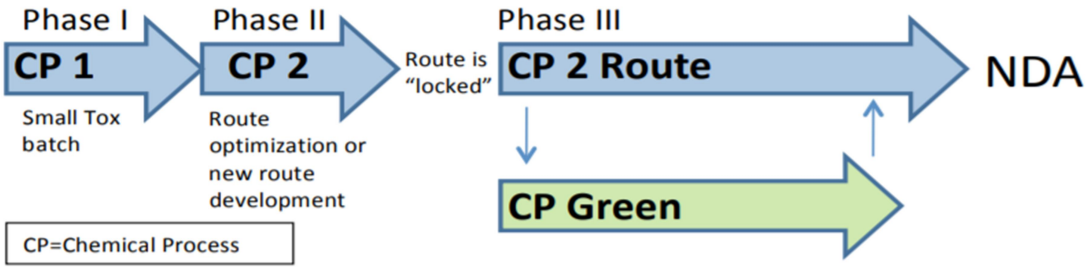
Two significant opportunities exist for FDA to greatly encourage Green chemistry in the pharmaceutical industry while ensuring safety.

1. By limiting the review of 2nd generation synthetic routes to new CMC sections only and clarifying expectations for analytical equivalence of a drug substance, FDA eliminates the perceived risk related to the reexamination of existing marketed products and dramatically influences the evolution of green manufacturing of pharmaceuticals.
2. The FDA enhances a greener process by providing clarification on a path to analytical equivalence with streamlined toxicological approaches. Pre- NDA a path to equivalence, will encourage green chemistry by pharmaceutical firms during phase III clinical studies to ensure the best technology and methodology is used for drug manufacture. These two opportunities seized in tandem will enable green chemistry principles to be applied throughout the development and marketed lifetime of a drug providing a giant leap forward in our constant evolution towards sustainable pharmaceutical sciences.

Pre-NDA Green Chemistry Development.

Another opportunity for the FDA to inspire Green Chemistry incorporation is pre-NDA filing, in parallel with phase III clinical studies. The typical development cycle of most drugs involves the generation of a small toxicological batch of material at Phase I by any synthetic means possible. This material is then used to determine the toxicological profile of the drug and determine if advancement is appropriate. If the compound appears acceptable, Phase II development begins in earnest with examining the early route used to make Phase I toxic material concerning process research and development concerns, such as raw material and reagent selections, robustness, safety, scalability, physical attributes, cost, etc...Which includes route optimizations and frequently leads to new route development to replace the inefficient

Phase I route with a manufacturing-ready Phase II route. After Phase II, a final route is selected and used to manufacture the material required for Phase III clinical trials. Once this has been accomplished, the Phase II manufacturing route is "locked." And development halts in anticipation of filing this route in the NDA. The Phase III clinical studies then begin and can take years to complete. During this time, new methodologies, technologies, catalysts, etc., are being developed by the scientific community, and the "locked" phase II route is potentially regressing in technological relevance. If, on the other hand, a team of scientists would continue to develop superior, green methodologies for manufacturing this drug (a CP-Green route), it is possible that a far superior route from an efficiency and environmental standpoint could be included at the time of NDA filing. Like 2nd generation routes, this enhanced green chemistry development would raise the quality of synthetic routes filed with the FDA and used for pharmaceutical manufacture. The key is to address the comparability of the drug manufactured via the CP-Green route with the drug used in the clinic and manufactured using the CP-2 route. There are many ways to compare drugs manufactured by generic firms using an altered methodology and the drug manufactured using the established, patented, and filed route. With the safety of patients being paramount and immutable, clarification on FDA expectations regarding streamlined toxicological approaches (such as bridging toxicology studies) that enable product equivalence and patient safety to be determined analytically (rather than clinically) will further encourage the investment in greener route development prior to NDA filing **[20]**.



European Legislation implemented

The regulations implement the following European Union (E.U.) directives:

• Council directive 78/610/EEC, on the approximation of the laws, regulations and administrative provisions of E.U. member

states on the protection of the health of workers exposed to vinyl chloride monomer;

• Council Directive 89/677/EEC, art.1 (3) the importation, supply or use of benzene and substances containing benzene, amending the Marketing and Use Directive, 76/796/EEC;

• In part, Commission directive 96/55/E.C., the second adaptation to technical progress of the Marketing and Use Directive;

• Council Directive 90/394/EEC, on protecting workers from risks related to exposure to carcinogens at work.

• Health and Safety (Safety Signs and Signals) Regulations 1996 (SI 1996/341)

• Radioactive Material (Road Transport) Regulations 2002 (SI 2002/1093)

• Packaging, Labelling and Carriage of Radioactive Material by Rail Regulations 2002 (SI 2002/2099);

• Carriage of Dangerous Goods (Classification, Packaging, and Labelling) and Use of Transportable Pressure Receptacles Regulations 1996 (SI 1996/2

• Good Laboratory Practice Regulations 1999 (SI 1999/3106) **[17]**.

California has become a pioneer in requiring sustainable chemistry. On June 23, 2010, California's Department of Toxic Substances Control (DTSC) released the Draft Regulation for Safer Consumer Products. The draft regulation sets a science-based process for the evaluation of chemicals of concern in products. It implements a vital component of the 2008 Green Chemistry Initiative. It provides legal, regulatory, and strategic consulting, testing, and complete implementation programs for compliance, enabling you to meet compliance objectives, including consulting, Scope and compliance requirements, Product assessments, Strategy to reach compliance, Chemicals Training and Auditing, Third-party screening, and testing.

Regulatory landscape/current approval:

The pharmaceutical industry's adoption of continuous manufacturing and the intrinsic green benefits will live or die with the regulatory agency's approval process. Emerging technologies have been a strategic initiative for innovation by the FDA.

Barriers to implementation of green chemistry in the United States: These are the significant barriers to implementing green chemistry.

- Farming barriers
- Economic barriers
- Regulatory barriers
- Technical barriers
- Organizational barriers
- Cultural barriers

Regulatory barriers in a pharma company wish to change certain parts of its production method for a product on the

market in the U.S. it must undergo a time–consuming and expensive ratification process with the FDA. If a company develops a safer pesticide or produces in less hazardous environment friendly, it must go through the registration with EPA under Federal insecticide, fungicide, rodenticide agency (FIFRA). These regulations meant to protect do not offer incentives for greener alternatives that provide environmental health benefits and create a significant barrier to the implementation of green chemistry **[21]**.

Safer chemical ingredient lists and color codes (SCIL): The listed chemicals are safer alternatives, grouped by functional use. Green circle (605): Low hazard based on experimental or modeled data. Half-circle (102): Expected to be a low hazard based on experimental or modeled data. Additional data would strengthen our confidence in chemical's status. yellow triangle (210): Met safer choice criteria for its functional ingredients class but may raise some hazard profile issues **[6]**.

Safer chemical ingredients list: 918 chemicals and 987 listings on SCIL on November 2017: By functional ingredients classes:

Antimicrobial Actives (7)	Polymers (59)
Chelating agents (22)	Preservatives and Antioxidants (34)
Colorants (44)	Processing Aids and Additives (149)
De-Foamers (12)	Skin conditioning agents (46)
Emollients (26)	Solvents (67)
Enzymes and Enzyme	Specialized industrial chemicals (14)
Stabilizers (30)	surfactants (282)
Fragrances (152)	Uncategorized (24)

The E.U. now has a regulation in place for the control of chemicals in the European market. Regulation 1907/2006, adopted in December 2006, entered into force on June 1, 2007. It creates an integrated system for the Registration, Evaluation, and Authorisation of Chemicals Hazards. (REACH) and establishes a European Chemicals Agency to manage the chemical system. REACH requires companies that manufacture and import chemical substances to evaluate their risks and to take the measures needed to manage such risks. The burden of proving the safety of the chemical substances placed on the market lies with the industry.[17]

Scope:

The regulation covers all manufactured or imported substances placed on the market or used either independently or in preparations. The following are excluded, however radioactive substances (coveredbyDirective96/29/Erratum)- substances under customs supervision in temporary storage, in free zones, or free warehouses to re-exportation.

Registration:

Registration is the key element of the REACH system. It was decided to phase in the registration process to allow the registration of some 30,000 substances benefiting from transitional measures. The pre-registration period begins one year after the regulation enters into force - i.e., June 1, 2008. Companies will have six months to submit the required information to the ECHA. The information required is fairly limited and used to set up Substance Information Exchange Forums (SIEFs), where pre-registrants will be obliged to share certain information.

Evaluation:

Evaluation enables the agency to check whether the industry is meeting its obligations and avoiding tests on animals. Two types of evaluation are foreseen: dossier evaluation and substance evaluation. Dossier evaluation is mandatory for all registrations providing for specific tests enumerated in Annexes IX and X of the regulation (these are the most demanding tests, usually carried out on vertebrates).

Authorization:

The aim is to guarantee that the risks related to such use are kept under adequate control. The substances are gradually replaced by other substances or technologies when this is economically and technically viable. The manufacture, market release, or use of such a substance can be "adequately" controlled; authorization will be granted **[18, 19]**.

CONCLUSION:

Here, we conclude green chemistry is a process through which we achieve safely manufactured drugs by eliminating hazardous chemicals. By placing alternative chemicals and by functional classification of chemicals, the toxic chemicals in the drug can be removed. The regulatory authorities overview the restrictions on toxic chemicals by issuing the guidelines for safer chemicals, ingredients, solvents. Various new chemicals are produced by applying green chemistry principles and making them more effectively sustainable. Through the guidance of the regulatory body, green chemistry provides a clean green chemical; it is also called clean chemistry. Thus, green chemistry successfully identifies harmful chemicals and shows ways to eliminate their risk. EPA's main aim is to

implement green chemistry principles in all sectors by 2030 to promote sustainability.

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