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Ecopharmacovigilance Regulatory Frame Work For Pharmaceuticals In Us And Eu Countries

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ABSTRACT
Pharmacovigilance, which identifies and prevents adverse drug reactions, has evolved over time, and new developments have emerged in recent years. Patient reporting and social media usage have become popular, and hospital-based data repositories and electronic health records have opened up new possibilities. In this essay, we aim to review these developments and predict the future of pharmacovigilance.Pharmacovigilance involves several steps, including identifying a signal, determining the signal, quantifying the alert, and managing the alarm. Each step requires a different set of techniques and skills. In managing drug safety, pharmacovigilance plays a vital role in identifying and preventing adverse drug reactions.This paper is based on the medical specialty of drug-induced diseases and the science of pharmacovigilance. Although pharmacovigilance has become increasingly regulated, this paper does not address specific rules or definitions from regulatory bodies such as the ICH, FDA, or EMA.As pharmacovigilance continues to evolve, it is crucial to consider new developments and predict future trends. The next chapter of big data and pharmacoepidemiology in pharmacovigilance may follow the previous chapters on spontaneous reporting, analysis of individual case reports, reporting patterns, and report databases

KEYWORDS: Ecopharmacovigilance, Pharmacovigilance, Environmental Risk Assesment (ERA), Regulatory Affairs(RA), Pharmaceuticals in the environmen(PiE),European Medicine Agency(EMA), Food and Drug Administration(FDA).

I. INTRODUCTION

Regulatory affairs (RA) is a critical profession that ensures pharmaceutical companies comply with international regulations for producing safe and effective drugs for human and veterinary consumption. RA professionals are responsible for every aspect of drug development, from clinical trials to post-marketing activities, to maintain the safety and efficacy of the products. Any lapse in safety or regulatory procedures can result in product recall, damaging the company's reputation and costing millions of dollars(1)

OBJECTIVE

The objectives of regulatory affairs include understanding and navigating the complex regulations and laws related to the pharmaceutical industry, ensuring compliance with these regulations, working with regulatory agencies, advising companies on regulatory aspects, and staying up-to-date with the constantly evolving regulations in different regions of the world

PHARMACEUTICAL REGULATORY AFFAIRS

Outsourcing has become common in the pharmaceutical industry for development, manufacturing, and quality control. The Contract Research Organization (CRO) sector is expected to grow by 10-12% due to increasing pharmaceutical R&D.(2)

REGULATORY AFFAIRS IN PRODUCT MANAGEMENT

For development, manufacturing, and quality control, outsourcing has grown widespread in the pharmaceutical sector. As pharmaceutical R&D increases, the contract research organisation (CRO) industry is predicted to rise by 10-12%. (3)

REGULATORY AFFAIRS IN CLINICAL TRIALS

RA specialists serve as liaisons between companies and regulatory agencies, ensuring compliance with all necessary regulations and guidelines. RA professionals are the primary

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contact point for international regulatory bodies, such as the USFDA and UKMCA, and interpret the complex regulations and guidelines to other departments in the company. They develop strategies to expedite the approval process and ensure compliance with government obligations, market demands, and evolving scientific conventions while balancing risks and benefits for health products.(4,5,6,7)

CHANGES IN REGULATORY ENVIRONMENT

In India, the pharmaceutical sector began conducting phase III trials after the introduction of `clinical trials registry and is currently working on a bill to regulate the medical device business. The government plans to establish the Medical Devices Regulatory Authority to control the medical device market(8)

REGULATORY AUTHORITY

Drug manufacturers and administrators have the same goal: to improve public health by ensuring that safe, effective, suitably branded pharmaceutical products according to strict value standards are developed, tested, evaluated, and approved for marketing in the shortest amount of time possible.(9)

REGULATORY BODIES IN THE WORLD

COUNTRY	REGULATORYAUTHORITY
India	Central Drugs Standard Control OrganizationDrugcontrollergeneralofIndia(DCGI)
US	FoodandDrugAdministration(USFDA)
UK	Medicines and Health care productsRegulatoryAgency(MHRA)
Australia	TherapeuticGoodsAdministration(TGA)
Japan	Japanese Ministry of Health ,LabourandWelfare(MHLW)
Canada	Health Canada
Brazil	Agency National degradation VigilanciaSanitaria(ANVISA)
SouthAfrica	MedicinesControlCouncil(MCC)
Europe	European Directorate for Quality of Medicines(EDQM)EuropeanMedicinesEvaluationagencies (EMEA)

PHARMACOVIGILANCE

Although all drugs have risks, some may also have benefits [10]. The dose is whatdistinguishes the drug from the poison because everything is poison and nothing is poison[11]. We reviewed the past of pharmacovigilance with an eye toward the future in an earlierpaper [12]. The world has changed somewhat in the last five years. Patient reporting hasgainedpopularityinadditiontothecustomaryspont

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aneousreportingbyhealthcareprofessionals. Social media usage has skyrocketed, and researchers are mining it in the hopeof discovering new security risks [13]. Hospital-based data repositories or electronic healthrecords have opened up new possibilities, and data resources like databases for the nation'shealthcare systems arenoweasilyaccessible.

Reviewing these developments and making another attempt to foresee the future thenext chapter in pharmacovigilance are the goals of the current paper. Will the next chapter ofbig data and pharmacoepidemiology in pharmacovigilance follow the previous chapters onspontaneousreporting,analysisof individual case reports, reportingpatterns,andreportdatabases?

To establish the contextfor reflection,let's look at the steps involvedin managingdrug safety, or pharmacovigilance: identifying a signal, determining the signal, which thenbecomes an alert; quantifying the alert, which can become an alarm; and managing the alarm,whichroughlycorrespondstohowadiseaseistypicallymanagedclinically:suspicion(symptoms),diagnosis(confirmation),evaluation(extentandseverity),andtreatment(followed by measles). Just as there isn't a single exam or test that can cover everything inclinicalmedicine,eachofthesestepscallsfor adifferentsetoftechniquesandskills**(Fig1).**

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Figure 1.Pharmacovigilance

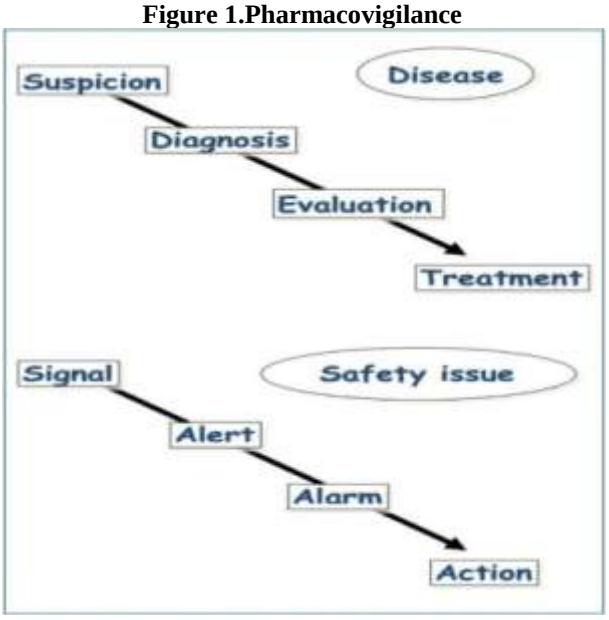

Figure 2.Management of disease and of safety issues.

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Therearefourimportantmethodsin Pharmacovigilancesuchas,

- Passivesurveillance.
- Activesurveillance.
- Cohorteventmonitoring.
- TargetedClinicalInvestigations

Adaptingandapplyingcommonmethodsusedin pharmacovigilancetoeco-pharmacovigilance

Compared to PV, EPV is a more recent and less matured discipline with fewer specified implementation methods and strategies(14). The main focuses of current EPV policies include emissions reduction during production, environmentally friendly drug design, sensible drug usage, take-back and management of unwanted medication. To clarify the model and implementation methodologies, more effort is required because these procedures are neither systematic nor explicit. The experience of PV canserve as the basis for EPV.(15,16,17)

Summaryofthepossibleapplicationofcommonl yusedmethodsofpharmacovigilance(PV) in the implementofeco-pharmacovigilance(EPV).

Methods	Characteristics	Pharmacovigilance	Ecopharmacovigilance
Spontaneousreporting	Contentofreports	Themostcommonlyused, standardized, passiveandvoluntarySuspectedADRs ofmarketeddrugs	Theuncontrolledreleaseofpharmaceuticalsintowastewaterortheallegednegativeeffectsofpharmaceuticalresidues
	Reportingentities	Bymanufacturers,consumers, patients,andeven thegeneral publicinsomecountries, healthcareprofessionals (includingdoctors, pharmacists,andnurses)	More dependent onManufacturers,hospitals,environmental researchers,consumers and the public
Intensivemonitoring	Content	Active and targeted Intensivemonitoring fortheuseof certain selected drugs on basisof clinical prescription dataduring a certain period oftime	Intensive monitoring forthe specific pharmaceutical products with higher volumeofuseandhigherpotentialenvironmentalrisks

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Databasestudies	Aim	SystematicandtimelyTo testhypotheses(i.e.the adverseeventis suspected ofbeinganADR)developed after signals have been detected in Spontaneous reports, in orderto facilitate the moretimelyidentificationandquantitationofADRs	Toacquiremorecomprehensivereal-timedataonpharmaceuticalresidues

Spontaneousreporting

Spontaneousreporting,whichisthemost popularmethodofPV,isa standardized andpassiveformused forreportingsuspectedadversedrugreactions(ADRs)ofmarketeddrugstoregulatoryagencies.Itprimarilydependsonthevoluntaryreportingbyhealthcareprofessionals(includingdoctors,pharmacists,andnurses),aswellasinsomecountriesbymanufacturers, consumers, patients, and even the general public (18,19,20,). Spontaneousreporting has been described as the backbone of data collection in PV, and the most importantfunctionsofwhicharetheearlyidentificationofpotentialsafety"signals"formedications,formulationofhypotheses,thenfurtherconfirmatoryinvestigations, sometimesregulatory warnings (21). Based on clinical suspicion, the "suspected" adverse reactionsmight be early identified and gathered into standardised databases in the national orregional PV centresutilising phone, paper, e-mail, or directly online via tablets, theInternet,andsmartphones.

Intensivemonitoring

By expressing issues with underreporting and the challenge of quantifying ADRs, intensive monitoring is an extension of spontaneous reporting that seeks to boost the reporting of ADRs connected to particular drugs. It entails documenting adverse side effects using questionnaires filled out by the prescribing doctor and clinical prescription data used to monitor medication use. By measuring the frequency of adverse events, this technique enables ADR quantification. It is the duty of pharmaceutical manufacturers to oversee their own medications.Databasestudies(22,23,24,) such as cohort and case-control studies, are an effective PV method for examining hypotheses developed after signals are discovered in spontaneous reports. Case-control studies look backward at newly identified ADRs, while prospective cohort studies monitor adverse events in a sizable population exposed to a medication. Both kinds of investigations can be done quickly and affordably, especially when the sample size is modest. Database studies, like cohort and case-control studies, are effective pharmacovigilance (PV) techniques for examining the safety of medications. By carrying out cohort studies to track pharmaceutical levels in environmental samples and retrospective case-control studies to look at potential pollution sources, these techniques can also be applied to environmental PV. These investigations present chances to look into various pharmaceutical contaminants and create a common

AIM & OBJECTIVE

AIM

The purpose of this understand and compare the ecopharmacovigilance regulation in Eruope and US. It is therefore necessary to establish an eco-pharmacovigilance system monitoring and collection of data which would eradicate the risk of pharmaceuticals entering into the surrounding.

OBJECTIVES

- It is compareing the similarities and the differences will give a better comprehension on the different strategies embraced by the different countries with the purpose of protecting the environment from exposure to harmful pharmaceutical drugs.
- "Targeted EPV" implementation focuses on targeted monitoring of the presence of high risk agents in the environment, targeted reporting of over standard discharge.

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 Many committees, as well as pharmaceutical companies, are working together for minimizing the potential impacts of medicine on the environment.
 Although the detected concentrations of pharmaceuticals in the environment are generally low, (ng/L to µg/L) potential direct and indirect risks for human and animal populations do exist and hence should be carefully monitored.
 There are several policies in place that can lessen the toxicity of the products in the environment, such as manufacturers' evaluation and minimization of hazards.
 Educating and encouraging the patients will helpthem to properly dispose the medicines.
 This illustrates the various ERA policies adopted globally emphasizing the current Indian scenario as well.

II. METHODOLOGY

The research was carried out to describe in detail about the role, impact and ecopharmacovigilance regulatory frame work in pharmaceutical sector .The purpose and the future aspects of ecopharmacovigilance in regulatory frame work in pharmaceuticals is also described.

SOURCE OF DATA

The majority of the data collection was done from the Guidance documents released in official website. Search engines such as Google, Google Scholar were exploited to obtain the data for the study Official guidelines are followed by the regulatory department in Europe and US, Several literatures and books were reviewed as the secondary source.

The following criteria's were used to evaluate the data collected for the analysis:

 Introduction and detailed description about pharamacovigilance and ecopharmacovigilance
 Review on current regulatory approval process in US and EUROPE
 A study on recent updates and changes.

ECOPHARMACOVIGILANCE:

"The research and activities concerned with the investigation, assessment, comprehension, and prevention of hazardous environmental impacts of pharmaceuticals."Otherwords,"science and actions related to detection, assessment, understanding, and avoidance of adverse effects or other difficulties related to presence of pharmaceuticals in the environment, which influence human and other animal species (25)

Need of ecopharmacovigilance:

 Active pharmaceutical ingredient represent consumption of emerging environmental contamination
 It is estimated worldwide consumption active compounds amounts to be some 100000 or more per year
 Even in trace amounts they are great concern due to their continuous introduction into the environment, their impact on ecosystem and human veterinary health is of great importance
 Now a regulatory requirements prior to launch of any new drug
 Several challenges that has to met EPV is to effective in practice like environment risk management plan

III. STUDY AND DISCUSSION

Whatisecopharmacovigilance(epv)?

Before introducing the EPV concept, some background is necessary on PIE and theERAofpharmaceuticals.

Definitionofepv

Velo is credited with creating the phrase "ecopharmacovigilance." (26) The titlesecopharmacology,environmentalpharmacology,pharmacoenvironmentology,pharmacovigilance, and ecopharmacostewardship have, however, been proposed in a numberof other studies to represent this recently growing subject. Although these articles introducethe idea of EPV and some approaches to it, they typically cover a much broader range thatencompassesallaspectsofsustainablepharmacy,including greendrugdesign,greenchemistryinprocess development,minimisingmanufacturingemissions,improvedprescribingpractises,andthemanagementofunusedmedications.

ECOPHARMACOVIGILANCE

Ecopharmacovigilance is the science and practice of identifying, evaluating, able tounderstand, and preventing adverse effects or other issues associated with the presence ofpharmaceuticalsintheenvironmentthathaveanimpactonpeopleandotheranimalspecies.(27)

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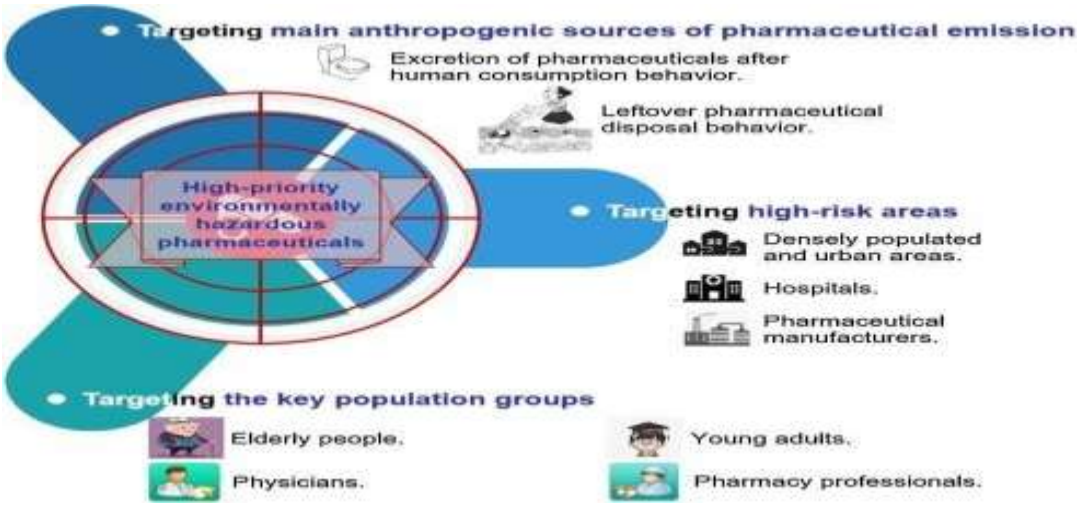

FIGURE3Ecopharmacovigilance

Ecopharmacovigilance is the identification, evaluation, comprehension, and avoidance of negative effects caused by pharmaceuticals in the environment. This includes the consequences of pollution by drugs, ways to reduce their release, and their regulation. India lags behind in EPV compared to the West, posing risks to public safety and the environment due to improperly disposed of expired or unused medicines.

SourcesofEntryofPharmaceuticalsintoEnvironment

The consumption of drugs is increasing in humans and animals, resulting in large quantities of drugs being excreted into sewage. Industrial waste from pharmaceutical companies also contributes to drug contamination in the environment.

Despite sewage treatment, some drugs are not entirely removed, leaving traces in water supplies, including cocaine and oral contraceptives.(28,29,30)

Drugs such as cocaine, antidepressants, antileptics, statins, hormones, paracetamol, diclofenac, and fluoroquinolones have been found in various water sources worldwide, including the Po River in Italy and the Niagara River.

Although the contamination is small, it still poses a risk of drugs unintentionally re-entering humans through drinking water.

FIGURE 4SourcesofEntryofPharmaceuticalsintoEnvironment

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Theemergenceofecopharmacovigilance

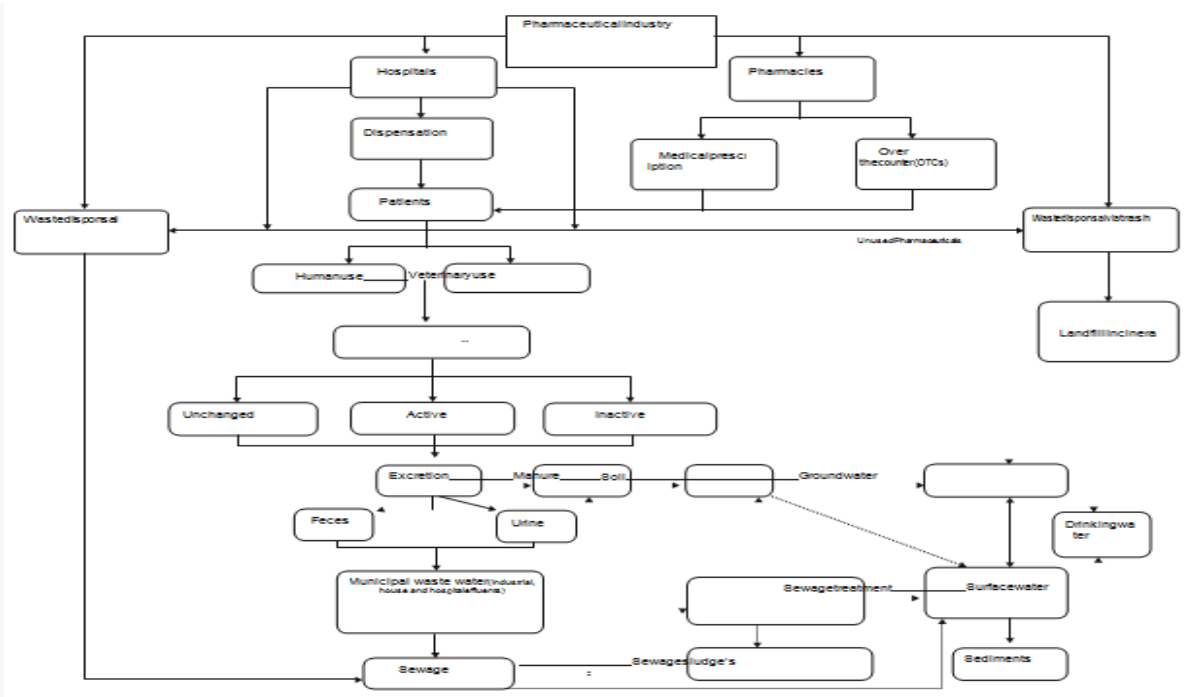
Interest has been shown in the topic of ecopharmacovigilance (EPV), which focuses on discovering, evaluating, understanding, and preventing adverse effects of drugs on the environment. By using green chemistry, EPV aims to develop environmentally friendly medications, promote responsible medicine use, and reduce production emissions. In terms of identifying, assessing, and treating EPV, the World Health Organization is worried. LifeCycleofPiE

Overviewofeco-pharmacovigilance

DaughtonandRuhoy(31)firstproposedtheideaofeco-pharmacovigilance,whichisdescribedas"thescienceandactivitiesconcerningdetection,assessment,understanding and prevention of adverse effects or other problems related to the presence ofpharmaceuticalsintheenvironment,whichaffectbothhumanandtheotheranimalspecies."(32) This closely resembles the World Health Organization's (WHO) definition ofpharmacovigilance (33), a field of study that looks for any negative effects of drugs onhumans after they have been taken. Pharmacovigilance systems collect, monitor, research,evaluate, and assess data from medical personnel, including physicians, dentists, pharmacists,nurses, and other health professionals, in order to be aware of adverse drug reactions. Couldstudiesonpharmacovigilancehelptoimproveeco-pharmacovigilance

Overviewofenvironmentriskassessment

In response to the adoption of a number of environmental laws, risk assessment inthe context of the environment first emerged in the United States in the 1970s: The Pure Airthe Federal Insecticide, Fungicide, and Rodenticide Act of 1970, the Safe Drinking Water Actof 1974, the Toxic Substances Control Act of 1976, and the Clean Water Act of 1977 aresome examples of legislation that regulated pesticide use. The newly established USEPA wastaskedwithenforcingtheseregulatorystatutes.Theselawsrequiredtheevaluationofenvironmental and public health risks as a foundation for regulatory decision-making, eitherexplicitly or implicitly. However, the USEPA offices and other regulatory organizations
thatuphold regulatory statutes have different interpretations of risk assessment. In 1981, the USNational Academy of Sciences was asked to review the "institutional means of assessment ofrisks to public health" due to the controversy that the risk assessments had caused (NRC1983)..



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Phases inRegulation		StudyObjective	RiskAssessment Stages	RiskAssessment Approach	Test/ DataSpecifications
PhaseI		ExposureAssessment	Pre-screening	Actionlimit	Consumptiondatalog Kow
PhaseII	Tier A	Initial predictionofrisk	Screening	RiskAssessment	Basesetaquatictoxicologyandfate
	TierB	Refinement andriskassessment	Extended	RiskAssessment	Extended data seton emission, fateandeffects

ECO-PHARMACOVIGILANCE OF PHARMACEUTICALS INUSAANDEUROPE

Although pharmaceuticals promote health, their production, usage, and disposal have a negative influence on the environment. Concern over their presence in aquatic environments, especially drinking water, is growing. To lessen dangers to the health of people and animals, the effects of medications on the environment are being researched.(34)

The incorrect disposal of drugs can have detrimental impacts on the environment, including the growth of germs that are resistant to antibiotics and the contamination of water sources. Environmental risk assessment (ERA) and ecopharmacovigilance (EPV) have been created to identify, evaluate, comprehend, and mitigate the harmful impacts of medications on the environment. Every prescription that poses a risk to the environment must be reported and properly evaluated to lessen its effects, according to legislation in the EU. ERA is made of (35)ofThrough a variety of pathways, pharmaceuticals pollute our environment by enteringthe environment. After using, patients contribute to this process as well. pharmaceuticals **.**Human pharmaceuticals may enter the environment through one or moreofthefollowingroutes:

- Releasefromthemanufacturingsite.
- Thediscardingofunusedmedicationbypatients,hospitals,orsuppliers.

Pharmaceuticalsthatpatientsexcreteintothewastewaterasmetabolites

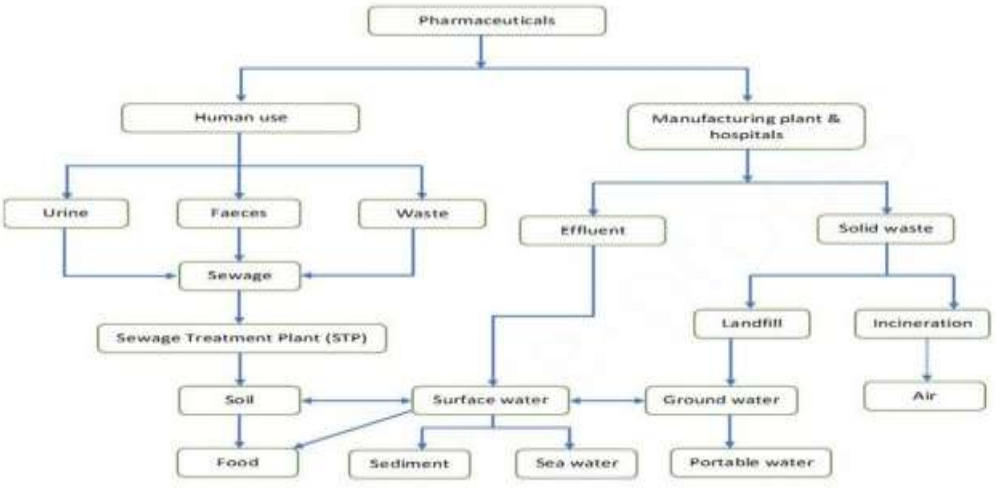

Figure5.Pathway into which the pharmaceutical enter into the environment

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STUDY AND DISCUSSION

EUEnvironmentalRiskAssessment (ERA)

Theprocessofdeterminginghowmuchofanenvironmentalimpacttheusageofchemicals will have is known as the Environmental Risk Assessment (ERA). The EU's ERAfor pharmaceuticals is outlined in Article 8(3) of Directive 2001/83/EC. According to theregulations, every medication that poses a risk to the environment must be disclosed and thenthoroughlyexaminedtoreduceitseffects.

Regardless of the authorization process, an ERA is seen as necessary (36). The ERAis not required for Type IA/IB variations, but it is required for Type II variations. Accordingto EMEA/CHMP (2006), Module 1.6 of the marketing authorization application must containtheERApaperTo guarantee that the applicant conducts the ERA properly, rules for the ERA ofmedicinal goods for human use were proposed. In addition to the present risk evaluationprocesses,thenewrulesthattheEMAhasadoptedrequirethathazardousandbio-accumulative waste be subjected to hazard assessments. As of June 30, 2019, the regulationswereineffect(37).Table1 displaysanoverviewofenvironmentalrisk assessment.**(Fig10)**

ERA CONSIST OF

PhaseI: exposureofdrugsubstancetotheenvironment.

1. PhaseII:assessmentoffateandeffectsintheenvironment.ThePhaseIIissubdividedinto:

a) TierA

b) TierB

Environmentalriskassessmentforantibiotics

Antibiotics need to be assessed specifically due to their unique mechanism of action.PhaseIIevaluationisappliedtoallcompartments,includingfateconsiderations,forantibiotics.Fortheaquaticcompartment,anOECDecotoxicitytestisavailable(38).

Antimicrobials and other pharmacological targets in the aquatic compartment shouldbe specifically evaluated (39). The information from science on lower tropic levels, whichare targeted for suitable sensitivity for antibacterial treatments andinclude bacteria, algae,and marine invertebrates (40).displays the test that was necessary for compoundswithanantibacterialmechanismofaction.

List oftestrequiredforactivesubstanceswiththeantimicrobialmodeofaction

Test	Testspecies	Endpoint
OECD201	Anabaenaflos-aquae (Cyanobacteria)	EC*10orNOEC*
OECD201	Synechococcusleopoliensis (Cyanobacteria)	EC10orNOEC
OECD201	Raphidocelissubcapitata (Greenalgae)	EC10orNOEC
OECD211	Daphniamagna (invertebrate)	EC10orNOEC

*EC- Effective concentration representing 10% of the maximum effectNOEC-no observedeffectconcentration

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IV. METHODS

The applicantmustdisclose information aboutany potential danger associated withhis chemical to the environment when submitting applications such as NDAs, ANDAs, INDs,andBLAs.TheUSplacesastrongemphasisonthe requirementforanenvironmentalassessment of those compounds, whose application has received many approvals, and at thepoint of introduction to water bodies, the concentration is approximately 1 ppb or higher. In some circumstances, the permitted moiety may have an effect on the compoundsalready present in the environment, or the applicant may claim that his molecules may haveunfavourableharmfuleffectsifpresentinquantitie soveraspecificthre focuses solely on the active chemical, and evaluations are based mostly on what happens toand how it affects the environment after being released into the environment. Data from testsconducted on the specified chemicals or from a literature study must be provided by theapplicant (41). focuses solely on the active chemical, and evaluations are based mostly on what happens toand how it affects the environment after being released into the environment. Data from testsconducted on the specified chemicals or from a literature study must be provided by theapplicant (41).

Estimatingthesubstance'srelease'senvironmentalfate isthefirststepintheevaluationprocess.Itmostlyconsist sof4stages,namely:

1. Identificationofsubstancesofinterest.
2. Physicalandchemicalcharacterization.
3. Environmentaldepletionmechanism.
4. Environmentalconcentrations

IDENTIFICATION OFSUBSTANCESOFINTEREST

The compoundsthatmight enter the environment are identified and listed at thisstage. The chemicals chosen for the investigations must have a valid justification and mustmake up more than 10% of the dose. The parentmolecule's information must be provided,and Substance Registry Services (SRS) will consider if there are structural similarities ordifferencesbasedonthatinformation.

PHYSICALANDCHEMICALCHARACTERIZ ATION

IDENTIFICATION OFSUBSTANCESOFINTEREST

The compoundsthatmight enter the environment are identified and listed at thisstage. The chemicals chosen for the investigations must have a valid justification and mustmake up more than 10% of the dose. The parentmolecule's information must be provided,and Substance Registry Services (SRS) will consider if there are structural similarities ordifferencesbasedonthatinformation.

PHYSICALANDCHEMICALCHARACTERIZ ATION

Numerous tests are included, including the octanol/water partition coefficient test, thewatersolubilitytest,thedissociationconstanttest,an dtheHenry'slawconstanttest(164)Fischer and Ballschmiter, 1998]. The octanol/water partition coefficient test must becarried out at pH levels 5, 7, and 9 if the according to .(42) and Fischer and, test substance isdiscoveredtodissociateorinteractwithwater.

ENVIRONMENTALDEPLETIONMECHANIS M

Data pertaining to this investigation must be provided since the test's main goal is toexaminethedepletionmechanism.Intheeventthatth edepletionlowerstheestimatedconcentration of the substance introduced into the environment, detailed information from theanalysis must be provided. No tests other than the microbial inhibition test are necessary inthese circumstances if a substance is found to be rapidly depleting. In order for a substance todegradequickly,itmust:

- Hydrolysist½(pH 5-9):≤24hours
- AerobicBiodegradationt½:≤8hours
- SoilBiodegradationt½:≤5days

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ComparisonofERAforpharmaceuticalinEUandUS

	US	**EU**
Category	**HumanPharmaceuticals**	
Title	Environmental Assessment(EA),Environmental ImpactStatement(EIS)	Environment RiskAssessment(ERA)
Legislation	National Environmental PolicyAct1969(NEPA),FederalFood,DrugandCosmeticAct(FFDCA) 21CFR25.15,40 CFR1508	Article8(3)ofDirective2001/83/EC,Regulation ECno .726/2004
Subject	HumanDrugsand Biologics	MedicinalProductfor humanuse
Guideline	GuidanceforIndustry-EnvironmentAssessmentofHumanDrugandBiological Application	Guideline on the Environmental RiskAssessment of the Medicinal ProductsforHumanUse
Authorities Responsible	FoodandDrugAdministration	EuropeanMedicine

	(FDA)&CentreforDrugEvaluationandResearch (CDER)	Agency (EMA) & Committee forMedicinalProducts forHumanUse(CHMP)
Analysisas	Products	Products
Assessmentof	New Products	New Products
Application	NDA,ANDA,IND,BLA	Formarketingauthorization
Approach	Tieredapproach(Tier1,Tier2,Tier3)	Phase-tiered approach(Phase I;PhaseII,TierA,Tier B)

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ExclusionCriteria	When the estimatedconcentrationofthes ubstanceat the point of entry into theaquaticenvironmentwillbe1 ppborlessor (EIC<1µg/L)	Whenitisclearthatthereisnoenvironmentalimpa ct(PEC<0.01µg/L)
Risk Assessmentcharacteri zation	EC50(LC50)/MEEC<10	PEC/PNEC≥1
Tieredapproach	Applicable	Applicable
Prioritylist	NotApplicable	NotApplicable
Submission	DM For MF whenRequired	Module1.6

5.2 EUANDUSdataondetectionofconcentrationofPharmaceuticalsandchemicalsintheenvironment(Table8)

Chemicals	**Concentrationra nge(µg/L)**	**Concentrationrange(µg/L)**	**country**	**Concentrationrange (µg/L)**	**Reference**
Antimicrobials/antibiotics					
Azithromycin	0.022–7.351	Riversandlakes;surface water;STPs; wastewater	U.S	90-320	Lopez-Sernaetal.,2012;
Ciprofloxacin	0.01–38.689				
Clarithromycin	0.002–8				
Clindamycin	0.02–0.50				
Cloxacillin	0.005–0.05				
Doxycycline	0.019–0.078				
Enrofloxacin	0.003–0.015				

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Erythromycin	0.009–7.545				
Lincomycin	0.004–0.11				
Metronidazole	0.009–12.315				
Ofloxacin	0.006–24.811		**Europe**	ND-3052	Siemens etal.,(2008)
Penicillin	0.003–0.064				
Roxithromycin	0.001–0.009				
Sulfamerazine	0.007–0.009				
Sulfamethazine	0.017–0.641				
Anti-epileptics					
Alprazolam	0.0044-0.168	Rivers andlakes; STPs;surfacewater; wastewater	U.S.	Althakafyetal.,2017;Gibsonetal.,2010;Patroleccoetal.,2012;Nannoue tal.,2015;	
Citalopram	0.009–0.888				
Diazepam	0.002–0.049				
Fluoxetine	0.014–0.24				
Lorazepam	0.017–1.325				
Nordiazepam	0.001–0.003		Europe		
Olanzepine	0.001-0.824				
Paroxetine	0.007–0.25				

Anti-inflammatory agents				
Acetylsalicylicacid	0.005–0.93	Riversandlakes;STPs; groundandsurfacewater ;seawater;wastewater;h ospitalandindustrialeffl uents	US	SanJuan-Reyesetal.,(2015)
Diclofenac	0.001–104.63			
Ibuprofen	0.001–100.40			
Indomethacin	0.051–0.15			
Ketoprofen	0.001–3.25		Europe	
Naproxen	0.001–1.717			
Nimesulide	0.001–1.717			
Paracetamol	0.016–3.034			

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Phenazone	0.010–0.271				
Hormones					
17α-Ethinylestradiol	0.021–3.18	STPs;lakes	US	0.2-9.6	Díaz-Torresetal.,2013, Martín et al.,2012;Pessoaet al., 2014;Yuetal.,2013
17β-Estradiol	0.001–0.776				
Estriol	0.008–0.83		Europe	ND-25	
Estrone	0.001–3.05				
Pharmaceuticalsusedin diabetes					
Glibenclamide	0.027–0.096	Rivers;STPs	Europe	_	Althakafy Lopez-Sernaetal
Metformin	0.003–9.08				
Sunscreenagents		WWTP Effluents	Europe	_	[Li etal.,2007] [Kasprzyk-Horderneta l., 2009]

*ND-Notdetected

V. SUMMARY AND CONCLUSION

- Daughton andRuhoywerefirstproposedeco-pharmacovigilance,forconcerningdetection, assessment, understanding and prevention of adverse effects of both humanandtheotheranimalspeciesbythepresence pharmaceuticalsintheenvironment.
- The aim of eco-pharmacovigilance to increase ERA and enable the forecasting ofpotentialenvironmentalissues.
- Inregulatorysciencefollowingamendmentswere implemented,TheEuropeanParliamentadoptedamendmentstothelegislationinSeptember2010(Directive2001/83/EC and Regulation EC No 726/2004 was done for expand the definition ofpharmacovigilanceformonitoring and assessing the risk of environmental effects ofpharmaceuticals to the comment until November 7, 2011.Unlike, In 1981 the USNationalAcademyofScienceswasaskedtoreviewthe"institutionalmeansofassessment of risks to public health" due to the controversy that the risk assessmentshadcaused(NRC1983)&theRedBook(NRC1983)offersaframeworkforassessing the risks to human health, including hazard identification, dose-responseevaluation,exposureevaluation,andrisk characterization.
- Many ERA procedures have been adopted by numerous nations and organizations,including the "Organization for Economic Cooperation and Development (OECD)" tosafeguard the environment. From that EU and US countries were find to be the bestone for assessment of ERA. According to EMEA/CHMP (2006), Module 1.6 of themarketingauthorizationapplicationmustcontaintheERApapers.
- In EU, ERA were done by phase I (exposure of drug substance to the environment) &phase II (Assessment of fate and effect in the

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environment) process and also done byTier I (Initial prediction of risk), Tier II (Refinement and risk assessment). Totally95% of antibiotic drugs possess risk to environment, for that EU country the followedphaseIIforERAdetection.

- In US, ERA were followed only Tier I (Initial prediction of risk), Tier II (Refinementandriskassessment)forpharmaceuticalseffectonenvironment.
- So far, we compared the regulatory frameworks for US and EU country for knowingthe drawbacks, from that we can identify the EU countries follow the more proced

Conclusion:

Thereisahighnecessitytoestablishaneco-pharmacovigilancesystemformonitoring and collection of data, which would reduce the hazardous pharmaceuticals frominvading the ecological system.Overall, the regulations for the environmental risk assessmentforpharmaceuticalsarebecomingstrict.Butthereisalsoaneedtoimplementtheseregulations particularyinUScountrytoavoidthe drawbacks occurredduringtheERAassessment.At present, there are no specific guidelines for ERA of pharmaceuticals in US.Nevertheless, it's expected to have strict regulations and legal requirement shortly.It is alsonecessary to regulate the environmental risk assessment from a few drugs to comprehensiveenvironmental monitoring of all pharmaceuticals across their life cycle. Lastly, there is a needtoimprovethewastemanagementsystem,which willbeahugeglobalchallenge.

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