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PHARMACEUTICAL PACKAGING SAFETY: A REVIEW ON EXTRACTABLES AND LEACHABLES AND QUALITY ASSURANCE PRACTICES

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ABSTRACT

Pharmaceutical packaging plays a leading role in the safety, stability and efficacy of drug products during their shelf life. However, substances known as extractables and leachables (E&L), which migrate from packaging material into the drug formulation, really compromise the good quality and safety for human life. This article reviews the different sources, types, and toxicological effects of E&L and the latest analytical techniques used for their detection, including GC-MS, UPLC-MS, and QTOF-LCMS. Various worldwide regulatory guidelines, including those of the USFDA and EMA, are discussed, with further emphasis on QA techniques to minimize contamination risks through risk-based approaches and adherence strategies. Real-life examples shall ultimately paint the picture in their application, highlighting actual issues. Consequently, limitations such as the lack of toxicological data and non-harmonized regulations will be tackled. With the promising safer and greener packaging systems, the emerging trends of greener materials and tamper-evident technologies shall also be weighed. This review tries to prove that pharmaceutical packaging needs a multi-disciplinary and internationally harmonized approach to ensure drugsafety and therapeutic efficacy.

INTRODUCTION

Packaging includes a variety of elements that enclose a pharmaceutical from the time of manufacture to the time of use. Packaging dispenses drugs, medical devices, medical treatments, and innovatively prepared products, such as nutraceutical medicines, in all conceivable forms of dosage to people all around the globe-as supplements, poultices, liquids, solids, powders, suspensions, or drops (1). Pharmaceutical packaging is divided into three layers. Primary packaging is the first level of packaging that comes into direct contact with the pharmaceutical product. Its main purpose is safe protection of the formulation with environmental, chemical, or even mechanical hazards. Common materials include glass (ampoules and vials), plastic (infusion containers and dropper bottles), and metals (ointment tubes). It may also include specialized forms such as strip and blister packs for tablets, and collapsible metal tubes for semi-solid preparations such as creams and ointments. Secondary packaging is the outermost layer enclosing the primary packaging to provide additional protection during handling, storage, and distribution. It also carries vital information on the usage of the product and Sundry data like manufacturing and expiry dates and batch numbers. The materials used here are paper, cardboard boxes, and printed leaflets. Tertiary packaging is related to large-scale storage and transport, such as pallets and large cartons, to help in stacking and protecting the products during shipment. (2)
Packaging acts as a vital element in regard to the pharmaceutical sector since its purpose is to ensure that the product remains protected throughout the entire course of its existence-from production through storage, distribution, and final use. The article states that pharmaceutical packaging protects drugs from environmental factors such as light, moisture, and oxygen, which may otherwise lead to spoilage, degradation, or contamination. In addition, adequate packaging will protect the drug from loss of potency, stability, and safety. The protective function of packaging will maintain hygiene and prevent microbial contamination, as well as preserve product quality in formulations that are adversely affected by environmental changes. It is also used for labeling vital details pertaining to the product, including dose, directions for use, and precautions to ensure proper administration and patient compliance. On the basis of the drug

characteristics and regulatory requirements, the packaging material may thus be made of plastic, paper, or glass and must be developed so as to remain unreactive and nontoxic, tamper-proof, and FDA compliant; hence very strongly attributing to the safeguards in whole for the drug itself. (14)

Heavy attention is given to packaging at every stage of a pharmaceutical product's lifespan-from production to patient use-to ensure drug safety. Besides working as a container, the packaging serves as the essential barrier against any factor that would otherwise compromise the medication's stability, efficacy, and integrity. Packaging ensures that the formulation is tightly sealed so that it should never have a chance to either leak or diffuse into an incompatible environment or to come into adverse interaction with external factors such as moisture, oxygen, or light, because all these could eventually deteriorate the product. Pharmaceutical packaging, in addition to containment, safeguards the drug from microbiological contamination, from physical damage, and from possible adulteration. So, packaging is also labeled with the necessary instructions, such as dose recommendations, batch numbers, expiration dates, and safety warnings, that allow both patients and healthcare professionals to use the product properly. For enhanced security, tamper-evident features and anti-counterfeit technologies are included against a backdrop of growing concern about counterfeit medicines. For the sake of convenience and safety, packaging enhancements should include child-resistant packaging and single-dose forms. Effective pharmaceutical packaging is the basic element upon which drug safety and, ultimately, public health protection and therapeutic outcomes hinge.(1)

The safety of medications is seriously threatened by the migration phenomenon in pharmaceutical packaging materials. To improve material performance, several additives like plasticizers, stabilizers, and antioxidants are added during the manufacturing of plastic, rubber, and other packaging materials. Nevertheless, these chemicals may seep into the medications from the packaging materials while they are being stored.[37] For the article, it is stated that leachables are chemicals that migrate into drug products from pharmaceutical packaging during production, storage, or administration. Extractables are those chemicals released in the laboratory under well-controlled conditions, and they form the source of leachables. Because leachables may alter drug efficacy and safety, they may be considered hazardous. States analytes are used to identify and quantify leachables, after which a toxicological risk assessment is undertaken to ensure patient exposure remains below acceptable limits.(3). Glass delamination consists of the separation of sheets or flakes of glass from the product contact surface. After the surface is chemically corroded, dissolved silicate network forms a gel that may spall and generate visible flakes in the medicinal product, according to the mechanism proposed for delamination.(39)

2. Extractables and Leachables

2.1 Definition , sources and examples

Extractables are chemical compounds that can be brought out from materials such as container-closure systems or medical devices when they are placed under specific laboratory conditions through a controlled extraction study. These substances are identified and determined in the extraction solution, and the data gathered-thus called the extractables profile-refers to the kinds and quantities of compounds present. This profile makes it possible to predict which substances may eventually migrate into the drug product during conditions of real use.(3)

Leachables are chemical substances, both organic and inorganic, that move from packaging materials, components, or delivery systems into a drug product during the usual conditions of storage and use or during accelerated stability testing. In more general terms, leachables are chemical compounds that migrate from packaging or any material in contact with the drug into the drug product during manufacturing, storage, distribution, or clinical use under normal conditions.(4)

Extractables are considered to be chemical entities released from pharmaceutical packaging or medical device materials under harsh laboratory conditions such as elevated temperature and aggressive solvents. These chemicals are found in components that are in direct contact with drug products, for example, stoppers, syringes, vials, tubing, filters, and storage bags. Materials used to fabricate these components-plastics and rubber-may contain additives, plasticizers, or by-products that can be extracted under stressing conditions. Though these materials preserve the drug quality and sterility, extractables have to be studied before release, as they could pose a risk if migrating into the product. Evaluating extractables determine which substances could emerge as leachables during storage or normal use and thus assist in the safety evaluation of pharmaceutical products. (5) Secondary sources encompass manufacturing equipment of tubing and gaskets, especially those made of silicone or Santoprene, which can release organic substances such as phthalates and antioxidants, or inorganic elements such as calcium and zinc. Extractables also can be released from other secondary components like labels, adhesives, or coatings. Such substances are identified in controlled extraction studies in order to evaluate the potential risk of migration into drug products. (7)

Leachables are chemical substances that are capable of moving from packaging, manufacturing, or delivery system components into a pharmaceutical product during normal storage or use. Substances can also leach into a pharmaceutical product from plastic containers, rubber closures such as stoppers and seals, single-use manufacturing systems including tubing, filters, and storage bags, as well as adhesives and printing inks on packaging materials. Even contact surfaces of processing equipment can contribute to leachable substances.(6) The article mentions that, in uncoated chlorobutyl and bromobutyl coverings, leachables do exist. During reflux with 2-propanol, trimellitates and other extractables seemed to have been promoted especially from the CB-1 closures. These were then leached into phosphate buffer formulations containing polysorbate 20 or 80 over a period of six months' storage at 40 °C/75% RH. Leaching was influenced by the types and concentrations of surfactants, in that higher concentrations were being leaked to at 1.0% polysorbate. (9)

Key extractables included antioxidant degradation products like bis(2,4-di-tert-butylphenyl) phosphate (bDtBPP), 2,4-di-tert-butylphenol, and 1,3-di-tert-butylbenzene, mainly from the breakdown of Irgafos 168. Silicone-based compounds such as dodecamethyl-cyclohexasiloxane and hexadecamethyl-heptasiloxane, used as lubricants, were also detected. Surfactants like Triton X-100 variants, plasticizers (phthalates, fatty acid esters), and inhibitors such as 4-tert-butylcatechol were identified. Degradation products of Irganox 1010 and 1076, including methylated and benzoquinone derivatives, were noted as well. (8)

2.2 Effect or risk associated of E&L on drug products

Extractables and leachables in plastic packaging can migrate into drug products with changes in their chemical makeup, resulting in consequences in their stability, efficacy, and safety. Many of these chemicals-monomers, additives, and degradation products-are registered carcinogens, reproductive toxicants, or endocrine-disrupting chemicals (EDCs). Some are also persistent and capable of bioaccumulation, providing long-term health hazards at even very low exposure concentrations. Further, very scanty information on non-intentionally added substances (NIAS) makes it difficult to carry out risk assessments thus making control of E&L important for safeguarding pharmaceutical products.(12)

Leachables—substances which migrate from packaging materials into drug products during manufacturing and storage—may jeopardize drug quality and patients' health. They may compromise or alter the drug's composition, stability, efficacy, and physical characteristics like taste or color. Some leachables are toxic and may have severe health consequences. These impurities become especially critical in liquid dosage forms, i.e., injectable or inhalers. If the limit is exceeded (e.g., Permitted Daily Exposure), recognitively the product has to be reformulated or denied approval. Some leachables, however, are more unpredictable and appear through interactions not seen in the initial set of extractable studies. (10) Extractables coming from drug products, if the extractables migrate there, harm product safety and quality. It was said that acrylic acid leached from the syringes and ended up reacting with a few therapeutic proteins and changing their activities. A degradant of Irgafos 168 (bDtBBP) was also found to be highly toxic in relation to cell growth. Depending upon material composition, solvent strength, contact time, and temperature, extractables can differ in types and

quantities. Such compounds may cause chemical interaction and toxicity, especially if present in amounts above their safety threshold such as the Analytical Evaluation Threshold (AET).(11)
Leachables coming from rubber stoppers, for instance, are detrimental to the quality and safety of drug products, especially biologics. This study finds that the oxidizing compound Luperox® 101, used as a polymerization initiator, had indeed been leaching from the clinical syringe stoppers. This chemical reacted with dichloromethane to produce 1,1,2,2-tetrachloroethane (TCE), a chemical known to be carcinogenic. Due to its oxidizing nature, the compound is alarmingly reactive and can probably chemically alter sensitive drugs such as proteins and stabilizers like polysorbates, considering it is not easily detected by common UV or MS methods. It could possibly alter the stability of drugs, lower their therapeutic effect, or even incite immune reaction, bringing into focus the importance of evaluating leachables associated with drug delivery systems (25)
In the realm of potential threats to pharmaceutical drug products, extractables and leachables might present substantial contamination risk as they may inflict migration from packaging systems, container-closure components, and manufacturing equipment into the actual drug formulation. These chemicals, which may include antioxidants, plasticizers, stabilizers, lubricants, colorants, vulcanizing agents, and even toxics such as lead, mercury, and cadmium, can in fact compromise the safety, identity, strength, quality, and purity of drug products. For example, residual monomers, oligomers, and numerous additives incorporated within polymers could simply leach out under usual storage conditions, and contaminate the drug product. Such leachables may interfere with the efficacy of the drug and induce toxicity when not adequately identified and controlled. Past use of harmful substances like carbon black in rubber, which resulted in the leaching of carcinogenic polyaromatic hydrocarbons, and bisphenol A in polycarbonate plastics, later discovered to be an endocrine disruptor, has shown the real dangers posed by uncontrolled leaeachables. (13)

2.3 Regulatory guidelines and Standards:

Among others, these publications are made to give further definition of the requirements of assessment of E&L: 21 CFR Part 211.94 stipulates that closures for drug products and containers shall not be reactive, additive, or absorptive to an extent which would alter the safety, identity, strength, quality, or purity of the drug beyond what is provided in the law. Chemistry, Manufacturing, and Controls Documentation of Container Closure Systems for Human Drug Packages (FDA, May 1999) Chemistry, Manufacturing, and Controls Documentation of Metered Dose Inhalers and Dry Powder Inhalers (FDA, October 1998) Chemistry, Manufacturing, and Controls Documentation of Industrial Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products (FDA, July 2002) Pharmaceutical Quality of Nasal and Inhalation Products June 2006 Guideline From EMEA Plastic Immediate Packaging Materials Guideline From EMEA May 2005. For the biological evaluation of medical devices, ISO 10993-12 and ISO 10993-17 give exhaustive instructions concerning how to extract samples of E&L and how much leachables are allowed to be present.(12)
On the leachables and extractables aspects, the USFDA guidelines are the most detailed, and they require the presence of leachables and extractables to be evaluated during drug development, especially for packaging materials in contact with the product. The USP chapters pertaining thereto are USP 1663 (extractables), USP 1664 (leachables), and USP 661 series (plastic systems). Testing may be performed with validated analytical methods-might include HPLC, GC-MS, FTIR, amongst others-and results evaluated against limit thresholds like TTC (Threshold of Toxicological Concern), SCT, QT, and AET for patient safety assurance.The EMA (Europe) regulates leachables and extractables under the guideline “Plastic Immediate Packaging Materials” and the corresponding CTD sections (3.2.S.6, 3.2.P.2.4, 3.2.P.7). Migration, sorption studies, and compatibility testing are required, along with toxicological evaluation under certain conditions of non-compendial packaging materials. The methods employed must either be pharmacopoeial or well-validated, and the packaging components must not compromise the quality or stability of the drug. (23)

3.Evalauation Techniques for Extractables and leachables

3.1 E and L studies

The paper represents a collection of various E&L studies where attempts have been made to identify and quantify chemical agents that migrate from pharmaceutical packaging and medical devices into drug products. It describes the use of controlled extraction studies (aggressive solvent to obtain all possible leachables) and leachables studies (real-use condition). Different extraction methods—simulated-use, exaggerated, and exhaustive—based on the existing regulations of USP and EP, and on the ISO 10993 system, are performed. The article stresses that solvent choice can influence E&L results, applying the Abraham solvation parameter model to project solvent behavior, identify equivalent solvents, and formulate drug product simulating solvents (for example, ethanol/water mixtures for sodium valproate). The same model is then used to evaluate solvent polarity and thus to estimate the solubility and migration ability of E&L compounds. This makes testing far more reliable, efficient, and scientifically prominent. (14,20)
Good planning for the extractable and leachable (E&L) study is essential for the identification of harmful chemicals that might migrate into pharmaceutical packaging or medical devices. The study involves five major steps: understanding the product and materials, designing an extraction method, analyzing the extracts, evaluating toxicological risk, and conducting a leachables study. Extraction methods are simulated, exaggerated, exhaustive, and accelerated; these extractions consider and study leached substances under both real and exaggerated-use conditions so that leachable substances are comprehensively detected and safety-estimated. Typically, leachable studies get done in drug development or stability testing, but they can also help in early-stage packaging choices. Knowing about extractables beforehand aids toxicological assessment. Factors such as the type and duration of contact must be considered since volatile compounds may even migrate via indirect exposure. Leachable studies can be conducted using actual drug products and packaging or through simulated systems under real-time and accelerated conditions. The results assist in evaluating leachables along with establishing safety limits and acceptance criteria. However, if formulation, packaging, or process alterations affect the leachable profiles, further studies may be needed.(15)

3.2 Instruments used

Gas Chromatography/Mass Spectrometry (GC/MS) Analysis:
To screen volatile and semi-volatile organic chemicals in extracted materials, a GC/MS instrument (Agilent 7890B/5977A) was used. The injector temperature was set at 250°C, and 2 mL of non-diluted extracts were injected onto DB-5MS at a flow rate of 1.0 mL/min of helium gas. The oven temperature was programmed from 50°C (column held for 4 minutes) to 300°C at 25°C/min and held for 8 minutes with a total run of 22 minutes. The MS scan specification 35-750 m/z gave detection for chemicals at ppm levels. A headspace GC/MS (Agilent 7890A/5975C) was used for the volatile leachables. Five-hundred microliters of the headspace was injected (Split 10:1) into the GC after 1:1 methanol-diluted leachables sample was sealed into a vial and heated to 85°C for 10 minutes. Both temperature program and HP-5MS UI column were the same as above. For the sake of consistency, the extractables analysis conditions were also kept consistent with that of the GC/MS. (16,21)
Ultra-Performance Liquid Chromatography–Mass Spectrometry (UPLC-MS) Analysis:
Pharmaceutical non-polar leachables by UPLCMS are detected. This method works for allowing screening for polar to non-polar compounds by ion sources such as ESI and APCI in a mass range of 100 to 1300 m/z. Due to its high sensitivity, UPLC-MS allows the detection of trace-level leachables including unknowns, which might have been overlooked in extractables investigations. The method development is done using mimic solvent systems, with verification at or below the AET using standard mixes to ensure accuracy and reliability in detecting potential leachables from packaging or equipment.(17)
Quadrupole Time-of-Flight Liquid Chromatography Mass Spectrometer (QTOF-LCMS)
This instrument's types included the Agilent 6545 system with Dual Agilent Jet Stream electrospray ionization (ESI) source in both

positive and negative ion modes. Having an accurate analysis of mass with structural information, the HRMS was very appropriate for identification of unknown extractables. It has all the features that allow its detection from very high m/z values (3200 m/z range) to low m/z values (80 m/z) and thus enabled one to detect compounds at trace levels. However, despite the relatively high RF variability, a QTOF-LCMS was central in structure elucidation and largely responsible for assessing extractables and leachables qualitatively. (18)

Headspace Gas Chromatography–Mass Spectrometry (HS-GC/MS):

The Headspace Gas Chromatography-Mass Spectrometry (HS-GC/MS) technique is employed for the qualitative and quantitative analysis of volatile organic compounds (VOCs) in drug formulations. The technique consists of sampling the gas phase above the liquid or solid sample with no direct injection, so the sample contamination is avoided. Volatile leachables giving off gases from packaging materials are vaporized, separated in a gas chromatograph, and then identified through mass spectrometry. Typically, an electron impact ion source at 70 eV is used under which molecules are fragmented into ions which are detected in the mass range of from 40 to 700 m/z. This is ideal for filtering out background noises generated by atmospheric gases. It is used most extensively in the identification of leachables that have low boiling points and exist only in trace quantities, thus forming the core of any leachable profiling program. (19)

High-Performance Liquid Chromatography (HPLC)

HPLC methods with UV and photodiode array detections were developed and validated for the determination of six extractables from elastomeric stoppers in a complex matrix of polyoxyethylated castor oil and ethanol. Three methods were optimized separately on different columns, using gradient elution with mobile phases of water, acetonitrile, and TFA. The methods were linear, accurate, precise, and sensitive enough to detect low ppm levels. Matrix matching between standards and samples was required to evade interference by the surfactant. These test methods ensure the accurate detection of extractables, which would otherwise pose hazards in terms of safety and quality of parenteral drug products. (26)

Ultra High Performance Liquid Chromatography- High Performance Mass Spectrometry (UHPLC-HRMS):

including plasticizers, UV stabilizers, bisphenol-based epoxy monomers, lubricants, and antioxidants, in any kind of parenteral product and to provide the user with an approximate amount of these additives. (38)

4.QUALITY ASSURANCE IN PHARMACEUTICAL PACKAGING SAFETY

4.1 Role Of Quality Assurance;

Pharmaceutical packaging intends foremost for the preservation of drug stability and safety. In order that patients are dispatched with drugs in dependable packaging, there shall be quality assurance or QA. In many instances, the lapse of the QA system is usually the cause of poor packaging resulting in leakages, breakages, or just damage of labels. By observing GMP and proper quality control, the passing along of faulty drugs can be stopped. Both the product and the packaging must not interact physicochemically and the container must provide proper protection of the product from light, moisture, air, and mechanical damages. FDA guidelines address such problems as particle leaching onto the drug, drug adsorption onto the packaging material, or degradation of the packing material. WHO also recommends proper sampling and testing during manufacture and packaging to assure batch homogeneity, detect adulteration, or keep product efficacy. Labels must also indicate how the product should be stored to maintain its stability for a given period of shelf life, whether freezing or refrigeration. (27)

Looking at the working of the Quality by Design (QbD) method in Quality Assurance, one notices a proactive nature in the packaging development lifecycle. The first step is to identify the drug product and packaging components' CQAs, such as moisture barrier, sterility, and container closure integrity, before risk assessment tools are employed to control risks associated with materials of construction and environmental exposures. The optimization of processes using DoE for monitoring purposes in real-time to assure process consistency is emphasized in QA.Packaging quality assurance is also concerned with life cycle management through continuous improvement, reevaluation of packaging systems, and adaptation to changes in materials, technology, or legislation. Ultimately, QA in packaging ensures the safety and integrity of pharmaceutical products from manufacturing to distribution. (28)

Quality Assurance represents an essential function in the core team responsible for patient-centric pharmaceutical packaging development. In fact, QA ensures the compliance of all packaging solutions with regulatory, safety, and quality-oriented considerations. QA must be heavily involved in the incorporation of new, patient-friendly design features to maintain product integrity and safety. QA entities collaborate with regulatory affairs, manufacturing, human factors, and also furnish support to user testing activities. Their role consists primarily of assessing the design for feasibility and risk profiling while overseeing quality to guarantee that the packaging is meaningful for patient use and sufficiently meets industry standards. (29)

5. Case studies:

A 36-month study evaluated the extractables and leachables (E&L) profile of the PLAJEX™ polymer-based prefilled syringe, made of a cyclo olefin polymer (COP) barrel and chlorinated isoprene isobutene rubber (CIIR) plunger. Water for Injection was stored in the syringes under controlled conditions and tested using GC/MS, LC/MS, and ICP-OES. Results showed no significant leachables compared to glass controls. Only trace amounts of three compounds—trimethylsilanol, N,N-dibutylformamide, and butylated hydroxytoluene—were detected, all below safety limits. Acrylic acid from label glue was also not detected after 45 months. In a comparative extractables study, COP barrels showed fewer elemental impurities than glass, and CIIR stoppers had a lower extractables profile than traditional BIIR stoppers. Overall, PLAJEX™ demonstrated excellent chemical compatibility and is well-suited for biologics.(22)

An extraneous impurity was observed at RRT 0.96 during the method development of an investigational drug product whenever lower levels were found in comparison to the 12.5 mg tablets. It was proven that the difference was attributable to sample dilution and further identified that the impurity came from the disposable syringe used during the filtration process. A deep-dive investigation, covering different syringe brands and different solvents, identified that the main extraction source was the rubber gasket. Eight extractables were characterized by LC-HRMS, NMR, and IR; among these, four were newly identified. This study established that disposable syringes can, even with water for injection, leach impurities that may affect drug product analysis.(24)

6. Challenges and limitations:

The absence of regulatory frameworks usually engenders multiple approaches by the industry, thus making E&L evaluation a highly complex issue. Despite the fact that good analytical techniques exist for the detection of E&L, safety toxicological assessments lack such standards. Then, the types of formulations and delivery methods for the drugs, along with their target patient populations, increase this complexity since they affect exposure assessments and safety thresholds. Since many leachables do not truly have complete toxicological profiles, determining compound-specific permissible daily exposure values(PDEs) very often necessitates relying on structure-activity relationships, in silico models (QSAR), or generic thresholds, for example, the Threshold of Toxicological Concern (TTC). Modern developments in analytical detection reveal trace levels that may not always be toxicologically relevant but still require evaluation, further complicating risk assessments, while conversion of analytical concentration into patient exposure values carries assumptions and uncertainty factors.(30)

Solvent polarity has been put forth as one of the main parameters affecting extraction and leaching of containers for pharmaceutical products, the general rule being that the lower the solvent polarity, the higher the leaching, such as the case with mixtures of ethanol. A great problem is that the real levels of leachables are in many cases lower than those anticipated because of the layered construction of the container, which slows migration and also prevents the establishment of equilibrium. For non-contact-layer leachables certainly, accumulation is usually limited by migration kinetics and not solubility.Apart from this, prediction of

E&L behavior remains very challenging, especially for short-term and low-temperature applications.(31)

These lines effectively describe the regulatory issues that have led to divergent risk assessment processes across the pharmaceutical industry. Divergent PDE values for the same substance may arise because companies tend to use different terminology, body weight assumptions, and sometimes safety criteria. Another big drawback is the lack of complete toxicological data for a large number of extractables and leachables, particularly for compound-specific limits. Here companies are forced into very precautious assumptions or generic criteria that can lead to overly stringent exposure limits and dis-crediting scientific credibility. Another great drawback is the complexity of route-to-route extrapolation; mostly, toxicological data are for oral exposure, where many pharmaceutical leachables are entering parenterally and some sort of bioavailability adjustment comes in, thus adding uncertainty. Further, a lot of leachables break down into other chemical entities because of their potentially different toxicological profiles, which also have to be considered in terms of safety evaluation. In light of these caveats, there is consensus on the need for thorough, systematic means to ensure that reliable safety assessments are conducted for E&Ls.(32)

There are challenges in the analysis of extractables and leachables (E & L), especially in parenteral drug products. As there is no international harmonized regulatory guidance, risk assessments are difficult to conduct uniformly. Relying upon in silico models such as Derek Nexus could lead to very cautious, if not sometimes questionable, predictions; experimental data, however, does not exist for numerous putative leachables. Dermal sensitization data from models such as the LLNA were widely used but were never validated for systemic or parenteral routes of exposure. Hence, dermal sensitization data are of questionable use for injected products. Also, sometimes, there can be misidentifications due to test artifacts or deterioration in aquatic conditions. The structural complexity of certain chemicals further complicates their classification and often requires expert judgment. Potency data, mainly EC3 values, are marked by variability and thus add to the uncertainty. It can be challenging to select an appropriate safety concern threshold (SCT) because that threshold should make a compromise between the sensitivity of the analyses and the toxicological risk. (33)

Testing for extractables and leachables (E&L) in lyophilized preparations involves an entirely different set of hurdles than working with regular liquid drug substances. The chief concern is that volatile or semi-volatile chemicals released from rubber stoppers gradually precipitate onto the surface of the lyophilized cake during storage since there's no equilibrium established in the vial's headspace. This slow accumulation of contaminants eventually increases the risk of contamination with time. Further, during the reconstitution, the compounds accumulated on the cake dissolve in the diluent, which in turn increases involvement of the solution with the packaging material for the introduction of impurities like trace metals or ionic species. Hence, due to their complexity, the safety studies for E&L must be undertaken so as to secure the safety, stability, and quality of lyophilized drug products. (34)

7.Trends and future prespectives:

Since olden times, letters bore tamper-evident designs, usually wax seals signifying that the letter had not been opened since it was written. Roman signet rings, for instance, were restricted to the owner and produced a signature so difficult that anyone attempting to reseal the letter through pressing the ring on the hot wax seal would not be able to duplicate the signature.(35) Tamper-evident packaging indeed contributes indirectly to reducing the risks of extractables and leachables (E&L) affecting pharmaceutical products. Its primary consideration is to act as a barrier against access by unauthorized persons and to reveal any unlawful access or tampering; however, it can also assist with preserving the integrity and stability of the packaging system itself.

With pharmaceutical counterfeiting being a global concern, it causes an enormous loss to the kind of billions, creating serious life-threatening situations. So, through modern packaging technologies of tamper seals, holograms, security inks, and RFID tags, it assures product authenticity and traceability. (36) Anti-counterfeiting packaging helps provide protection from extractables and leachables by ensuring that drugs remain in their originally tested containers. This is to prevent tampering or repackaging into materials that may release toxic substances.

The future perspectives of extractables and leachables (E&L) emphasize the equivalence of sterilization technologies, particularly X-ray and gamma irradiation for SU biopharmaceutical manufacturing equipment. The study shows that both irradiation methods yield qualitatively and quantitatively similar extractable profiles and, therefore, may be used interchangeably. It highlights that the X-ray sterilization method is an appropriate alternative driven by the limited availability of cobalt-60 for gamma sterilization, already recognized by regulatory bodies such as USP <665> and 21-CFR 179.45. The paper also stresses the importance of risk-based qualification, employing standardized protocols (e.g., the BPSA guidelines) encompassing physical, chemical, and biological testing of SU devices. The study suggests workflows and equivalency plots for efficient visualization and comparison of E&L data. On behalf of these, the findings argue for wider acceptance by regulatory bodies and safer, more flexible manufacturing using SU systems. (36)

Green packaging materials are sometimes referred to as eco-friendly, nature-friendly, or environmental-friendly packaging materials. Packaging that produces its products using environmentally friendly materials causes little to no damage to the type of packaging. These eco-friendly drug packaging materials are frequently identified by eco-labels. (40) Finally, eco-friendly packaging lessens extractables and leachables by using safer materials like biopolymers and recyclable glass that do not contain harmful additives such as phthalates or BPA. It also shuns multilayered plastics and employs cleaner processing techniques, which use very few chemical stabilizers, thereby reducing the likelihood of contamination.

DISCUSSION

Pharmaceutical packaging is essential for maintaining drug safety, stability, and efficacy. However, extractables and leachables (E&L) from packaging materials—such as plastics, rubbers, and adhesives—pose serious risks by potentially migrating into drug products, altering their quality or causing toxicity. Despite advancements in analytical techniques like GC-MS and UPLC-MS, predicting and controlling E&L remains challenging due to limited toxicological data, especially for non-intentionally added substances. Regulatory frameworks by the USFDA, EMA, and others provide essential guidance, but global standardization is still lacking. Quality Assurance (QA) plays a pivotal role in overseeing packaging safety through risk assessment, compliance checks, and continuous monitoring. Innovations like tamper-evident and eco-friendly packaging offer promising solutions by reducing contamination risks and enhancing patient safety. Moving forward, harmonized regulations, improved toxicological databases, and green material adoption will be key to developing safer, sustainable pharmaceutical packaging systems.

CONCLUSION

Anything in pharmaceutical packaging should be a utmost act to ensure drug stability, efficacy, and patient safety. On the other hand, extractables and leachables (E&L) from packaging materials are an ever-present challenge with possible ramifications on product quality and data on public health. The mitigation of such risks is achieved by a robust analytical framework, without compromises on regulatory compliances, and with a proactive approach toward quality assurance. Pharmaceutical products and pharmaceuticals, in general, are no fields for stagnant technologies; instead, we must embrace innovations in packaging such as tamper-evident features, eco-friendly materials, and risk-based design approach, etc. Concerted global harmonization effort, together with continuous research and regulatory alignment, is needed to keep pharmaceutical packaging on the highest safety and quality standard.Greater collaboration is needed between industry, regulators, and the scientific community to strengthen testing strategies and entry toxicological data gaps. Future packaging solutions should also be oriented to prioritize patient safety, sustainability, and material innovation.

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