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Research Article

Quality by Design (QbD): A New Horizon For Robust Analytics in Extractable and Leachable Study For Packaging Components

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Abstract

When drug products is packed in plastic container systems, chemical entities may leach from the container and accumulate in the product thereby causing an increase in the toxicity of the drug product. It is necessary that the drug product's manufacturer demonstrate that any such leaching does not occur to the extent that the leached substances adversely affect the product's safety and / or efficacy. One method for accomplishing this objective is via analysis of the drug product to identify and quantify the leached substances. When a particular packaging system is utilized for multiple drug products, one reaches the point, after testing numerous drug products, where the leaching properties of the packaging system are well known and readily predictable. The Quality by Design (QbD) principle can be simply stated as follows - once a system has been tested to the extent that the test results are predictable, further testing can be replaced by establishing that the system was operating within a defined design space.

Key words: CQA, CCS, QbD, Extractables, Leachables, PQRI, AET

INTRODUCTION

Packaging must be a barrier to the external environment and maintain the sterility and efficacy of the drug product. Depending upon the contents, packaging may also serve to shield the drug product from oxidation, light degradation and moisture permeation. The packaging must clearly identify its content and may include dosage information and hazard warnings. Finally, a package may help to ensure accurate dosage of a drug product, in a easy and full proof way. Satisfying all of these functional requirements includes testing of a spectrum of components and materials, plastic containers, metal springs, elastomeric valves and gaskets, adhesives and coatings. While these materials may meet the functional goals of the CCS (Container Closure System), if quality is considered at the beginning of the process, harmful contaminants may inadvertently be introduced into the drug product.

This is not just a thought experiment, as there is ample history and data of harmful packaging additives leaching to stored medicaments. Up until the 1980s, carbon black was added to rubber during the manufacturing to make it suppler. It was also added to elastomers used in everything from asthma inhalers to baby bottle nipples, until it was shown that cancer causing polyaromatic hydrocarbons leached from rubber made with carbon black. Bisphenol A (BPA) is used as a building block in polycarbonate bottles and as a liner in metal cans and was also common in baby bottles. But, now BPA has been known to be an endocrine disrupt or and is a banned plastic additive in several states.

A standard extractable and leachable programme begins by coaxing potential leachables from processing or packaging materials in an exaggerated extraction study. Components are shredded and placed in solvents of varying polarity, regardless of the final drug solvent. The solvent component mixture is then heated at elevated tempera-

ture to extract all potential impurities in a short period of time. These chemicals are then identified by various analytical techniques, typically Inductively Coupled Plasma Mass Spectrometry (ICP-MS), High Performance Liquid Chromatography-mass spectrometry (HPLC-MS) and Gas chromatography-mass spectrometry. Extractables of concern are highlighted and targeted in the leachable study. Not all extractables are leachables but because it is not always clear which components may leach out under storage conditions likely to be encountered, methods are developed to detect the extractables in the product matrix. During finish product testing, it will be useful to quantify the leachable impurity in the presence of the drug product.

Definition

Extractables -

Are organic and inorganic chemical entities that can be released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction under laboratory conditions. Depending on the specific purpose of the extraction study, these laboratory conditions (e.g: solvent, temperature, stoichiometry etc) may accelerate or exaggerate the normal conditions of storage.

Leachables-

Organic and inorganic chemical entities, typically a subset of extractables, that migrate into a drug formulation from any product contact material as a result of direct contact under normal process / storage conditions or accelerated drug product stability studies.

Nature of Migrating substances

Several different types of components that can comprise a CCS (Container Closure System) may be in contact with the drug product during various time intervals. The CCS (Container Closure System) components may be of a primary or secondary nature, and each component can be made of different polymers with a range of formulation ingredients. The release of these ingredients, when in direct contact with the drug product, can be the result of diffusion through the thickness of the package, at the package/drug product interface, and through the product. In the case of primary components, a drug product can be contaminated by the transmission of molecules through the polymer. Permeation rate depends upon the amount of permeation and thickness of the wall in relation to the time of exposure, area and pressure drop across the wall. The magnitude of permeation is related to the free volume between the molecules of the polymer structure and the type of permeation along with other chemical and physical factors. The impact on the drug product from a substance permeating through or from a polymer is related to the solubility or reaction of the substance and diffusion in the drug product.

The concentration of migrant in the polymer, along with the volume of drug product, contact area and time all influence the capacity for leachables, as does the polymer density, thickness and ratio of migrant to polymer at equilibrium. The change of concentration of a particular migrant within a diffusion volume follows Fick's second law:

$$\partial c/\partial t = D\partial c^2/\partial x^2$$

where c = concentration, t = time, x = distance and D = diffusion coefficient. Theoretical diffusion can be estimated based on the material's specific constants, diffusion coefficients and relative molar mass of each migrant. Mathematical migration modeling can be accomplished by assuming that there is homogeneity in the CCS (Container Closure System) and a lack of resistance from boundaries, and that the total amount of migrant in the CCS (Container Closure System) relative to the drug product remains constant. The time predicted for drug product contamination is variable but it can be useful to provide estimates of certain leachables, to aid in the selection of materials early in the drug development stage or to indicate parameters that can be used as a basis for experimental conditions.

The goal of an extractable study is to identify as many compounds as possible that have the potential to become leachables. Although it is not expected that many of those extractables will actually leach into the drug product at detectable levels, a materials extractables profile provides critical information in pursuit of a comprehensive leachable test.

Packaging Materials Associated with Parenteral Products

Components that is in contact with drug products and suitable for the pharmaceutical and medical device industries have a wide variety of applications and diverse functions. The principle classes of materials used in CCS (Container Closure System) are plastic, elastomers, glass, metals, inks/coatings, adhesives and paper. Whether an individual component or a combination of components are employed in single-use devices, intermediate- or long-term storage applications, the material science must be understood in order to make informed decisions. The route of administration is a significant factor to determine the components to be evaluated, the amount of information needed to ensure patient safety and satisfy regulatory requirements. Inhalation, injectable, transdermal and ophthalmic dosage forms have a high degree of concern for package-product interaction and it is the regulatory expectation to assess leachables. Common CCS (Container Closure System) components used in different dosage forms are listed in Table 1 along with typical materials of construction.

The list of components and materials serves as an example and is not intended to be inclusive of all possibilities. Other sources of potential leachables to be considered include drug product storage, process and filling equipment, such as tanks, filters, reactors and disposable systems. Contamination from the CCS (Container Closure System) and equipment used in the manufacturing process for biologic protein products are of particular concern for contamination, since leachables can have a negative impact on the patient as well as the protein products, as expressed by Markovic. A multi-component and multi-material CCS (Container Closure System) poses greater potential for package-dosage form interaction in conjunction with the affinity of migrants to the dosage form. The propensity for package interaction is related to the chemical constituents and nature of drug product matrices, i.e. solutions, emulsions, suspensions creams, solids, gels, aerosols, ointments. Leachables are a function of potential migrants (extractables) and their transport properties. There are scores of potential leachables to be considered as a result of migration, degradation and/or interaction. Plastics components will have many low molecular weight compounds that are not part of the polymer backbone which originate from polymer residuals, processing aids or performance additives. These are considered as suspected leachables. Examples of the different classes of plastic additives are found in Table 2.

Further information on specific chemical entities related to polymer materials and allowable migration and formulation limits, as sanctioned for foodstuffs, can be found in the Official Journal of the European Union, Commission Directive 2007/19/EC and USFDA CFSAN Inventory of Effective Food Contact Substance (FCS) Notifications.[7]

Table 2: Typical Plastic Additives

- Lubricants
- Antistatic Agents
- Initiators
- Stabilizers
- Impact Modifiers
- Antioxidants
- Bactericides
- Catalysts
- Blowing Agents
- Processing Aids
- Plasticizers
- Colorants
- Brighteners
- Release Agents
- Vulcanizing Agents

Existing Regulatory Guidance's for Extractable and Leachables:

a) Federal Food Drug and Cosmetics Act

b) GMP CFR 211.94 – Drug Product Containers and Closures

c) GMP CFR 211.160 – General Requirements

d) D & C Act 1940 / Rules : Schedule M - India

e) EU directives

f) International guidelines of EMEA & Health Canada

g) Standard compendia – USP / EP / IP / ICH Q4, Q6A, Q8

Table 1: CCS Components & Materials

Dosage Form	Components	Examples - material of construction for Container Closure Systems (CCS)
Inhalation	MDI/DPI components, canisters, valves, gaskets, blister packs, bottles, actuators, mouthpiece, pumps, closures, liners, label/inks	polyolefins, styrene butadiene rubber, ethylene propylene diene monomer, rubber, thermoplastic elastomers, polyacetal, polyesters, polyamides, acrylics, epoxies, paper / paperboard, metals, glass
Injectable	SVP <100 ml/LVP >100ml cartridge, syringe, vial, amp-oules, flexible bag, closures / plungers, injection ports, needles, adhesives, inks, overwraps	polyolefins, butyl rubber, ethylene propylene diene monomer rubber, polyvinyl chloride, polyurethanes, polycarbonate, acrylics, poly-amides, polystyrene, thermoplastic elastomers, silicones, polyesters, epoxides, cellophane, fluoropolymers, styrenics, paper / paperboard, metals, glass
Ophthalmic	bottles, droppers, screw caps, liners, tips, tubes/liners, labels/ink	polyolefins, acrylics, vinyls, epoxies, polyamides, thermoplastic elastomers, polyesters, cellophane, glass, paper / paperboard, metals
Transdermal	adhesives, membranes, barrier films, reservoir, coatings, blister packs, preformed trays, overwraps, substrates, topical aerosol components	polyolefins, acrylics, vinyls, polyamides, polyesters, styrenics, rubber material thermoplastics, metal
Associated Components	nebulizers, dosing spoons, dropper, dosing cups	polyolefins, glass, rubber, thermoplastics, polyesters

The responsibility of providing the appropriate CCS (Container Closure System) information to regulatory authorities is that of the sponsor. The ultimate goal is to manufacture a safe drug product, hence satisfying regulatory requirements. The regulatory environment is continually evolving based on regulatory concerns, industry experience and best practices.

There is new GMP guidance advocating the QbD (Quality by Design) process outlined in Quality Systems Approach to Pharmaceutical cGMP Regulation in accordance with ICH Q8 Pharmaceutical Development and ICH Q9 Quality Risk Management. The main USFDA guidelines governing CCS (Container Closure System) suitability include: (i) Container Closure Systems for Packaging Human Drugs and Biologics, (ii) draft Metered Dose Inhaler (MDI) and Dry Powder Inhaler and (iii) Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products.

The European Medicines Agency (EMEA) and Health Canada have also published guidelines encompassing the same scope. Globally, the recommendations are similar with respect to conducting extraction, interaction/leachable, migration, compatibility and toxicology studies on CCS (Container Closure System). There is an allowance for the use of plastics meeting EP (European Pharmacoepia) criteria that is specific to the European Medicines Agency (EMEA) guideline. Compendia tests are required for CCS according to both EMEA and USFDA, but results are limited to the information that can be used to conduct a comprehensive leachable study. There is also some difference in the requirement between EMEA and the U.S. regarding extractable testing for DPI dosage forms. Overall the guidelines require thoughtful interpretation. Working within a QbD framework will reduce the uncertainty associated with the amount and type of data needed to scientifically justify CCS suitability.

The highest level of concern in relation to drug product / CCS interaction is that of the inhalation route of administration. In August 2006, the Product Quality Research Institute (PQRI) approved

Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products as an industry accepted standard. This document proposes the use of threshold values, and details best practices for leachables and extractables studies within the spirit of the QbD (Quality by Design) principles. The basic premise of the PQRI (Product Quality Research Institute) document is to obtain CCS information early in the development phase to enable selection of appropriate components that have been scientifically justified, based on desired performance in relation to safety.

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	Non-solid dosage form: High	Solid dosage form (Powders): Medium	Solid dosage form: Low
Highest	Inhalation Aerosols / Solutions; Injections / Injectable Suspensions	Inhalation Powders Sterile Powders / Powders for Injection;	
High / Medium	Nasal Aerosols / Sprays Ophthalmic Solutions / Suspensions Transdermal Ointments / Patches		
Low	Topical Solutions / Suspensions; Topical / Lingual Aerosols; Oral Solutions / Suspensions	Topical Powders; Oral powders	Oral Tablets / Oral (Hard and Soft Gelatin) Capsules

(i) Characterize packaging / delivery systems, packaging components, combination product medical device components, manufacturing compo

nents and their various materials of construction.

(ii) Facilitate the timely development of safe and effective dosage form packaging / delivery systems, manufacturing systems and processes by assisting in the selection of components and materials of construction.

(iii) Understand the effects of various manufactur-

ing processes (e.g, sterilization) on packaging components and their potential leachables

(iv) Establish the worst case potential leachables profile in a manner which facilitates leachables studies, the development of leachables specification and acceptance criteria (should these be required), and the safety evaluation/qualification of potential and actual leachables.

(v) Establish the worst case potential leachables profile in a manner which facilitates the safety evaluation / qualification of leachables when it is not scientifically possible to determine actual leachables.

(vi) Facilitate the assessment of patient exposure to chemical entities resulting from direct contact between a patient's body tissues (e.g. mouth, nasal mucosal device component (e.g, a metered dose inhaler's plastic actuator)

(vii) Facilitate the establishment of qualitative and quantitative leachables-extractables co-relation

(ix) Facilitate the development of extractables specification and acceptance criteria for packaging components, combination product medical device components and material of construction.

(X) Facilitate investigations into the origin(s) of identified leachables whose presence causes out of specification results for a marketed product.

LEACHABLES STUDY DESIGN

Although leachables studies may be accomplished at any time during the drug product development/ manufacturing lifecycle, it is most appropriate that leachables studies occur during late stage product development or during formal product stability assessment.

This is the case because the most appropriate leachables assessment is conducted as follows:

(i) The assessment is performed on the actual drug product and not simulations thereof

(ii) The assessment is performed with the actual packaging and delivery system in the form it will be commercialized, not with a prototype or on system components.

(iii) The related extractables assessments are accomplished on the same lots of packaging components used to manufacture the drug product lots on which the leachables assessments are performed.

(iv) The assessment is performed on product that is manufactured under conditions that reflect the actual commercial processes of production of the drug product and the packaging/delivery system, filling of the drug product into the packaging/delivery system, post-filling treatment of the filled packaging (e.g., terminal sterilization), distribution, storage, and clinical use. Although leachables studies may include accelerated storage conditions, they cannot be limited to accelerated conditions and must include real-time assessment.

Additionally, leachables assessments may be appropriate on certain occasions post-market. The design of any particular leachables study depends on the purpose and goals of the overall leachables assessment.

Leachables studies can also be performed early in the drug product development process (e.g., preclinical stage) in order to facilitate the selection of packaging components and their materials of construction. Such leachables studies are particularly useful for certain “high-risk” dosage forms where selecting appropriate packaging components and materials of construction is critical. A variety of packaging components and materials of construction can be evaluated at the same time and drug product leachables profiles determined and evaluated for each configuration.

For primary packaging systems or combination drug/device products this can be accomplished by using either the drug product formulation or a placebo formulation in contact with the proposed packaging system. In the latter case, the placebo formulation can be considered as a simulating solvent to characterize extractables as probable leachables (see *Simulation Studies*). In either case, the leachables study conditions (i.e., time, temperature, etc.) should be based on conditions that are relevant for either the use-life or shelf-life of the drug product. Preclinical development stage leachables studies can be designed in a systematic way in order to support QbD processes and principles. It is important to also note that during early stage drug product development for high-risk dosage forms, leachables characterization is recom-

mended for any drug product batches that are used as test articles in any definitive toxicology or clinical studies.

For "low-risk" dosage forms (e.g., solid orals, topical powders) leachables studies conducted throughout development might be appropriate in order to assess, and thereby avoid, problems with packaging systems that might appear either in later stage development or marketed product.

During later stage development of high-risk dosage forms in support of product registration, when the final market form of the packaged drug product is available, leachables studies may be accomplished on definitive registration batches of drug product during the course of overall product stability studies. The results of these leachables stability studies can be used to establish leachables-extractables correlations, identify trends in leachables accumulation levels, evaluate individual leachables and qualify them on a safety basis, and develop leachables specifications with acceptance criteria (should these be required). For inhalation aerosols and other OINDP, leachables testing should be an integral part of the larger ICH registration stability program, and storage conditions and stability time-points should be planned accordingly. For cases where a packaging/delivery component is in direct contact with the patient (e.g., a metered dose inhaler or dry powder inhaler actuator mouthpiece), chemical entities that a patient might be exposed to can be evaluated as extractables (i.e., potential leachables) using appropriate simulating fluids under time/temperature exposure conditions relevant to the intended use.

Drug product leachables studies may also be appropriate in many cases where necessary or desired changes in a marketed drug product are made. Such leachables studies are normally required to support change-control processes for many high-risk dosage forms, particularly those with in-place leachables specifications and acceptance criteria, and could also be appropriate for other dosage form types, drug/device combination products, etc. Changes may include but are not limited to: composition of the drug formulation; manufacturing processes for the drug product; primary and secondary packaging components or their materials of construction; manufacturing or assembly processes for primary and secondary packaging components or their materials of construction; and delivery system(s) that are part of the drug product labeling. Any change that results in the patient being exposed to a different leachables profile than the one approved during registration will require leachables studies as part of any change-control process unless adequate scientific justification is provided to the contrary.

Although low-risk dosage forms (e.g., solid orals, topical powders) typically do not rigorously require leachables studies as part of the drug product registration process, it is possible that leachables could appear in drug product impurity profiles either during registration stability studies or in marketed products. For example, it has been documented that chemical additives in label adhesives can migrate through plastic primary packaging and appear in impurity profiles of solid oral dosage forms packaged within these containers. Thus, it is appropriate to consider performing leachables studies on "low-risk" dosage forms in certain cases. If leachables assessment is not performed proactively, such an event could lead to an OOS result for a development or marketed product and require an "emergency" leachables study as part of an investigation process.

The design of this type of leachables study depends on the particular situation; however, in general it would be necessary to identify and quantify the leachable(s), evaluate safety and possibly qualify the leachable(s), and correlate the leachable(s) with packaging component extractables. It is also possible that leachables could result from contact with manufacturing equipment and tertiary packaging systems (e.g., shipping materials).

The leachables studies described above have different purposes and overall goals but require similar types of information for their proper design. First, it is important to have information as to the identities and maximum possible accumulation levels of all potential leachables. The packaging component manufacturers may provide chemical composition details for the packaging/delivery system and various materials of construction, as well as details regarding the manufacturing processes for these components and materials.

Such information may be in the form of material safety data sheets, technical data sheets, test re-

ports, or confidential communications, and can be used to infer potential leachables. An extractables assessment (including an extraction study) can also be accomplished on packaging components and/or their materials of construction to directly assess potential leachables. Regardless of how the chemical information is obtained, it is important to ensure that all possible sources of potential leachables from the finished packaging system are considered. These may include chemical entities from any of the primary and secondary packaging components and their materials of construction, coatings, cleaning, lubricating, cutting, sterilization, assembly, or other processes associated with the manufacture of the final packaging/delivery system as used in the drug product. The chemical information on the packaging and delivery system is used to create a list of potential leachables and their possible accumulation levels.

Potential leachables have a significant chemical diversity, and therefore a diversity of physical and chemical properties, including polarity, volatility, solubility, etc. Whereas relatively volatile compounds can more readily migrate into any type of formulation through indirect contact, non-volatiles generally require direct contact. Two aspects of formulation contact should be considered: The nature of the formulation contact (i.e., direct or indirect) and the time of contact (transient or continuous). If the formulation is not in direct contact with the packaging component (e.g., inhalation powder in a capsule packaged in a blister) then it is less likely that any relatively nonvolatile compounds would migrate into the formulation from the packaging system; however, volatile compounds might. If the formulation is only briefly contacting the packaging component (e.g., an inhaler mouthpiece) it is less likely that any migration of chemicals from the component would occur on this transient timescale. However, if the formulation is in continuous contact with the packaging component (e.g., parenteral in a bag delivered through an administration set) then all types of compounds could potentially migrate into the formulation.

A rigorous leachables assessment considers leachables from other than primary packaging, such as necessary secondary packaging and, in certain situations, tertiary packaging. If the primary packaging consists of a semi permeable polymer (e.g., a low density polyethylene container), then potential leachables from labels, inks, adhesives, etc. that are used in the secondary packaging must be evaluated. Similarly, volatile compounds that are present in tertiary packaging (e.g., wooden pallets, cardboard boxes, plastic overwraps, etc.) could migrate into a contained in such a plastic bottle, and these potential leachables should be considered in the event of an unknown impurity OOS situation.

Various characteristics of the drug product formulation must also be considered in designing any leachables study. For example, formulations are typically either solids or liquids, and it is well documented that physical state affects the leaching process. In the event that a formulation has a change in state during the course of production (e.g., lyophilization; liquid to solid) then the leachables study should be designed taking into consideration the time periods that the formulation is expected to be in each physical state. In the event that a formulation has a change in state during the course of use (e.g., nebulization of a liquid to vapor) then consideration should be given to both the leachables acquired during storage from the container of the liquid and those acquired during use of the prescribed delivery device. In addition, typically only the final packaged product is evaluated for leachable.

However, there may be cases in which an intermediate (e.g., bulk capsule for an inhalation powder) is stored for long periods of time in different primary packaging (e.g., foil pouch) from which compounds may leach. If these compounds that migrate from bulk packaging persist through the drug product's manufacturing process and are entrained in the finished drug product, then they are properly treated as leachables.

The nature of any contact that the packaging and delivery system has with the patient must also be considered. If the contact is only surface contact, then the likelihood of direct chemical migration to the patient is much less than if the contact is with mucosa, tissue, bone, or dentin. The various contact categories are described in *The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants* 1031 or ISO 10993 (*10*).

Elements of QbD -

QTPP –

Quality Target Product Profile is the basis for the design of the drug product and its packaging. it is at this stage that the team will describe the intended use, route of administration, dosage form, patient population, chronic versus short term usage etc. Any changes in the QTPP will require evaluation of the impact of this change in proceeding quality design elements.

CQA –

Defined as a physical, biological or microbiological property or characteristic that should be within an acceptable range to ensure the desired product quality. While it is not possible at the QTPP stage to define all potentially harmful leachables, one can certainly prohibit known harmful additives such as BPA. One can also set baseline CQA that require packaging and production components meet basic entry level quality attributes. CQA for specific leachables are added after conducting extractable risk assessment. For example -the analysis of risk posed by dosage form. A leached impurity in an inhalation or parental product poses a higher risk than the same impurity in an oral or topical product.

Risk Assessment-

An Ishikawa diagram can be made by the design and quality team to assess the potential risks leading to a reasonable extractable and leachables assessment. Considerations should be given to materials sourced, formulation, storage conditions and sterilization techniques.

Techniques like comparison matrix (CM), Risk Estimation Matrix (REM), Preliminary Hazard Analysis (PHA) and Failure Mode Effect Analysis (FMEA) are commonly used for risk assessment studies and screening can be accomplished through low resolution experimental designs like Fractional Factorial design, Taguchi design and Plackett-Burman design.

Elemental impurities in drug products as per ICH Q3D may arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. The PDEs established in this guidance are considered to be protective of public health for all patient populations. In some cases, lower levels of elemental impurities may be warranted when levels below toxicity thresholds have been shown to have an impact on other quality attributes of the drug product (e.g., element catalyzed degradation of drug substances). In addition, for elements with high PDEs, other limits may have to be considered from a pharmaceutical quality perspective and other guidance's should be consulted (e.g., ICH Q3A)

ICH Q3D presents a process to assess and control elemental impurities in the drug product using the principles of risk management as described in ICH Q9 using the risk assessment tools. This process provides a platform for developing a risk-based control strategy to limit elemental impurities in the drug product.

Health based risk assessment is conducted following the completion of leachable study stage which is typically performed using data on leachables obtained under real-time storage conditions for drug substances and drug products. In certain cases, leachables observed under accelerated storage conditions may be included as a part of the risk assessment. A summary describing the observed leachables and their concentrations, the drug product indication, route of administration, dosing regimen, frequency of dosing and patient population should be prepared. This information is used to compute the estimated daily intake (dose) of the leachable. The PQRI (Product Quality Research Institute) group introduced the concept of safety thresholds for leachables that were observed in OINDP's (Orally inhaled and nasal drug product). Based on their investigations, a safety concern threshold of 0.15µg/day and a qualification threshold of 5 µg/day is recommended for leachables and chemical impurities observed in OINDPs (Orally inhaled and nasal drug product).

FLOW DIAGRAM OF QbD APPROACH

Target Measurement	Determine what to measure and where/when to measure it. Develop measurement requirements based on product QTPP and CQA
⚜	
Select Technique	Select appropriate analytical technique for desired measurement. Define method performance criteria.
⚜	
Risk assessment	Assess risks of method operating parameters and sample variation. Can use risk assessment tools (FMEA)
⚜	
Method development / validation	Examine potential multivariate interactions (DoE and design space). Understand method robustness and ruggedness
⚜	
Control strategy	Define control space & system suitability, meet method performance criteria
⚜	
Continual improvement	Monitor method performance ; update as needed as process and analytical technology evolves

The health-based risk assessment is based on knowledge of systemic toxicity, route specific toxicity and mutagenic potential of a compound. Information such as compound estimated daily intake (EDI) and / or acceptable daily intake (ADI) values and / or other risk-assessment determinations are established. ADI's fare calculated for leachables for which adequate toxicology data are available. The EDI is a risk-assessment calculation used for pesticides, food additives etc used to define the daily intake of a chemical that during an entire lifetime appears to be without appreciable health risk based on all known facts. ADIs are typically calculated from No Observed Adverse Effect Level (NOAEL) values by dividing by safety and / or modifying factors (eg., 10 fold). Dividing by these factors allows for animal-to-human and human-to-human variability, experimental differences, and mechanistic or pharmacokinetic considerations.

In absence of sufficient toxicity data to calculate an ADI, a qualitative structure-activity relationship (QSAR), assessment is conducted.

The qualification threshold of 5 mg/day is applied to leachable structures for which QSAR assessment does not result in mutagenicity and / or carcinogenicity alerts. Leachable structures for which a QSAR assessment results in mutagenicity and / or carcinogenicity alerts are assigned a safety concern threshold of 0.15μg/day.

Design space-

The relationship between the materials selected the manufacturing process and critical quality attributes are described in the design space. Within the design space, it is important to work with the packaging component supplier to understand what potential sources of variability exists for each packaging component, especially those with greatest product contact and highest risk. Once variability is known, one can assess the impact of this variability on component leachables, and in turn, how these leachables may affect drug product quality. Quality variables controlled in the design space included composition of drug product, composition of packaging system, configuration of packaging system and conditions of contact. When controlling for these variables, the product package interaction and leachable parameters within the design space can be so well known after sufficient evaluation, that subsequent leachable profiles can be predicted.

Control strategy-

The next step in QbD process is the control strategy. What are the planned sets of controls based on the design space that will ensure end product quality ? It is sensible to apply control upstream - to the component extractable specification - where the source of variability is likely. If the component has a new extractable due to lack of manufacturing consistency, it may not be picked up during leachables assessment if the wrong column or method is used.

Lifecycle management-

Finally, the last stage in Quality by Design (QbD). It is important to partner with the material supplier to understand the potential changes in their processes. A vendor quality agreement will help to ensure adequate notification of any changes in process or materials. It may be useful to proactively source and assess alternative material, in case of business failures or or unacceptable changes.

ESTABLISHING A LEACHABLES – EXTRACTABLES CORRELATION

A leachables-extractables correlation is established when actual drug product leachables can be linked both qualitatively and quantitatively with extractables from corresponding extractables assessments of individual packaging components. Leachables-extractables correlations are important for several reasons, including justifying the use of routine extractables release tests of packaging components as an alternative to leachables testing during stability studies for high-risk drug products, establishing the source of a leachable producing an OOS (Out Of Specification) result for a low-risk drug product, change control, and ongoing quality control, etc.

A qualitative correlation is demonstrated when a leachable is linked either directly or indirectly to an extractable (i.e., potential leachable). For example, hexadecanoic acid observed in a leachables profile can be directly linked with hexadecanoic acid observed in the extractables profiles of one or more primary packaging components. The ethyl ester of hexadecanoic acid observed in the same leachables profile can be indirectly linked with hexadecanoic acid observed in one or more extractables profiles, if ethanol is a known drug product formulation constituent and it is shown that an esterification reaction can occur in the drug product during storage. For an appropriate quantitative leachables-extractables correlation to exist, the quantity of any individual leachable over the shelf-life of a drug product must be mathematically related to the quantity of the corresponding extractable. One of the more simple mathematical relationships between an extractable and a leachable is that the quantity of the leachable in the drug product should be less than or equal to the quantity of the corresponding extractable.

For example, the concentration of Butylated hydroxy toluene (BHT) present in a drug product formulation was determined to be 5 μg/mL. BHT was extracted from a primary packaging system component at a level of 300 μg/component. If the drug product packaging system incorporates one of these components per dosage form and the packaged formulation has a volume of 50 mL, then

a quantitative leachables-extractables correlation is established, as BHT was extracted in the amount of 300 μg (300 μg/component × 1 component) and was leached in the amount of 250 μg (5 μg/mL × 50 mL). As a result, it can be concluded that on the average 50 μg of BHT is unaccounted for, and this quantity was either not leached from the packaging component into the formulation (likely) or lost by some other process (less likely).

For high-risk drug products, leachables-extractables correlations may be established over-multiple batches of drug product (accelerated or at end of shelf-life) and multiple batches of packaging components. Extractables studies should ideally be conducted on lots of components that were used to manufacture the drug product batches used in primary stability studies (and therefore on the drug product batches on which leachables testing was conducted to establish leachables-extractables correlations).

If the maximum level of any specific leachable in the formulation during stability studies was substantially greater than the calculated maximum potential accumulation levels of that same leachable as established by the extraction study, and the extraction studies were conducted on the same lots of components used to make the primary drug product stability batches, it must be concluded that the extraction study was inadequate and therefore a leachables-extractables correlation for that specific leachable cannot be established.

In this case, either a more complete extraction study must be performed in which the extractable level exceeds the maximum level of the leachable, or the leachable must be controlled as such in the drug product specifications for shelf-life stability testing, and release testing as an extractable at the component level is inadequate to control this leachable.

If a leachable-extractables correlation cannot be established, possible explanations include: inadequate extractables assessments of packaging components; unreported changes in packaging component composition or manufacturing processes; unreported changes in the identity of packaging components.

Quantitative methods - Analytical method validation considerations

Validation of quantitative leachables methods should be accomplished according to industry accepted practices, criteria and standards. The extent of validation required depends on the goals of the leachables study in which the analytical method is being utilized. System suitability tests and criteria should be developed for each leachable method.

Special considerations for individual validation parameters relative to leachables methods are as follows -

(i) Accuracy and precision -

These parameters are typically evaluated using drug product samples spiked with known amounts of target leachables. The choice of drug product spiking matrix used for these evaluations should be one that has had little-to-no contact with the packaging materials used in the final drug product and therefore little to no measurable levels of endogenous leachables. Suitable spiking matrices can include freshly manufactured drug product and simulated drug product vehicles. Spiking levels should be determined based on results from accelerated stability studies or estimated from the known amounts of potential target leachables determined from extraction studies.

(ii)Linearity and range –

The best accuracy and precision are achieved when the validated linear range considers the potential maximum accumulation levels of each target leachables.

(iii) Limit of detection / Limit of quantitation -

To detect and quantitate unknown leachables, the limit of quantitation should be at or below the designated analytical threshold ie, AET.

(iv) Specificity -

Evaluation of method specificity can be accomplished by evaluating chromatographic purity in spiked and non-spiked drug product samples using for eg GC/MS (Gas chromatography – Mass spectrometry) or LC/MS (Liquid chromatography – Mass spectrometry) or LC/DAD (Liquid chromatography – Diode Array Detector).

(V) Robustness -

A design of experiments statistical approach with consideration of critical analytical method parame-

ters should be used to create robustness evaluation protocols.

Leachables specification and acceptance criteria -

The validated analytical methods and information obtained from those methods can be used to develop drug product leachables specifications and limits. In certain cases, most commonly encountered with high risk dosage forms (such as OINDP – Orally inhaled and nasal drug product), it may be meaningful, useful and at times required to routinely monitor finished drug products for leachables.

It is important to note that leachable specifications should be applicable to a product during all stages of its shelf life, including release and at the end of shelf life. This is the case since leachables accumulate over the entire shelf life of a drug product.

When a change occurs in a product for which leachables specifications and acceptance criteria have been established, it is important to review the analytical method and reevaluate the acceptance criteria and make adjustments as appropriate and scientifically justified. A change in components that results in an increase in leachables concentrations beyond the levels qualified will necessitate the toxicological evaluation of the proposed levels as would be the case for any impurity.

Assessing the Completeness of an Extractables Assessment

The completeness of an extractables assessment can only be judged against the overall goals of the assessment. For example, an extractables assessment accomplished solely for materials characterization might include one extracting solvent, one extraction technique, and one set of extraction conditions; along with a materials-based threshold (e.g., 10 ppm w/w).

Such an extractables assessment might be considered complete if all extractables above the defined threshold were identified to the confident level (defined above) and quantitated. For an extractables assessment designed to establish a rigorous leachables-extractables correlation for a high risk drug product, where a challenging safety threshold might apply (e.g., 0.15µg/day), good scientific practice and due diligence requires the following:

Generation of extracts should be accomplished with

1. Multiple solvents or extracting media with varying extracting power based on the known extracting power of the drug product vehicle;

2. Multiple and complementary extraction techniques, including those with the capability for volatiles analysis;

3. Extraction conditions that allow equilibrium to be achieved.

Characterization of extracts should use

1. Multiple and complementary analytical techniques;

2. Careful sample preparation, keeping the analytical technique(s) in mind;

3. A systematic process for identification and quantitation of extractables.

In this case, the extractables assessment might be considered complete if all extractables above the defined threshold were identified to at least the confident level, quantitated, and correlated both qualitatively and quantitatively with drug product leachables data (if available) and the known ingredients in the packaging system, packaging component(s), or material(s) of construction.

It should be noted that limited extractables assessments with relatively narrow goals can be accomplished to required completeness with a relatively focused effort. For example, extraction studies designed to quantitate the levels of specific chemical additives in specific packaging components/materials can be done with specified extraction parameters and analytical methods. The reader is also referred to various sources which describe extractables assessments and extraction studies for pharmaceutical applications, as well as other general sources which refer to extractables assessments for medical devices and food contact.

Case studies:

Effect of radiation on the stability of formulations

The effects of temperature, light and humidity are commonly studied on the stability of formulations. Du et al. presented the stability of formulations in

space. The factors affecting the stability of medicines in space were different such as increased exposure to radiations (ionizing radiations of protons and heavy ions), excessive vibrations, microgravity and carbon dioxide-rich environment etc. In this study, medicine kits containing 33 formulations were stored in the International Space Station for up to 880 days. Table 7 shows the time when the payloads were sent back to earth for analysis and the radiation doses to which these formulations were exposed.

It is very clear that the formulations were exposed to significantly higher doses of radiation at the Space Station. Table 8 lists the number of formulations failing the chemical potency requirement. As expected, a significantly higher percent of formulations failed the chemical potency requirement. Each kit contained 33 dosage forms including 22 solid, 7 semisolid and 4 liquid (ophthalmic and injectable) formulations. In the case of Ciprofloxacin and Promethazine, liquid formulations showed a greater effect of radiation on stability compared to the solid dosage forms. Certain APIs such as levothyroxine, dextroamphetamine, promethazine, trimethoprim, sulfamethoxazole and clavulanate appeared to be more susceptible to the radiation effects.

Keeping these results in mind, it is important to develop a packaging system which will protect the formulations from radiations, and at the same time, will fulfill constraints of storage in space. Parenteral formulations are mostly in liquid form and might be more susceptible to radiation effects. Commercial flights fly over 30,000 feet altitude and the exposure to radiation is higher. Work is needed to be done in this area in terms of stability of SDFs and role of packaging.

In a review article, Curry et al. summarized problems and challenges involved in the selection of ready-to-use closures for parenteral products. Elastomers are defined as materials that can be stretched to twice their original lengths and that can quickly return to their original dimensions without permanent deformation. Butyl and halobutyl are the most common elastomers used to help to retain headspace inert gases and provide a good barrier for water vapor transmission. However, they tend to shed particulates after irradiation. Ethylene propylene material tends to cross-link and turns slightly yellow upon irradiation. Authors recommended a close collaboration between the closure manufacturers and with the pharmaceutical manufacturers. The deep understanding of the details of the polymer(s), cure systems, and additives and their effect on the product would help "custom design" ready-to-use closure composition and sterilization processes of the closure.

Table 7 : Comparison of cumulative radiation dose between the ground control and at the International Space Station

Payload	# of days	Radiation dose, Control, mGy	Radiation dose, Space flight, mGy
1	0	4.54	1.93
2	353	4.84	44.12
3	596	5.06	74.53
4	880	5.45	110.70

Table 8 : Number of formulation (out of 33) failing the chemical potency requirement

Payload	# of days	Control (%)	Space flight (%)
1	0	0 (0)	1 (3)
2	353	2 (6)	11 (33)
3	596	8 (24)	17 (52)
4	880	16 (48)	24 (73)

Glass flakes in injectable liquids

Appearance of glass flakes in the injectable liquids is not uncommon. The real problem is their transparent nature, which makes it difficult to detect them. In a study, Iacocca et al. [11] examined three carboxylic acid model drugs and stored them in 3 different types of Type I glass vials – A. Type I glass treated with Ammonium sulfate to reduce surface alkalinity, B. Uncoated Type I, and C. Type I coated with silicon dioxide. The vials were exposed to a depyrogenation temperature of 250°C or 350°C for 4 hours. The formulations were exposed to terminal sterilization cycles of 0 or 2 and the samples were stored at 5°C, 25°C, 40°C and 60°C. Some of the key observations in this study were as follows: Variation in the depyrogenation temperature did not affect the number of glass flakes in the product. The pH of formulation decreased from about 9.5 to about 8 during storage. In the ICP-

OEC analysis, higher amounts of dissolved silicon were observed in Formulation A. The storage temperature also had an impact on the dissolved silicon – the higher the temperature, the higher were the dissolved silicon levels. SEM analysis showed breakage of glass flakes mainly in formulation A. Based on the Spectrex data, the greater number of particles were observed in A and at 60°C as compared to those generated at 40°C. The authors assigned the lack of glass durability to the combination of the nature of the drugs and the pH of the solution.

Prediction of Lyophilization cycle parameters

The Lyophilization process provides unique advantages and has been used in many products. In this article, lyophilization is considered as a packaging step rather than a part of formulation manufacturing. In a research article by Mockus et al., Bayesian treatment was added to the primary drying modeling. There are three critical steps in freeze-drying: 1) Freezing of the drug solution in partially stoppered vials, 2) Primary drying to produce a cake, and 3) Desorption phase for secondary drying. During the freezing step, the temperature at which the first crystals of ice appear is termed as a nucleation temperature. Nucleation temperature is affected by several formulation and process factors. In the primary drying step, temperature should not go beyond the eutectic temperature or else the cake could collapse. Some of the factors affecting the primary drying could be the composition of formulation, pressure differential, rubber stopper resistance for water vapor release, heating rate etc. The main goal of this study was to determine the duration of primary drying. The number of temperature gauges and their correct placements are critical in determining the exact primary drying end point. In this study, it was shown that the resistance of dry layer mass transfer was product specific and it was a function of the nucleation temperature. Authors developed a mathematical model to predict the end point of primary drying time. In general, for the freeze-drying process, the design space would generally vary for different products.

Cannon and Shemeley studied the effect of vial design on the sublimation rate during the primary drying of lyophilization cycle. The sublimation rate was influenced by the heat and mass transfer rates. The composition of glass vials could affect the thermal conductivity. Other factors influencing the process were the vial diameter, the vial's bottom radius, and the fill volume. The bottom concavities did not substantially influence the sublimation rate.

FDA's Quality Control Approach-

I. Characterize / Identify all possible extractables and establish a profile for each packaging component.

II. Establish a correlation between extractable and its leachables potential

III. Set meaningful acceptance criterion for a given extractable in corresponding incoming packaging components, based on its qualification level and actual observed data.

IV. Set meaningful acceptance criterion for a given leachable based on actual observed data in the drug product.

Conclusion:

As scientific progress continues to be made, methodologies are advanced, sources are better controlled, materials improve and processes are upgraded and better measured and controlled, the best practice to assess the risk of leachables will further evolve. Science and understanding are not static. However, the fundamental understanding of all the technical issues regarding leachables and toxicological safety will continue to be applied to achieve a knowledge based risk assessment. A key step in extractable/leachables assessment is the establishment of a comprehensive extractable compound profile for materials and components. Characterization of unknown compounds, particularly if present in complex mixtures of organic molecules, is not a trivial exercise and often requires sophisticated capabilities, deep expertise and knowledge of material and component composition and history. Extractable and leachable assessment of given materials represents a dynamic rather than static target since development and use of new polymers, elastomers, processing agents and additives, as well as upstream changes, affect lot-to-lot materials composition and properties. Establishment of comprehensive, accessible exact mass spectral libraries will aid greatly with screening polymer and elastomer extracts for common

additives and extractables.

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