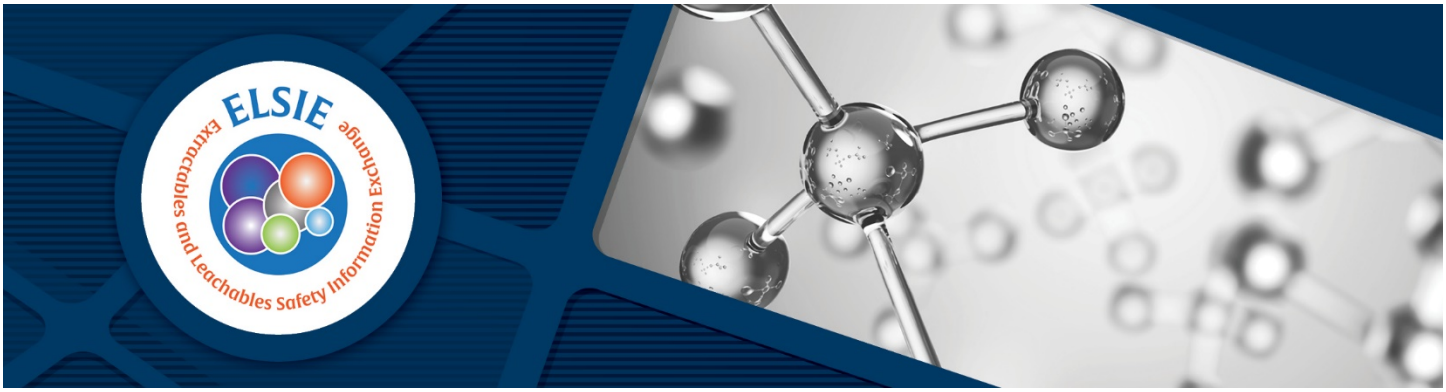


SCREENING AND MATERIALS SELECTION

for Leachables and Extractables Management

INTRODUCTION

Materials and components used in the manufacture, storage and use of pharmaceuticals (small molecule and biologics) and devices in drug delivery systems should be evaluated for extractables and leachables (E&L) where they are in direct contact with the active pharmaceutical drug substance (DS), drug product (DP), process fluids or indeed in direct contact with the patient (ICH Q7, 21 CFR 211.65(a)). Thus, it is key and reflective of regulations that, in order to reduce risks associated with some leachables, pharmaceutical companies, in collaboration with material and component suppliers develop and use an appropriate knowledge base for screening and material selection for products in development and during lifecycle decision making.

This paper describes an approach for early and subsequent assessments of materials and/or components under consideration for use in pharmaceutical active drug substances (DS) and drug product (DP) manufacturing processes, container closure systems, and drug delivery devices. This approach may be considered as a “hazard appraisal process” or HAP, which may be used within a broader ICH Q9-type risk management process. The HAP can assist in understanding key aspects of a screening and/or materials selection process such as what data is available; how to gain access to it; assess its weighting to the scenario in hand; how to build an informed hazard assessment or profile in a consistent manner to then communicate with stakeholders.

An example decision process flow is provided to capture the elements of a HAP, with the inclusion of six case studies for materials and component screening to exemplify its potential use with a diversity of scenarios, to reasonably reflect current pharmaceutical development and lifecycle practices.

GAPS AND CHALLENGES

Some current gaps and challenges that face pharmaceutical manufacturers specifically with respect to executing an effective material and component hazard assessment include but are not limited to:

- Absence of a common regulatory framework for assessment, control and lifecycle management of E&L, which includes consideration of screening and materials selection.
- Absence of globally aligned safety thresholds.
- Limited access to supplier data, the data being non-contemporaneous in nature or non-standardised in structure.

- The wide diversity of conditions (be they extractables or leachables studies) under which E&L data is collected can make extrapolation to specific scenarios more challenging.
- The overall large diversity of potential E&L that could be present for a given material/ component and conditions of use and the absence of a common accessible knowledge base.

Articulation of a rationalized process, such as a HAP, for screening and materials selection, within a larger risk management process for leachables, can help address some of these opportunities, responsibilities and challenges.

Within a typical risk management framework, such as that noted in ICH Q9, the screening and/or materials selection activity may be envisioned to occur prior to risk assessment (highlighted at the beginning of Figure 1) and may be applicable in a new product development or lifecycle management scenario.

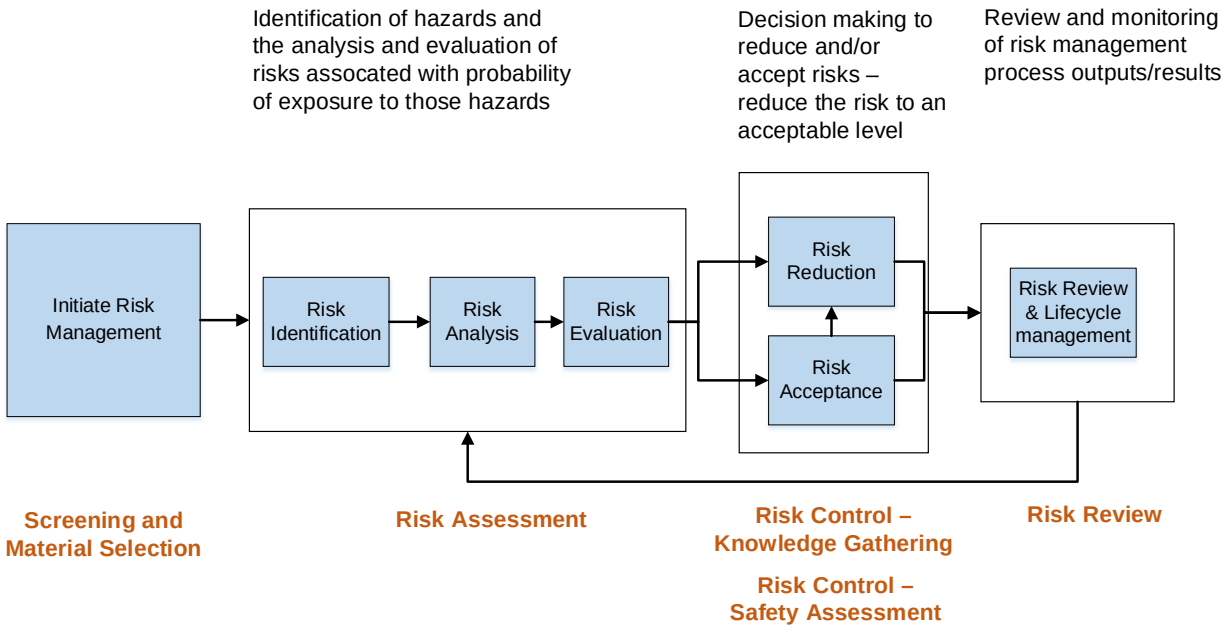


Figure 1. Risk management framework for leachables, based on ICH Q9 risk assessment process.

A HAP for screening and materials selection provides a framework to collate and classify existing knowledge providing a consistent and considered output which could then feed into a formal technical product-based risk assessment process. This approach is consistent with general risk management principles including the identification of hazards, evaluation of the risks followed by mitigation and control. A HAP facilitates a structured review of appropriate materials and components, and informed decision-making as to general fitness of materials and components for their intended purpose and stage of development. Note that a HAP is not the same as risk assessment and risk control, but rather entails evaluation of supplier information and prior knowledge to inform these later steps in the risk management process,

SCOPE

Materials and components in scope include those used in manufacturing process systems, those in direct contact with DS or DP during bulk storage and as part of packaging, container closure systems (CCS) or a drug delivery device, as well as secondary packaging. As per USP, “materials” are materials of construction, and “components” are packaging components (USP <659>, Packaging and Storage Requirements).

The topic is relevant throughout the development and commercial stages of pharmaceutical products (including biologics) and drug delivery devices, thus there may be partial convergence with aspects of lifecycle management and change control relating to E&L. The philosophies described here could be considered for use in advance of the anticipated ICH Q3E guidance on E&L which may apply to commercial products as well as those in development.

Materials and components not in scope would generally include those that do not come into direct contact with the DS, DP or process fluids. Medical devices such as pacemakers, stents, etc. are out of scope. General considerations for design of experiments or generation of actual data are also out of scope as these are covered in the risk control- knowledge gathering paper.

Figure 2 describes an E&L hazard appraisal framework concept and the key aspects that would be explored by a company as it gathers existing knowledge and undertakes an initial hazard assessment. This knowledge gathering and science and risk-based control strategy can evolve alongside the development lifecycle of a medicinal product. Key considerations would include the full utilization of existing regulatory guidelines and pharmacopoeial standards and leveraging other information including historical data sets, published studies, and data modelling.

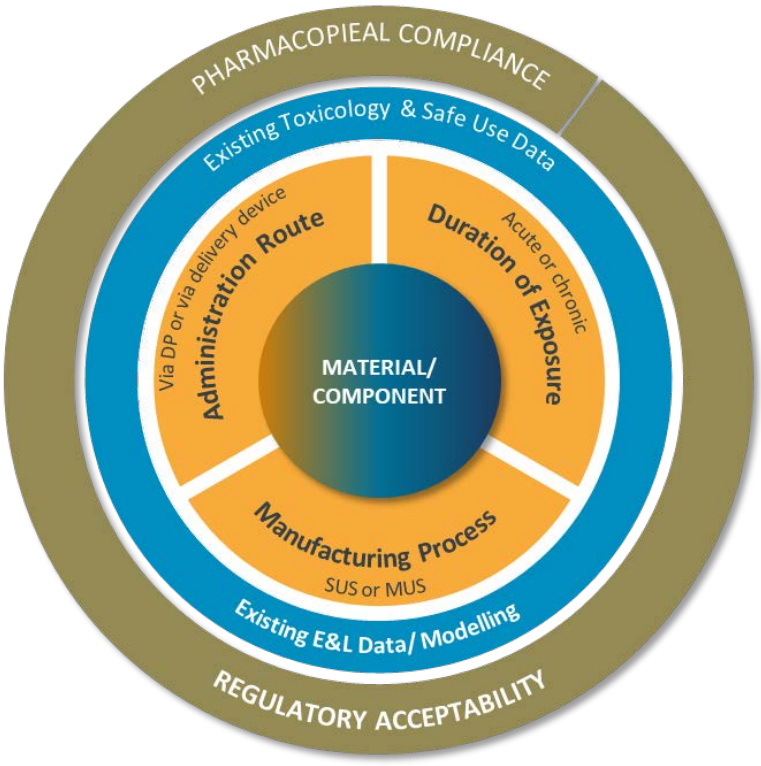


Figure 2: Conceptual representation of an E&L Hazard Appraisal framework.

EXAMPLE HAZARD APPRAISAL PROCESS (E&L HAP)

Fundamentally, the E&L HAP framework presented utilizes existing approaches and established principles. These include key considerations such as route of administration, prior safe use, likelihood of CCS interaction, the manufacturing process, and the magnitude and duration of exposure to the patient be it via the DS or DP. The main elements of the HAP process flow are shown in Figure 3. This includes some key questions that should be traversed for any E&L assessment, for example around potential contact with the DS or DP and whether the material or component will be part of the container closure system or the manufacturing process.

Figures 5, 6, and 7 (Appendix 1) depict the hazard "grids" relevant for manufacturing, route of administration and CCS interactions. These grids essentially provide a scaffold or prompts around which a hazard level can be assigned, they have a basis in either regulatory guidance or general Pharma industry practice.

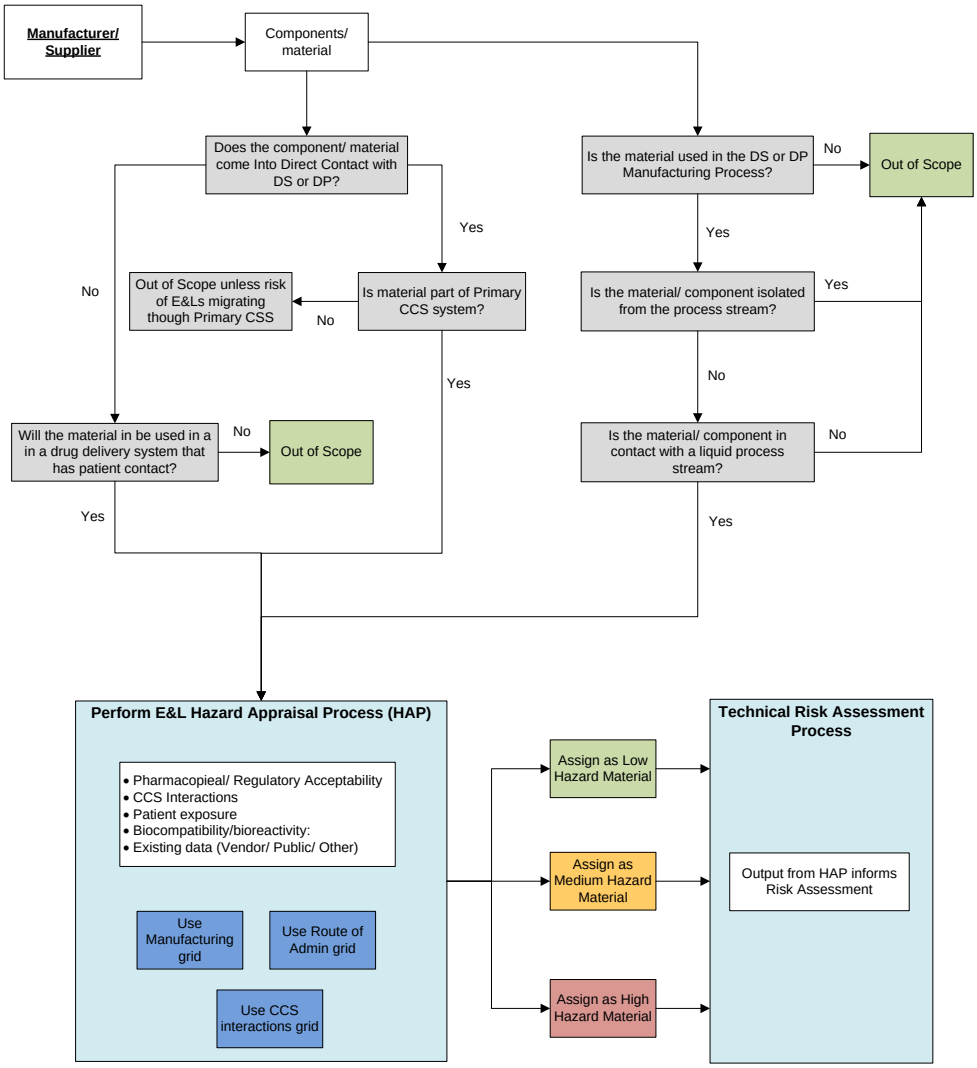


Figure 3: Summary process flow for screening materials and components with respect to extractables and leachables management

Thus, Figure 3 above and the hazard grids (Figures 5-7) provide a suggested framework through which pharma could review available data, and make consistent, informed decisions on the initial hazard category that new components or materials can be allocated from an E&L perspective and, where multiple component or material options are available, allow an initial relative ranking. For precedented / existing / previously used components or materials, the framework remains applicable with the expectation that the hazard appraisal would be mitigated by a larger applicable dataset (e.g., “use data”).

As mentioned above the process flow in Figure 3 provides an example set of initial questions (grey boxes) to identify only those components or materials that require an assessment HAP.

Existing information on the materials/ components and required compliance/ safety aspects can be gathered from a diversity of sources, examples of which are summarized in Figure 4. Appendix 2 provides a more extensive list of references. These represent sources of data that can feed into the relevant elements of the HAP.

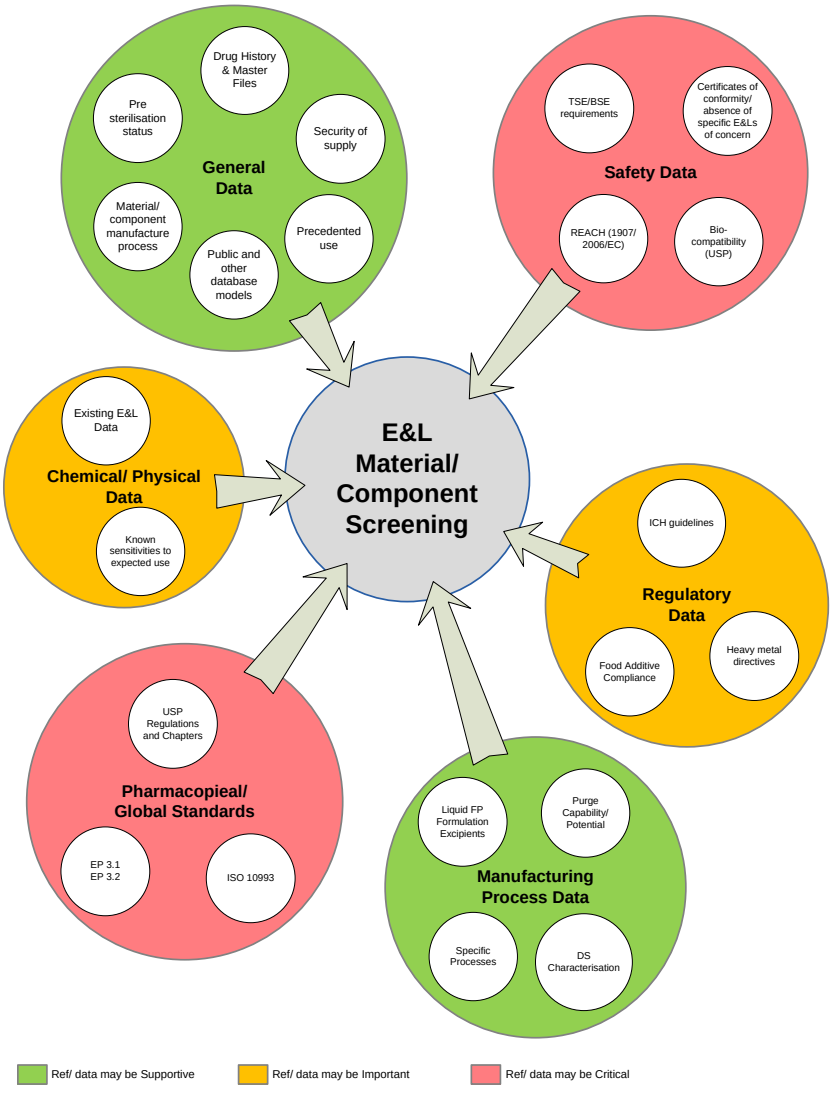


Figure 4: Examples of E&L information sources for material and component screening.

Regulatory (Compendial) Requirements

For new materials or materials subject to change control, there are various regulatory regulations, Pharmacopoeial and other standards in place. For example, USP, for plastic materials and elastomers intended for use in pharmaceutical environments (see appendix 2). The draft USP <665> in conjunction with <661.1> and <661.2> provides an appropriate “suitability for use” framework to evaluate plastic materials under consideration for use, solely targeting processes involving liquid streams. Other comparable standards such as Ph. Eur. chapters 3.1 and 3.2, and ISO are also in place. Refer to Appendix 2 for a comprehensive listing.

Evidence of this compliance (including characterization) should be provided by the material or component manufacturer. Where materials and components subsequently change, to maintain control and ensure the risk profile does not increase, the manufacturer and/or suppliers can work to ensure that the appropriate change control process has been completed with evidence of continuing compliance against standards being provided to the pharmaceutical company. Overall compliance allows a low hazard assignment to the materials/ components. For commercial products data should be generated to confirm regulatory compliance. The default would be testing against the current pharmacopoeial standards (e.g., USP, Ph.Eur.).

Alternative sources of data may be utilized to confirm regulatory acceptance with the appropriate scientific rationale and hazard evaluation. This could include but is not limited to food contact compliance, manufacture’s data, comparator data, etc. During the development cycle a formal technical risk assessment should be undertaken and the appropriate data generated.

Food Contact Requirements

Where pharmacopeial data unavailable or limited in early development, as a minimum materials and components should meet the requirements of current regulations such as (EC) No 1935/2004, (EU) No 10/2011 and amendments and 21CFR Parts 172–179. Where materials and components subsequently change, to maintain control and ensure the hazard profile does not increase, the manufacturer and suppliers should ensure that the appropriate change control process has been completed with evidence of continuing compliance against the standards being provided to the pharmaceutical company. .

Certificates of conformity and absence of specific E&Ls of concern

Available evidence should be gathered to confirm absence or assurance below current permissible tolerable daily intake (e.g., 4 mcg/kg/day or lower) for special case E&L such as BPA, PAHs, PNA’s MCP, N-nitrosamines, nitrites, etc. The expectation is that the supplier or manufacturer will provide the appropriate conformity statements to Pharma.

Existing CRO/ other E&L data

Any other information, in additional to evidence of compliance, relevant to E&L should be requested from vendor/supplier and CROs and/or gathered from internal company sources. This can be a broad range of information including vendor DMF (drug master file) or DHF (design history file), consortium and public E&L data. It may indeed also include modelling information.

Examples of Hazard Grids

Container Closure System Interaction Hazard Grid (Figure 5)
The FDA’s Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing, and Controls Documentation, provides a framework against which an

assessment of the CCS interaction hazard can be determined. This is a key area for consideration for a HAP given the relative contact duration and in terms of DP lifecycle, the relative proximity to the patient.

Exposure Duration Hazard Grid (Figure 6)
Consideration of the anticipated exposure profile to the patient should be undertaken with specific consideration of the dosing regimen. Again, this is a key area of consideration for a HAP particularly for chronic dosing of drug products. Single acute dosing presents a relative low hazard while the hazard will be increased where chronic dosing is required. Precedented use of these components in comparative scenarios may be used to form part of the assessment following the principles within the draft USP <665>. The principles of ICH M7 (small molecule) and ISO-TS 21726:2019 (devices) can be adopted for and provide a relevant framework and tables for the HAP assessment and the hazard category for exposure.

Manufacturing Interaction Hazard Grid (Figure 7)
A review of the expected DS and/or DP manufacturing process should be undertaken to understand the impact of direct contact materials and components to the DS or DP with respect to E&L as these process equipment related leachables - may affect CQAs of the DP or present a safety hazard by their presence in the DP. A diverse range of conditions may impact the manufacturing E&L hazard (e.g., sterilization or high temperatures, solvent type, storage, duration, etc). Comparable data will greatly facilitate understating of the manufacturing hazard.

Biocompatibility testing

While biocompatibility testing is strictly not encompassed within the assessments of E&Ls, there is significant overlap in terms of patient safety considerations. Some materials have the potential to come into direct or indirect contact with the drug product and the patient and thus should be also assessed for their potential to trigger an adverse biological response. These are typically materials used in a CCS component that contacts the drug product during storage/ use and then could come into contact (i.e., skin, mucosal, etc.) with the patient during administration of DS or DP. Biocompatibility can be deemed a material property, indicating a baseline level of acceptability for its intended use with respect to toxic, injurious, or immunological responses in living tissues. Thus, when evaluating materials or components during the early screening and selection process, consideration should be given to type of body contact, duration of patient contact, clinical/commercial use, and total surface area of the material/component. There are various standards and guidelines in the public domain that address biocompatibility testing including the globally recognized ISO 10993 standard for biological evaluation of medical devices (see Appendix 2)

CASE STUDIES

There is a large diversity of E&L scenarios that may present to pharma during development. The six case studies presented here attempt to exemplify that diversity, with a spread of components/material, hazard category and across the development life cycle. For each, the available information is assessed following the thought processes outlined in the decision trees and relevant elements of the HAP.

Overall, the case studies arguably demonstrate the use of HAP as an approach for E&L subject matter experts to structure and communicate a hazard assessment of materials or components with development teams and to provide some guidance on next steps. The output is an example to justify using or not using materials/ component, to proceed to use if additional information/supportive evidence is generated as part of a product specific technical risk evaluation or indeed to rank order several materials/ components. In actual application, the process and output will vary be case by case. Below is a list of the six case studies provided and their HAP assessment.

Case Study	Scenario	HAP Assessment
1	Evaluation of a New DS Process Container	Low to Medium
2	Change of drug product preservative storage bag	Low to Medium
3	Supplier change to the size of a resin reactor	Low to Medium
4	Selection of material for a closure system for a new product	High
5	Supplier change to resin transportation mode and increased antioxidant level	Low to Medium
6	Evaluation of a material of construction for a single dose DPI	High

The studies are largely based on real cases but will include some hypothetical data to better convey the scenario.

Case Study 1: Evaluation of a New DS Process Container

BACKGROUND:

As part of the manufacturing process of a small molecule, a process stream of the final, non-isolated DS requires transfer from one location to another for final isolation. A couple of options are under consideration for the holding and transferring of the solution, one of which is the use of a semi rigid single use process container, which is manufactured from a tri-layer film containing LDPE as contact layer, polyester outer layer and an adhesive tie layer in-between.

Relevant attributes for the DS manufacturing process stream:

Attribute	Value
Drug substance	Final API in solution, prior to isolation
Concentration	4 g/L intermediate
Matrix	Buffer pH 5.5: methanol 90:10
Storage duration	Typically, up to 14 days, exceptions up to 28 days at 2ºC to 8ºC

Relevant drug product Quality Target Product Profile (QTPP) Attributes:

Attribute	Value
Route of Administration	Intra venous
Drug product type and concentration	50 mg/mL Ready to dilute injection
Maximum Daily dose	1 g/day given over a 4-hour continuous period (once/day)
Treatment duration	Up to7 days treatment period, up to 3 treatment periods per year

ASSESSMENT:

Pharmacopoeial Requirements

Method	Title	Source	Result	Requirement Weighting*
USP <85>	Bacterial endotoxins test	Supplier of container	Pass	Important
USP <87>	Biological reactivity tests, in vitro	Supplier of container	Pass	Important
USP <88>	Biological reactivity tests, in vivo	Supplier of container	Pass	Important
USP <661>	Plastic packaging systems and their materials of construction	Supplier of container	Pass	Critical
EP 3.2.2.1	Plastic containers for aqueous solutions for infusion	Supplier of container	Pass	Critical
ISO 10993-4	Biological evaluation of medical devices. Selection of tests for interactions with blood	Other	Non-hemolytic	Supportive

* The requirement weighting is used to assign the level of applicability and importance being attributed to the particular pharmacopoeial information versus the material or component or scenario and should be assessed on a case by case basis.
Critical: Information that the Regulatory Authority would require.
Important: Information that would be expected to be gathered by pharma during development/ provided as required.
Supportive: Information from public domain, food references, etc.

Existing Extractables and Leachables Data review

Note: This data is a compilation of supplier, internal and other information, including E&L levels, SCT values, etc. Thus, the format/ content type will vary for each scenario.

Parameter	Condition – 30 days / 75ºC			
	Water	**50% Ethanol**	**Acidic**	**Alkali**
Total Organic Carbon	25 ppm			
Organic Compound				
Volatile	-	1,3 di-t-butyl benzene	-	-
Semi-Volatiles	-	2,4 di-t-butyl phenol	-	-
Non-Volatiles	-	Irganox 1076	-	-
Extractable Metal	Boron & Potassium	Sodium & Boron	Boron	Potassium
pH Stability	Decrease from pH 6.5 to pH 4.5	Decrease from pH 6.7 to pH 4.5	Static at pH 0	Static at pH14

Precedented Use and Existing Leachables Data

While there is no specific extractables or leachables information available internally on the use of this specific type of container or material, there is an extensive body of data (both internally and externally) available on polyethylene as contact material which demonstrates precedence and gives confidence in the potential use of this material in this application and would be expected to present a low leachable hazard.

HAZARD APPRAISAL PROCESS:

Pharmacopoeial Requirements: Low Hazard

The above weightings have been applied to demonstrate the criticality of this data based on the intended use of the containers. Supplier information has demonstrated that the plastic container material has met the main pharmacopoeial requirements (USP <661> and EP 3.2.2.1), the availability of this critical information facilitates a low hazard assignment. Data is also available for other requirements which has a lower weighting. Bacterial endotoxins, biological activity tests and blood interactions that have been given a medium/low weighting due to the additional processing that the contained drug substance solution will undergo during isolation and drug product manufacture. It is recognised that the contained solution is the finished drug substance and could be impacted.

Container Closure System: High Hazard

Based on the drug substance in liquid form being in contact with the plastic container, forming a high likelihood of interaction with the packaging, and the highest degree of concern for the route of administration, the CCS HAP supports a high hazard assignment. It is noted that 1,3 di-tert-butyl benzene, 2,4 di-t-butyl phenol and Irganox 1076 have been identified as extractables from the containers. These are standard additives, routinely found as leachables in these types of materials. With the exception of 1,3 di-tert-butyl benzene (degradant), a significant body of toxicological safety data exists. While these E&L impurities are considered not to be of concern, the lack of data on the degradant indicates a potential hazard that would need to be considered further.

Exposure Duration: Medium Hazard
The dosing regimen expected for the drug product is short duration on a non-regular basis over the patient's lifetime. Based on this information the exposure duration is given a Medium hazard assignment.

Manufacture: Low to Medium Hazard
Based on the composition of the drug substance matrix (including low percentage methanol), the duration of contact (up to 28 days) and the proximity of the container in relation to the finished drug product, there is potential for the identified compounds to be extracted. However, this is mitigated by the storage temperature (2ºC to 8ºC) for the container. Based on this data and limited information on precedented use in similar environments, the manufacture hazard assignment is Low to Medium.

CONCLUSION:
The overall HAP assignment for the container is considered Low to Medium Hazard. It is recognized that the CCS hazard is deemed high, with due consideration and understanding of the body of data available on the potential extractables and leachables. The impact of 1,3 di-tert-butyl-benzene, 2,4-di-tert-butyl-phenol and Irganox 1076 on the end drug product, are considered low and should be evaluated during a specific technical assessment as potential leachables in the final drug product.

Case Study 2: Change to drug product preservative storage bag

BACKGROUND:
A pharmaceutical project team have decided to change from the current process bag (5 L, contact surface polyethylene) used to store a compounded preservative to an alternative bag (10 L, contact surface Ethyl Vinyl acetate). Thus, this represents both a contact material change and surface area change. This preservative is stored in the bag at 2ºC to 8ºC for up to 12 months. The preservative is then used during formulation of a drug product and the bag is discarded. It is only the product preservative fluid that comes into direct contact with the bag. Manufacturing process remained the same except the step where the preservative is transferred to the new bag.

Relevant information about the preservative is shown in the table below.

Relevant drug product QTPP attributes

Attribute	Value
Final Product type	Formulated injectable drug product P
Fluid Matrix	Preservative in Water for Injection (WFI)
Shelf-life	12 months at 2ºC to 8ºC
Final drug product presentation	Multi-dose vials (MDV)
Route of administration	Intramuscular injection
Maximum Daily dose	0.65mL/dose
Treatment duration	Once a year

ASSESSMENT:

Pharmacopoeial Requirements (HAP)

Pharmacopoeial requirements were evaluated for new Bioprocess bag and found to meet all requirements as specified in the table below. Evaluation involved reviewing all available information from the supplier regarding the criticality of the set test methods data and assigning a requirement weighting for the intended use.

Supplier information demonstrated that the plastic container material met the main pharmacopoeial requirements (USP <661> and EP 3.2.2.1), the availability of this critical information facilitates a low hazard assignment.

Methods	Title	Source	Result	Requirement Weighting*
USP <85>	Bacterial endotoxins test	Supplier or other information	Pass	Important
USP <87>	Biological reactivity tests, in vitro	Supplier or other information	Pass	Important
USP <88>	Biological reactivity tests, in vivo	Supplier or other information	Pass	Important
USP <661>	Plastic packaging systems and their materials of construction	supplier or other information	Pass	Critical
EP 3.2.2.1	Plastic containers for aqueous solutions for infusion	Supplier or other information	Pass	Critical
ISO 10993-4	Biological evaluation of medical devices. Selection of tests for interactions with blood	supplier or other information	N/A	N/A

* The requirement weighting is used to assign the level of applicability and importance being attributed to the particular pharmacopoeial information versus the material or component or scenario and should be assessed on a case by case basis. Critical: Information that the Regulatory Authority would require.
Important: Information that would be expected to be gathered by pharma during development, provided as required.
N/A-does not apply since the container closure is not a classified as a medical device.

Certificates of conformity were evaluated for any E&Ls of concern including nitrosamines, polynuclear aromatics and others. No concerns were found.

Existing Extractables and Leachables Data Review

Extractables vendor data was previously evaluated internally while qualifying the new Bioprocess bag for use with another product “Q” and a risk assessment report was written. A simulation study was also conducted for that bag of the same material of construct (MOC) with product Q (with a comparable dosage) and a final summary report was written. Both reports were reviewed, and overall E&L data was compared with the set Safety Concern Threshold (SCT) and summarized in the table below.

Note: This data is a compilation of supplier, internal and other information, including E&L levels, SCT values, etc. Thus, the format/ content type will vary for each scenario.

Leachable ID / Detection Method	Vendor Extraction data for proposed bag with model solvents	Simulation study with product Q
All Inorganics by ICP-MS	<SCT	<SCT
All volatile organic compounds by HS-GC-MS	<SCT	<SCT
All semi-volatile organic compounds by direct-GC-MS	<SCT	<SCT
All Non-volatile organic compounds by LC-MS	<SCT	<SCT

<SCT= Less than Safety Concern Threshold (1.5 µg/dose)

All extractables (potential leachables) levels were less than SCT (1.5 µg/dose) for the intended use of product Q. Product Q and product P have similarities in terms of pH and storage shelf-life and for that reason the E&L risk for using new Bioprocess bag with the preservative for product P was ranked low to medium. Medium ranking was assigned conservatively since there was no E&L data for the bag with direct contact with product P.

Precedented Use and Existing Leachables Data

No E&L data was available for the bag with direct contact with product P.

HAZARD APPRAISAL PROCESS (HAP)

HAP parameters and ranking were summarized in the table below

Parameter	HAP Hazard Ranking
Pharmacopeia Requirements	Low
Container Closure System Interactions	High
Concern with compatibility/ Biocompatibility	Low
Patient Exposure	Low
Manufacture	Not Applicable

Pharmacopoeial requirements and compatibility: Low Hazard

Pharmacopoeial requirements and compatibility parameters were ranked low since there were no obvious concerns from available information. The new Bioprocess bag was previously used with product Q which has similar pH and storage conditions as product P that uses the preservative and therefore E&L profiles would probably be similar.

Exposure Duration: Low Hazard

Considering the route of administration (intramuscular injection), and administration frequency of once per year the exposure to patient was ranked low.

Container Closure System: High Hazard

The container closure system interactions with preservative for product P was ranked High as that is the only possible means to pose a risk to patient safety when the final container drug product is formulated. Because of direct contact of preservative to the bag and storage duration of up to 12 months before

formulation, there is potential to have leachables in the preservative and subsequently in the final drug product.

CONCLUSION:
The overall HAP assignment was ranked as low to medium hazard pending an E&L technical assessment for the new Bioprocess bag direct interaction with the preservative for product.

Case Study 3: supplier change the size of the resin reactor:

BACKGROUND:
The resin supplier has decided to change the reactor size used to manufacture resins from large size reactor to a smaller one (half size). These resins are used for the primary film in bags used to accommodate aqueous and lipid emulsion solutions. The supplier claims that the chemical nature and manufacturing process of the resin remained the same and the only change is the size of the reactor. Given the surface area to volume change, the downstream impact may increase E&L impurities.

Relevant drug substance manufacturing process stream attributes:

Attribute	Value
Drug substance	Aqueous and lipid emulsion solutions
Bag format	150 mL, 500 mL, 1L, 2L, 3L
Storage duration	Bags are stored empty up to 3 years, during compounding can be stored for 9 days in fridge and 3 days at room temperature.

Relevant drug product QTPP attributes:

Attributes	Value
Route of Administration	Intra venous
Drug product type and concentration	Range of concentrations
Maximum Daily dose	1 bag is used per day regardless the volume[a, b, c]
Treatment duration	> 10 years (as worst case scenario treatment)

a. Total parental nutrition therapy can be given for a lifetime; however, an individual container of solution will only be infused over a maximum of 24 hours based on the exact needs of the patient. For example, if a patent requires 2L per day, the solution will be prepared in 2L bag and will not get two bags of 1L.
b. Infusion Therapy Standards of Practice, Infusion Nurses Society, Volume 39, S1- 2016.
c. ASPEN Safe Practices for Parenteral Nutrition, Journal of Parenteral and Eternal Nutrition Volume 28, No 6 – 2004.

ASSESSMENT:

Pharmacopoeial Requirements

Method	Title	Source	Result	Requirement Weighting*
USP <85>	Bacterial endotoxins test	Supplier of container	Pass	Important
USP <87>	Biological reactivity tests, in vitro	Supplier of container	Pass	Important
USP <88>	Biological reactivity tests, in vivo	Supplier of container	Pass	Important
USP <661>	Plastic packaging systems and their materials of construction	Supplier of container	Pass	Critical
EP 3.2.2.1	Plastic containers for aqueous solutions for infusion	Supplier of container	Pass	Critical
ISO 10993-4	Biological evaluation of medical devices. Selection of tests for interactions with blood	Other	Non-hemolytic	Supportive

* The requirement weighting is used to assign the level of applicability and importance being attributed to the particular pharmacopoeial information vs the material or component or scenario and should be assessed on a case by case basis.
Critical: Information includes anything that the Regulatory Authority would require.
Important: Information that would be expected from pharma during development, provided as required.
Supportive: Information from public domain, food references, etc.

Existing Extractables and Leachables Data Review (Data compiled from existing in-house E&L data on the previous material)

Note: This data is a compilation of supplier, internal and other information, including E&L levels, SCT values, etc. Thus, the format/ content type will vary for each scenario.

Parameter	Condition – 3 days / 37ºC			
	Water	50% Ethanol	Acidic	Alkali
Total Organic Carbon				
Organic Compound				
Organic extractables	-	Nonanoic acid Hexanoic acid Octanoic acid Cyclohexanone 1-Hexanol, 2-ethyl		
Extractable Metal	NMDL	NMDL	NMDL	NMDL

NMDL: not more than detection limit.

Precedented Use and Existing Leachables Data
There is extensive extractables information available internally on the precedented use of this specific type of container made of this material that was manufactured in the large size reactor, which gives confidence in the potential use of this material

HAZARD APPRAISAL PROCESS
Pharmacopoeial Requirements: Low Hazard
Weightings have been applied to demonstrate the criticality of these tests based on the intended use of the containers. Supplier information has demonstrated that the plastic container material has met the main pharmacopeial requirements (USP <661.>, USP<88> and EP 3.2.2.1, EP 3.1.7, ICH Q3D, ISO10993-4/5/6/10), along with statements declaring that the material doesn't contain Bisphenol -A and Bisphenol -S, chlorinated compounds, natural rubber and DEHP. The availability of this critical information facilitates a low hazard assignment. It is recognized that reactor size change may impact the leachable profile as the surface area to size increased.

Container Closure System: Medium Hazard
Based on the drug substance in liquid form coming into contact with the plastic container, forming a likelihood of interaction with the packaging, and the highest degree of concern for the route of administration, the CCS HAP is considered to be medium since the bag remains empty during storage and in solution contact only during compounding or administration. It is noted that nonanoic acid, hexanoic acid, octanoic acid, cyclohexanone, and 1-hexanol, 2-ethyl have been identified as extractables from the containers (bags). These are standard compounds routinely found as leachables in these types of materials and a significant body of toxicological safety data exists. While these are not E&L impurities of concern their presence indicates low potential hazard but their concentration may increase due to reactor size change that would need to be considered further.

Exposure Duration: High Hazard
The dosing regimen expected for the drug product is short duration but possibly on regular basis over the patient's lifetime. Based on this information the exposure hazard is High.

Manufacture: Low to Medium Hazard
Based on the composition of the drug substance matrix (including lipid emulsion), the duration of contact (up to 9 days after filling) and the proximity of the container in relation to the finished drug product, there is

potential for the identified compounds to be extracted, however this is mitigated by the storage temperature (2ºC to 8ºC) for the container. Based on available data, the manufacture hazard is Low to Medium.

CONCLUSION:
While the exposure duration hazard is considered high, the overall HAP assignment is considered to be Low to Medium hazard, with the consideration and understanding of the body of data available on these potential extractables and leachables. The impact of the measured extractables on the end drug product, are considered low and should be evaluated during a specific technical assessment as potential leachables in the final drug product.

Case Study 4: Selection of material for a closure system for a new product:

BACKGROUND:
During the development of new product, a material selection was required for the closure system of the container. One of the candidate materials that was suitable for the intended use is based on polycarbonate polymer. Polycarbonate material is known to leach Bisphenol A and based on internal data this leachable is found to increase in concentration during product shelf life.

Relevant DS manufacturing process stream attributes:

Property	Value
Drug substance	Aqueous and lipid emulsion solutions
Bag format	500 mL, 1L, 2L.
Storage duration	Filled bags are stored for up to 24 months at room temperature.

Relevant drug product QTPP Attributes:

Property	Value
Route of Administration	Intra venous
Drug product type and concentration	Range of concentrations
Maximum Daily dose	2L
Treatment duration	<1 month

ASSESSMENT:

Pharmacopoeial Requirements

Method	Title	Source	Result	Requirement Weighting*
USP <85>	Bacterial endotoxins test	Supplier of container	Pass	Important
USP <87>	Biological reactivity tests, in vitro	Supplier of container	Pass	Important
USP <88>	Biological reactivity tests, in vivo	Supplier of container	Pass	Important
USP <661>	Plastic packaging systems and their materials of construction	Supplier of container	Pass	Critical
EP 3.2.2.1	Plastic containers for aqueous solutions for infusion	Supplier of container	Pass	Critical
ISO 10993-4	Biological evaluation of medical devices. Selection of tests for interactions with blood	Other	Non-hemolytic	Supportive

* The requirement weighting is used to assign the level of applicability and importance being attributed to the particular pharmacopoeial information versus the material or component or scenario and should be assessed on a case by case basis.
Critical: Information that the Regulatory Authority would require.
Important: Information that would be expected to be gathered by pharma during development/ provided as required.
Supportive: Information from public domain, food references, etc.

Precedented Use and/or Existing Extractables and Leachables Data Review

Note: This data is a compilation of supplier, internal and other information, including E&L levels, SCT values, etc. Thus, the format/ content type will vary for each scenario.

There is no extractables or leachable information available internally or provided by the supplier on this material.

HAZARD APPRAISAL PROCESS:

Pharmacopieal Requirements: High Hazard

Bisphenol A is considered as a substance of very high concern (SVHC), such toxic compounds should be avoided in the material of construction of CCS.

Container Closure System: High Hazard

Based on the drug substance in liquid form coming into contact with the plastic container, forming a likelihood of interaction with the packaging, and the highest degree of concern for the route of administration, the CCS HAP is considered to be high since the bag remains in storage for 24 months in continuous solution contact. Further the maximum daily doses of the drug product is high as it can be up to 2 L per day.

Exposure Duration: Medium Hazard

The dosing regimen expected for the drug product is for long duration (per day) but the treatment period can be for less than one month.

Manufacture: High Hazard

Based on the composition of the drug substance matrix (including lipid emulsion), the duration of contact is long (24 months) and the proximity of the container in relation to the finished drug product, there is high potential for Bisphenol A to be extracted, mainly during steam sterilization and mitigated to the solution.

CONCLUSION:

The overall HAP assignment is considered to be High hazard, with the consideration and understanding of the behaviours of the potential extractables and leachables. The impact of the potential extractables on the end drug product are considered high and the use of this material should be avoided in this container.

Case Study 5: supplier decides to change the resin transportation duration and increase antioxidant content.

BACKGROUND:

Resin supplier decided to increase the transportation duration and increase the concentration of the antioxidant (BHT) up to 3 fold compared to historical levels. No other changes are occurring to the resin. These resins are used for the closure system (tube) of the bag that represent < 1% of the total surface area of the solution contact in the container. The bags are used to accommodate aqueous and lipid emulsion solutions. The supplier claims that the antioxidant degrades during the transportation and low concentration remains in the resin. The associated risk of this tube change is represented by potential migration of BHT to the drug solution during compounding or administration to the patient and associated potential presence of increased BHT related degradants.

Relevant DS manufacturing process stream attributes:

Attribute	Value
Drug substance	Aqueous and lipid emulsion solutions
Bag format	150 mL, 250 mL, 500 mL, 1L, 2L, 3L & 4L
Storage duration	Bags are stored empty up to 3 years, during compounding can be stored for 9 days in fridge and 3 days at room temperature.

Relevant drug product QTPP attributes:

Attribute	Value
Route of Administration	Intra venous
Drug product type and concentration	Range of concentrations
Daily dose	1 bag is used per day regardless the volume, driven by daily dose
Treatment duration	> 10 years

ASSESSMENT:

Pharmacopoeial Requirements

Method	Title	Source	Result	Requirement Weighting*
USP <85>	Bacterial endotoxins test	Supplier of container	Pass	Important
USP <87>	Biological reactivity tests, in vitro	Supplier of container	Pass	Important
USP <88>	Biological reactivity tests, in vivo	Supplier of container	Pass	Important
USP <661>	Plastic packaging systems and their materials of construction	Supplier of container	Pass	Critical
EP 3.2.2.1	Plastic containers for aqueous solutions for infusion	Supplier of container	Pass	Critical
ISO 10993-4	Biological evaluation of medical devices. Selection of tests for interactions with blood	Other	Non-hemolytic	Supportive

* The requirement weighting is used to assign the level of applicability and importance being attributed to the particular pharmacopoeial information vs the material or component or scenario and should be assessed on a case by case basis.
Critical: Information that the Regulatory Authority would require.
Important: Information that would be expected to be gathered by pharma during development/ provided as required.
Supportive: Information from public domain, food references, etc.

Existing Extractable and Leachables Data review

(Data compiled from supplier E&L data on the current and previous material)

Note: This data is a compilation of supplier, internal and other information, including E&L levels, SCT values, etc. Thus, the format/ content type will vary for each scenario.

The supplier provided E&L testing of the volatiles and semi volatiles in the resin and targeted the BHT in both old and new resins, a small increase of BHT values were observed in the new resin. Further, the supplier provided comparative FTIR and NMR analysis between the old and the new resin, were the results overlay.

Parameter	Condition – 3 days / 37ºC			
	Water	Hexane		
Total Organic Carbon				
Organic Compound				
Organic extractables	-	BHT Antioxidant Soft segment of oligomer		
Extractable Metal	-	-	-	-

Precedented Use and/or Leachables Data Review

There is no extractables information available internally on the precedented use of this specific type of container made of this material that was manufactured with the old resin, the supplier provided E&L data on the antioxidant comparison between the old and the new resin.

HAZARD APPRAISAL PROCESS:

Pharmacopoeial Requirements: Low Hazard

Weightings have been applied to demonstrate the criticality of these tests based on the intended use of the containers. Supplier information has demonstrated that resin material has met the main pharmacopeial requirements (ISO10993-5/6/10/11), ASTM F756, US 21CFR 189.5, US 21CFR 700-72 EU 2004/C 24/03 along with statements declaring that the material is doesn't contain or has intentionally addition of Bisphenol, heavy metals, Phthalates, halogens, natural Rubber, silicone or residual solvents. The resin is compliant with the list of compounds in EU REACH (SVHC) and RoHs Directive 2002/95 EC. The supplier provided evidence that the antioxidant content in the resin doesn't exceed 0.5% w/w of the resin. The availability of this critical information facilitates a low hazard assignment. It is recognised that BHT levels may impact it leaching to the final solution.

Container Closure System: Low Hazard

Based on the drug substance in liquid form coming into contact with the plastic container, forming a likelihood of interaction with the packaging, and the highest degree of concern for the route of administration, the CCS HAP is considered to be medium since the bag remain s empty during storage and in solution contact only during compounding or administration. However, the tube made of the new resin has a total surface area that represents only 1% of the total solution contact area of the container with the solution. It is noted that additional BHT and other antioxidants have been identified as extractables from the containers, in addition to that coming from the resin. These are standard compounds routinely found as leachables in these types of materials and a significant body of toxicological safety data exists. Antioxidant indicates potential hazard as the concentration increased due to addition of BHT during transportation of the resin.

Exposure: Medium Hazard

The dosing regimen expected for the drug product is short duration but possibly on regular basis over the patient's lifetime. However, the tube comprises only 1% of the total solution contact, thus exposure hazard is considered medium.

Manufacture: Low to Medium Hazard

Based on the composition of the drug substance matrix (including lipid emulsion), the duration of contact (up to 9 days after filling), the bags being left empty till required, and the proximity of the container in relation to the finished drug product, there is potential for the antioxidants to be extracted, however this is mitigated by the storage temperature (2ºC to 8ºC) for the container and the small contact surface area. Based on this data and limited information on precedented use in similar manufacturing processes, the hazard is Low to Medium.

CONCLUSION:

The overall HAP assignment is considered Low Hazard, with the consideration and understanding of the body of data available on these potential extractables and leachables, the impact of the measured extractables on the end drug product, are considered low and should be evaluated during a specific technical assessment as potential leachables in the final drug product

Case Study 6: Selection of material of construction for use in a single dose DPI.

BACKGROUND:

As part of product development of a single dose dry powder inhaler (SDI) the device engineers were considering the use of ABS (Acrylonitrile-Butadiene-Styrene) plastic as the material of construction for the device because of its superior mechanical properties. Since the ABS material would be in direct contact with the drug product, the extractables and leachables team was consulted to ensure ABS would not present chemical or toxicological concerns.

Relevant attributes for the DS manufacturing process stream:

Attribute	Value
Drug substance	Inhaled biologics; dry powder
Concentration	10 mg/device
Excipients	Two excipients: peptide and sugar
Storage duration	Up to two years at room temperature in moisture protective foil overwrap

Relevant drug product QTPP attributes:

Attribute	Value
Route of Administration	Inhalation
Drug product type and concentration	Dry powder 10 mg/inhalation
Maximum Daily dose	1-2
Treatment duration	lifetime

ASSESSMENT:

Pharmacopoeial Requirements

Method	Title	Source	Result	Requirement Weighting*
USP <87>	Biological reactivity tests, in vitro	Supplier of container	Pass	Important
USP <88>	Biological reactivity tests, in vivo	Supplier of container	Pass - Class VI	Important
USP <661>	Plastic packaging systems and their materials of construction	Supplier of container	No data available	Critical
21 CFR 177.1020	Indirect food additives: polymers	Supplier of container	Pass	Supportive

* The requirement weighting is used to assign the level of applicability and importance being attributed to the particular pharmacopoeial information vs the material or component or scenario and should be assessed on a case by case basis.
Critical: Information that the Regulatory Authority would require.
Important: Information that would be expected to be gathered by pharma during development/ provided as required.
Supportive: Information from public domain, food references, etc.

Existing Extractables and Leachables Data Review (Data compiled from supplier of container)

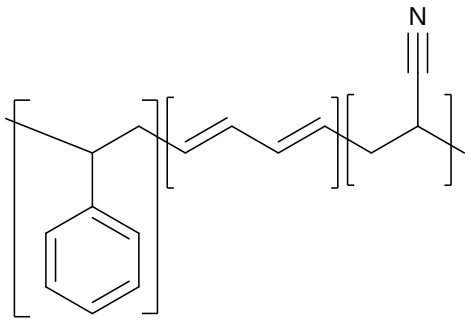
Note: This data is a compilation of supplier, internal and other information, including E&L levels, SCT values, etc. Thus, the format/ content type will vary for each scenario.

No data available from the supplier.

Precedented Use and Existing Leachables Data
While there is no extractables information available from the supplier, extractables data from a DPI constructed with ABS by a different vendor is available. The data is of poor quality because the vendor was overly aggressive with the extractions and was unable to deconvolute over 100 peaks. Very few of the extractables species were identified. It was clear that secondary/tertiary reactions occurred during extractions and many of the peaks in the extractables analyses were the result of the extraction procedure.

HAZARD APPRAISAL PROCESS:
Pharmacopoeial Requirements: Medium Hazard
Except for a statement confirming the material meets the biological reactivity requirements set-forth by USP there is no information available that that material or component meets pharmacopoeial requirements for plastic materials of construction or that it is suitable for use as a plastic packaging system for pharmaceutical use. The biological reactivity data in conjunction with a lack of physicochemical and/or extractables information leads to HAP rating of medium.

Container Closure System: Medium/High Hazard
The drug substance in dry powder form coming into contact with the plastic container, presents a medium likelihood of interaction with the packaging. However, based on knowledge of ABS copolymer there is a likelihood that the ABS could produce small leachates (i.e., monomers) that would react with the drug product and given the highest degree of concern for the route of administration, the CCS HAP is considered to be medium/high. Since this is a dry powder formulation, the non-volatile extractables are unlikely to present a hazard. The volatile and semi-volatile extractables are likely to be the main sources of leachables. Based on the limited data available and the structure of the ABS monomer (see below), small molecules arising from the breakdown of the polymer and reactions products formed during polymerization and device manufacturing are expected to be the main extractables of concern.



Additionally, the API and one of the excipients are peptides and reaction between a leachate and either of those molecules was of concern. As there was little reliable extractables data the initial materials assessment had to use structure-reactivity consideration. Butadiene, if released, could react with the drug formulation under long term stability conditions. Other small alkenes could also be problematic. Another class of extractables and leachables that was considered was carbonyls, specifically formaldehyde and acetaldehydes. The former has a strong affinity to amines and previous experience with similar materials demonstrated formaldehyde reacts to form an adduct with an amine. In addition, styrene could produce

many related products of concern, e.g., α-methyl styrene, alkyl benzenes, cyclo-hexenes, etc.) and acrylonitrile could form various forms of nitriles that were semi-volatile or volatile. The cross-reactions of the three components of the ABS monomer with the API or excipient could form semi-volatile and volatile compounds. There are other species likely present in the ABS material such as antioxidants (e.g., Irganox 1010, Irgafos 168, etc.) and fatty acids but these are less likely to react with the formulation and are deemed to be of low toxicological concern.

Volatile and semi-volatile compounds are of particular interest since the final drug product will be sealed in a foil overwrap to protect against moisture. While the foil overwrap will prevent moisture ingress it will also serve as barrier to trap species that would migrate out of the ABS material and into the dry powder formulation.

Exposure Duration: High Hazard
The dosing regimen expected for the drug product is chronic use over the patient's lifetime. Based on this information the exposure hazard is High.

Manufacture: Low Hazard
Not relevant to this case study. The ABS is preformed prior to filling and as such the manufacturing process will not impact this case study

CONCLUSION:
The overall HAP assignment is deemed high hazard. The CCS hazard is high because of lack of reliable vendor data and based on the structure-reactivity of the monomer. The potential impact on the drug product is primarily the reaction of volatile and semi-volatile leachables with the API and/or excipient. Based on the above initial materials assessment an extensive extractables study should be conducted prior to proceeding with the use of ABS as a material of construction for the single dose inhaler. Also, materials known to have fewer extractables and adequate mechanical properties, e.g., PBT, should be considered for the device material.

CONTACT US

For more information, please contact us at ELSIE.REPLY@faegredrinker.com

APPENDIX 1:
Hap hazard grids

Figure 5: CCS Interaction Hazard Grid

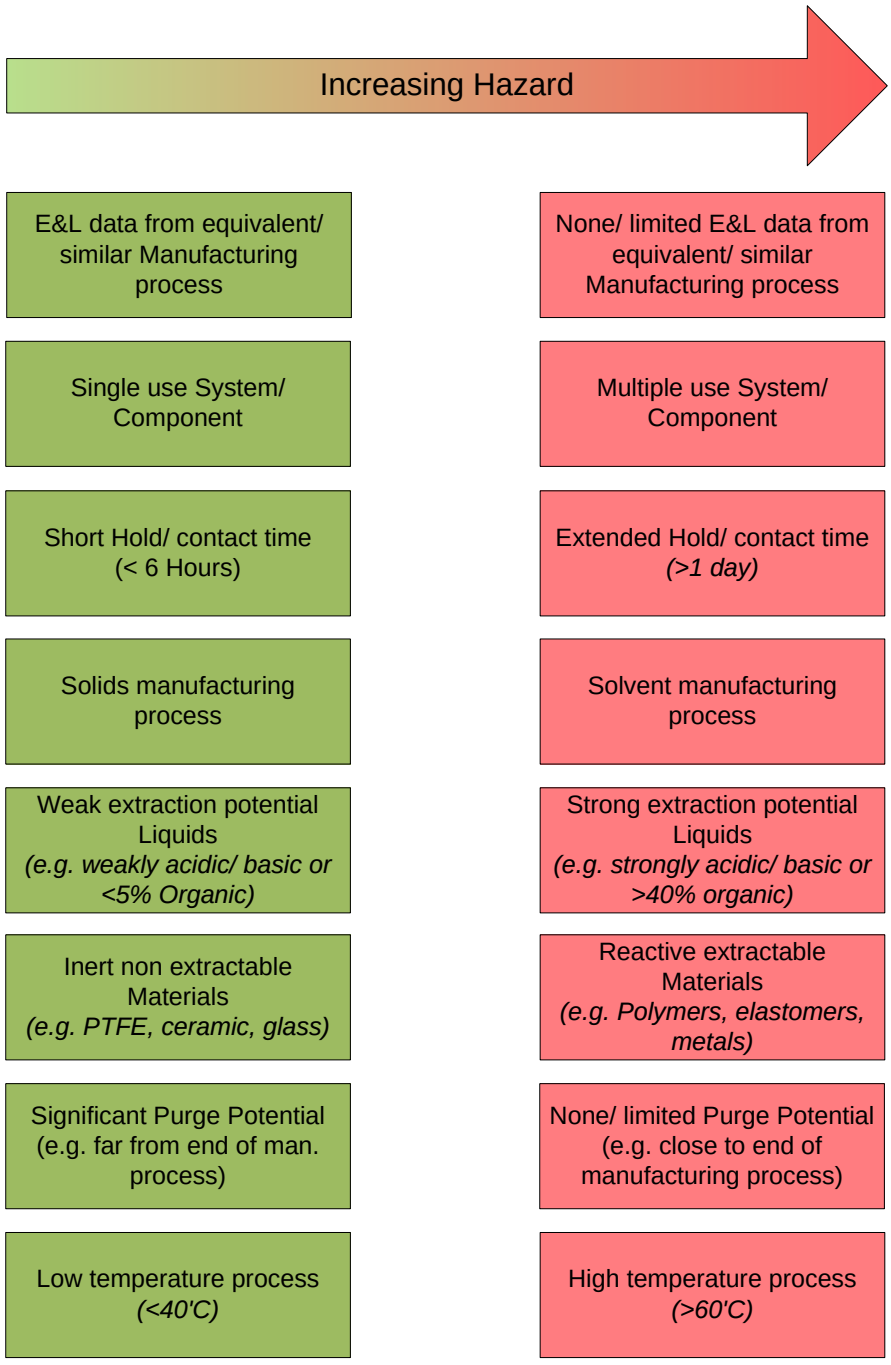
Degree of Concern associated with the Route of Administration	Likelihood of Packaging Component – Dosage Form Interaction		
	Low	Medium	High
Highest	Sterile Powders and Powders for Injection; Inhalation Powders	Injections and Injectable Suspensions; Inhalation Solutions	Inhalation Aerosols and Sprays
High	-	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	Transdermal Ointments and Patches
Low	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders		Topical Solutions and Suspension; Topical and Lingual Aerosols; Oral Solutions and Suspensions

*Adopted from Guidance for Industry - Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing, and Controls Documentation (FDA, May 1999)

Figure 6: Exposure Duration Hazard

FACTOR	EXPOSURE DURATION HAZARD		
	Low	Medium	High
Dosing Regimen	Acute Dosing Small amount or volume delivered to patients	Multi-Acute Dosing Small amount or volume delivered to patients, repeated over a significant time	Chronic Dosing Large amount or volume delivered to patients

Figure 7: Manufacturing Interaction Hazard



APPENDIX 2:
Data and compliance references relevant to an E&L HAP

	Reference Title	Designation	Comments
1	ICH Q9, Quality Risk Management. International Conference on Harmonization. 2005	Regulatory Guidance	Provides principles and examples of tools for quality risk management that can be applied to the different aspects of pharmaceutical quality.
2	ICH M7 (R1) - assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk	Regulatory Guidance	Outlines recommendations for assessment and control of mutagenic impurities that reside or are reasonably expected to reside in final drug substance or product, taking into consideration the intended conditions of human use.
3	ICH Q6A.1999. Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances.	Regulatory Guidance	
4	ICH Q6B, 1999. Specifications: Test procedures and acceptance criteria for biotechnological/biological products.	Regulatory Guidance	
5	ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients	Regulatory Guidance	
6	Container closure Systems for Packaging Human Drugs and Biologics – CMC documentation, May 1999	FDA Guidance (CDER/CBER)	This guidance supersedes FDA Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics, issued in February 1987 and the packaging policy statement issued in a letter to industry dated June 30, 1995 from the Office of Generic Drugs

	Reference Title	Designation	Comments
7	21 CFR 211.65(a) – Equipment Title 21 – Food and Drugs. Chapter I – Food and Drug Administration Department of Health and Human Services Subchapter C – Drugs: General Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals Subpart D -- Equipment	US Code of Federal Regulations	Notes that equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance
8	21 CFR 211.94 Drug Product Containers and Closures. Code of Federal Regulations, Title 21, Volume 4, Subchapter C, Part 211, Subpart E, Section 211.94. US Food and Drug Administration: Rockville, MD, 1 April 2010.	US Code of Federal Regulations	Mentions extractables and leachables from drug product containers and closures
9	21 CFR 600.3 Definitions. Code of Federal Regulations, Title 21, Volume 7, Subchapter F, Part 600, Subpart A, Section 600.3. US Food and Drug Administration: Rockville, MD, 1 April 2010.	US Code of Federal Regulations	Mentions extractables and leachables from drug product containers and closures
10	USP <1661> Evaluation of plastic packaging systems for pharmaceutical use and their materials of construction	US Pharmacopoeia	Informational Chapter Communicates key concepts behind ⟨661⟩ and related sub-chapters, ⟨661.1⟩ ⟨661.2⟩, & to provide additional info & guidance regarding applicability of these chapters
11	USP <1663> Assessment of extractables associated with pharmaceutical packaging/ delivery systems	US Pharmacopoeia	Informational Chapter. Framework for design, justification and execution of an extractables assessment for pharmaceutical packaging and delivery systems

	Reference Title	Designation	Comments
12	USP <1664> Assessment of drug product leachables associated with pharmaceutical packaging/ delivery systems	US Pharmacopoeia	Informational Chapter. Framework for design, justification and execution of an extractables assessment for pharmaceutical packaging and delivery systems
13	USP <1664.1> Orally inhaled and nasal drug products	US Pharmacopoeia	This section addresses specific considerations for leachables in orally inhaled and nasal drug products (OINDP), including metered dose inhalers (MDIs); nasal sprays; inhalation solutions, suspensions, and sprays; and dry powder inhalers (DPIs)
14	USP <1665> Characterization of Plastic Materials, Components, and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products.	US Pharmacopoeia	Informational chapter. Draft as of 2019
15	Draft USP <665>	US Pharmacopoeia	Standard If the CCS use is precedented, then assessment can be closed with no materials safety testing
16	USP <661> Plastic packaging systems and their materials of construction	US Pharmacopoeia	Standard This chapter provide standards for plastic materials and components used to package medical articles (pharmaceuticals, biologics, dietary supplements, and devices). This effectively says that if the CCS use is precedented, then assessment can be closed with no materials safety testing.

	Reference Title	Designation	Comments
17	USP <661.2> Plastic packaging Systems for Pharmaceutical use	US Pharmacopoeia	Standard This chapter applies specifically to plastic packaging systems. A product's packaging system is deemed chemically suited for its intended use, with respect to safety, if it meets the requirements in this chapter.
18	USP <661.1> Plastic Packaging & Materials of Construction	US Pharmacopoeia	Standard The purpose of this chapter is to provide test methods and specifications for plastic materials of construction used in packaging systems. Individual plastic materials of construction are deemed to be well characterized and appropriate for use if they meet the requirements in this chapter or are used in a packaging system that meets the requirements in <661.2>
19	USP <661.4> Plastic medical Devices used to deliver or administer Pharmaceuticals	US Pharmacopoeia	Draft under development
20	USP <381> Elastomeric closures for injections	US Pharmacopoeia	Standard This chapter applies to closures used for long-term storage of preparations defined in the general test chapter Packaging and Storage Requirements ⟨659⟩, Injection Packaging
21	Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC	EU Regulation	

	Reference Title	Designation	Comments
22	EP 3.1.3-7	Ph. Eur. (European Pharmacopoeia) general chapter	Materials used in the Manufacture of Pharmaceutical Containers
23	EP 3.1.9	Ph. Eur. (European Pharmacopoeia) general chapter	
24	EP 3.1.1.4-5	Ph. Eur. (European Pharmacopoeia) general chapter	
25	EP 3.2.2.1	Ph. Eur. (European Pharmacopoeia) general chapter	Pharmaceutical Containers
26	EP 3.2.3	Ph. Eur. (European Pharmacopoeia) general chapter	
27	EP 3.2.4	Ph. Eur. (European Pharmacopoeia) general chapter	
28	EP 3.2.9	Ph. Eur. (European Pharmacopoeia) general chapter	
29	EP 3.3	Ph. Eur. (European Pharmacopoeia) general chapter	Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes.

	Reference Title	Designation	Comments
	REACH (1907/2006/EC)	EC-Regulation	REACH is the Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals. It entered into force on 1 June 2007. It streamlines and improves the former legislative framework on chemicals of the European Union (EU). Manufacturers and importers will be required to gather information on the properties of their chemical substances, which will allow their safe handling, and to register the information in a central database run by the European Chemicals Agency (ECHA)
30	PQRI Recommendations for Orally Inhaled and Nasal Drug Products	Best Practices	A non-profit consortium of organizations working together to generate and share timely, relevant, and impactful information that advances drug product quality and development. Covers recommendations addressing safety thresholds, safety qualification, and best practices for extractables and leachables testing for OINDP
31	Biophorum operations group (BPOG) - Best Practices Guide for Evaluating leachables in Biopharmaceuticals	Industry Practices	Extractables testing protocol for evaluating leachables in biopharmaceuticals
32	USP<87> (in vitro bio reactivity assessment)	US Pharmacopeia	Under revision
33	USP <88> (in vivo bio reactivity assessment)	US Pharmacopeia	Under revision
34	USP <1031>) PDG (Pharmacopoeial alignment group)	US Pharmacopeia	Under revision

	Reference Title	Designation	Comments
	ISO 10993-4	International Organization for Standardization	Contains general requirements for evaluating the interactions of medical devices with blood. It describes a) a classification of medical devices that are intended for use in contact with blood, based on the intended use and duration of contact as defined in ISO 10993-1, b) the fundamental principles governing the evaluation of the interaction of devices with blood, c) the rationale for structured selection of tests according to specific categories, together with the principles and scientific basis of these tests
35	ISO 10993 (5, 6, 10, 11, 18)	Independent International Organization for Standardization	Biocompatibility (In vitro Cytotoxicity, local effects, irritation, Skin Sensitization, Systemic Toxicity data from supplier to meet)
36	Food Additive Compliance (21CFR parts 172-189, EU 2002/72/EC),	US Code of Federal Regulations	CRF is the codification of the general and permanent rules that were published in the US federal Register (FR) by the Executive departments and agencies of the US Federal Government
37	21 CFR 177.1520 Part 177 Indirect Food Additives: Polymers Subpart B--Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces	US Code of Federal Regulations	CRF is the codification of the general and permanent rules that were published in the US federal Register (FR) by the Executive departments and agencies of the US Federal Government
38	21 CFR Part 184: Direct Food Substances Affirmed as Generally Recognised as Safe. (GRAS)	US Code of Federal Regulations	

	Reference Title	Designation	Comments
39	(EU) 10/2011: Plastic materials and articles intended to come into contact with food and all subsequent amendments up to (EU) 202/2014.	EU regulation	
40	(EU) 202/2014 Amendment to (EU) 10/2011	EU regulation	
41	2003/32/EC (TSE/ BSE)	EU Commission directive	Directive covers specifications in relation to risks of transmitting TSE. Applicable to medical devices which utilise tissue from bovine, ovine and caprine species, or deer, elk, mink or cats rendered non-viable or non-viable products derived from such tissue.
42	EN ISO 22442 (TSE/ BSE)	International Organization for Standardization	This part of ISO 22442 is intended to provide requirements and guidance on risk management related to the hazards typical of medical devices manufactured utilizing animal tissues or derivatives such as a) contamination by bacteria, moulds or yeasts; b) contamination by viruses; c) contamination by agents causing Transmissible Spongiform Encephalopathies (TSE); d) material responsible for undesired pyrogenic, immunological or toxicological reactions. For parasites and other unclassified pathogenic entities, similar principles can apply.

	Reference Title	Designation	Comments
43	EP 5.2.8 (TSE/ BSE)	Ph. Eur. (European Pharmacopoeia)	Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (This chapter is identical with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products – Revision 3, (EMA/410/01 rev. 3).
44	Douglas J. Ball, Daniel L. Norwood, Cheryl L. M Stults and Lee M. Nagao, Leachables and Extractables Handbook, John Wiley & Sons, Hoboken, NJ (2012).	Reference Book	Describes development and application of safety thresholds for Orally Inhaled and Nasal Drug Products (OINDP). Discusses best practices for evaluation and management of leachables and extractables throughout the pharma product lifecycle by providing practical knowledge about how and why safety thresholds were developed. Also illustrates how to apply these concepts and principles to products beyond OINDP,
47	Medical Grade Plastics, VDI-Richtlinien, Berlin, July 2019.	VDI Standard	Provides definition of “medical grade plastics” and information to meet the standard, within framework of European medicines regulation and medical device regulation, and EMA guidelines
45	Dennis Jenke, Compatibility of Pharmaceutical Products and Contact Materials, John Wiley & Sons, Hoboken, NJ (2009).	Reference Book	

	Reference Title	Designation	Comments
46	Recommended Baseline Requirements for Materials used in Orally Inhaled and Nasal Drug Products (OINDP), IPAC-RS, 9 February 2017	Industry Practices	International Pharmaceutical Aerosol Consortium for Regulation and Science. Industry consortium of companies that develop OINDP.
48	Martin F. Sheridan (Ed.), The Vanderbilt Rubber Handbook 14th Edition, R.T Vanderbilt Co., Norwalk, CT (2010).	Reference Book	
49	Hans Zweifel, Ralph D. Maier and Michael Schiller (Eds.), Plastics Additives Handbook 6th Edition, Carl Hanser Publishers, Munich and Cincinnati (2009	Reference Book	
50	Dennis Jenke, Development and Justification of a Risk Evaluation Matrix To Guide Chemical Testing Necessary To Select and Qualify Plastic Components Used in Production Systems for Pharmaceutical Products, PDA Journal of Pharmaceutical Science and Technology, Vol. 69, No. 6, 677-712 (2015).	Journal Article	
51	Daniel L. Norwood, Lee M. Nagao and Cheryl L. M Stults, Perspectives on the PQRI Extractables and Leachables “Safety Thresholds and Best Practices” Recommendations for Inhalation Drug Products, PDA Journal of Pharmaceutical Science and Technology, Vol. 67, No. 5, 413-429 (2013).	Journal Article	
52	Jenke D. Safety risk categorization of organic extractables associated with polymers used in packaging, delivery and manufacturing systems for parenteral drug products. Pharm Res. 2015; 32:1105-1127.	Journal Article	